



**OSE Immunotherapeutics**

Limited Company (société anonyme) with a Board of Directors with a capital of €3,596,607.60

Registered office: 22 Boulevard Benoni Goullin 44200 Nantes

479 457 715 Nantes Trade and Companies Register

# 2020 UNIVERSAL REGISTRATION DOCUMENT INCLUDING THE ANNUAL FINANCIAL REPORT



This Universal Registration Document has been filed on April 15, 2021 with the AMF, as the competent authority and without its prior approval, in accordance with Article 9 of (EU) Regulation 2017/1129. The Universal Registration Document may be used for the purposes of a public offer of securities or the admission of securities to trading on a regulated market if it is supplemented by a securities note and, where applicable, a summary and its supplement(s). The whole is approved by the AMF in accordance with EU Regulation 2017/1129.

Pursuant to Article 19 of Regulation (EU) No 2017/1129 of the European Parliament and of the Council, the following information is incorporated by reference in this registration document:

- The consolidated financial statements and the corresponding audit reports appearing on pages 198-270 of the Universal Registration Document for fiscal year 2019 filed with the AMF on April 15, 20 under No. D18-0418 (<https://www.ose-immuno/financial-statements>)
- The consolidated financial statements and the corresponding audit reports appearing on pages 178-237 of the universal registration document for fiscal year 2018 filed with the AMF on April 26, 2019, under No. D19-0424 (<https://www.ose-immuno/financial-statements>)

Parts not included in such document(s) are either irrelevant to the investor or covered elsewhere in the registration document or universal registration document.

Copies of this Universal Registration Document are available, **on request and free of charge, during normal business hours, at the registered office of OSE Immunotherapeutics, 22 Boulevard Benoni Goullin, 44200 Nantes, and on its website ([www.ose-immuno.com](http://www.ose-immuno.com)), as well as on the AMF website ([www.amf-france.org](http://www.amf-france.org)).**

The information incorporated by reference should be read in accordance with the cross-reference table at the end of this universal registration document. Any information not indicated in this cross-reference table but forming part of the documents incorporated by reference is provided for information purposes only.

## WARNING

*This Universal Registration Document and the documents incorporated herein by reference, contain information about the Company's objectives and development areas. This information is sometimes identified by the use of the future or conditional tense and by forward-looking terms such as "consider", "envisage", "think", "aim", "expect", "intend", "should", "aspire", "estimate", "believe", "wish", "may", or, where applicable, the negative form of these same terms, or any other variant or similar terminology.*

*The reader's attention is drawn to the fact that these objectives and development areas depend on circumstances or events whose occurrence or outcome is uncertain.*

*These objectives and development areas are not historical data and should not be interpreted as guarantees that the facts and data referenced will occur, that assumptions will be correct or that objectives will be achieved. By their very nature, these objectives may not be achieved and the statements or information appearing in this Universal Registration Document may prove to be erroneous, without the Company in any way being obliged to update them, subject to applicable regulations and, in particular, the French Financial Markets Authority's General Regulation.*

*Investors are advised to give careful consideration to the risk factors described in section 3 of this Universal Registration Document, "Risk factors", before making any investment decisions. The occurrence of some, or all, of these risks is likely to have a negative impact on the Company's business, financial position, net financial income or its objectives. In addition, other risks that the Company has not yet identified or considers immaterial may have the same negative impact and investors may lose all, or part, of their investment.*

*This Universal Registration Document also contains information about the Company's business as well as the market and industry in which it operates. This information is primarily taken from studies carried out by internal and external sources (analysts' reports, expert studies, industry publications and any other information published by market research companies, public corporations and bodies). The Company believes that this information gives a true and fair picture of the market and the industry in which it operates and faithfully reflects its competitive position. Although this information is considered to be reliable, it has not been independently verified by the Company and the Company cannot guarantee that a third party using different methods to gather, analyze or calculate this market data would obtain the same results. The Company, the Company's direct or indirect shareholders and investment services providers cannot give any assurances or guarantees as to the accuracy of this information.*

*The global epidemic of the COVID-19 coronavirus continues to evolve rapidly. The extent to which the COVID-19 coronavirus is likely to affect the Company's business and clinical trials will depend on future developments, which cannot be predicted with certainty, such as the ultimate geographic distribution of the disease, its duration, travel restrictions and social distancing measures in the European Union, the United States and other countries, business closures or disruptions and the effectiveness of measures taken in these countries to contain and treat the disease. In addition, the extent of the adverse impact of this epidemic on the financial markets and on the Company's share price is unknown at this time. As of the date of the Universal Registration Document, the global economy is heavily impacted by the epidemic.*

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## **1 Responsible persons, third-party information, experts' reports and approval from the competent authority**

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### **1.1 Person responsible for the Universal Registration Document**

Alexis Peyroles

Chief Executive Officer Director

OSE Immunotherapeutics Registered office: 22 Boulevard Benoni Goullin, 44200 Nantes, France

Telephone: +33 (0)2 28 29 10 10

Email: alexis.peyroles@ose-immuno.com

Paris office : 100 avenue de Suffren, 75015 Paris, France

### **1.2 Statement by the Person Responsible for the Universal Registration Document**

"After having taken all reasonable measures to ensure that this is the case, I hereby certify that the information contained in this Universal Registration Document is, as far as I am aware, accurate and does not omit any material facts.

I hereby certify that, as far as I am aware, the financial statements have been prepared in accordance with applicable accounting standards and give a true and fair picture of the assets and liabilities, financial position and net income of the Company and of all the companies included in its scope of consolidation, and that the management report appearing on page 261 faithfully reflects the business developments, net income and financial position of the Company and of all the companies included in its scope of consolidation and that it describes the main risks and uncertainties faced.

Nantes, April 15, 2021

Alexis Peyroles

Chief Executive Officer Director

### **1.3 Statement by a person acting as an expert in respect of this document**

None

### **1.4 Third-party information**

On the date of this document, the Company does not have any information sourced from third parties, nor has it received, or been notified of, any expert statements or declarations of interest.

### **1.5 Approval of the Universal Registration Document**

As the Company has had a Registration Document approved by the AMF for at least two consecutive fiscal years and subsequently filed such documents on an annual basis, this Universal Registration Document has been filed without prior approval from the AMF, in accordance with Article 9.3 of EU Regulation 2017/1129 of the European Parliament and of the Council of June 14, 2017. It may, however, be reviewed at a later date by the French Financial Markets Authority, the competent authority, where the latter deems this necessary.

## **2 Auditors**

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### **2.1 Statutory Auditors**

#### **Joint Statutory Auditor**

##### **Ernst & Young and Others**

Represented by Mr. Cédric Garcia

Tour First—1-2 place des Saisons

92037 Paris La Défense Cedex, France

Start date of first term: appointed by decision of the sole shareholder on April 27, 2012

Duration of current term: six fiscal years from the date of appointment (decision taken by the Combined General Shareholders' Meeting of June 13, 2018)

End date of current term: at the end of the General Shareholders' Meeting called to approve the financial statements for the fiscal year ending on December 31, 2023

#### **Joint Statutory Auditor**

##### **SA RBB business advisors**

Represented by Mr. Jean-Baptiste Bonnefoux

133 bis rue de l'Université, 75007 Paris, France

Start date of first term: appointed by the General Shareholders' Meeting of September 17, 2014

Duration of current term of office: six fiscal years from the date of appointment (General Shareholders' Meeting of June 16, 2020)

End date of current term of office: at the end of the General Shareholders' Meeting called to approve the financial statements for the fiscal year ended on December 31, 2025

### **2.2 Information on auditors that have resigned, been removed or not been reappointed**

None

### **3 Risk factors**

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Investors are advised to consider all the information contained in this Universal Registration Document, including the risk factors described in this chapter, before deciding to acquire or subscribe for shares of the Company.

The risk factors set out in this Universal Registration Document are limited to only those risks that the Company considers, at the date of this document, to be specific to it and/or its securities and that are important for making an informed investment decision, as corroborated by the content of this Universal Registration Document and as may be corroborated by those indicated in a future securities note.

In preparing this document, the Company has assessed the importance of risk factors based on the likelihood of their occurrence and the estimated magnitude of their adverse impact. It has thus categorized the various risks according to its scientific and economic model, namely:

- Risks related to the development of its drug candidates: the Company is working on drug candidates at the pre-clinical and clinical stages, which implies certain specific risks related to experimental and theoretical research, or to the early phases of verification of the properties of a potential future drug;
- Risks linked to the partnership strategy: the Company currently has two products in partnership (with Boehringer Ingelheim and Servier), which implies various risks inherent in the relationships with its partners and the development phases to be carried out;
- Risks related to marketing drugs: the Company is working towards the future marketing of drug candidates, either within the framework of its partnerships or for products that it could market itself in certain geographic areas; in all cases, this implies obtaining the regulatory approvals necessary for such marketing;
- Risks linked to intellectual property rights: being in a research field, the Company is highly exposed to risks related to the protection of its intellectual property, mainly patents but also other intellectual property;
- Risks related to capital requirements: research programs are very capital intensive and without new money, the Company would not be able to pursue all of its programs and projects. Although the Company was able to take advantage of the resources generated by the licensing agreements, it also chose to seize market opportunities by raising €18.6 million from institutional investors at the end of 2020. In view of its plans, the Company will certainly need additional capital, and market financing could lead to a further dilution of shareholders.

The Audit Committee thus reviewed the risk mapping prepared by the Company's Management. This chapter, prepared in line with this mapping, was submitted to the Audit Committee at its meeting of March 22<sup>nd</sup>, 2021.

As of the date of this Universal Registration Document, the risks described below are those identified by the Company as being likely to materially impact its business, outlook, financial position, income or ability to achieve its objectives. The Company highlights the fact that in accordance with the article 16 of the Prospectus Regulation n°2017/1129, only the most important risks are listed and the list below is not exhaustive and others risks, currently unknown or, at the date of this Universal Registration Document, considered as unlikely to have a significant negative impact on the Company, its activity, its prospects, its financial situation, its results and its development, could exist or might happen.

The table below summarizes the main risks organized according to the five categories described above. Within each category, the residual risks remaining after the implementation of management measures are classified according to the level of criticality (combination of probability of occurrence and estimated impact) assessed during risk mapping. Only risks assessed with a "significant" level of criticality are detailed in this chapter.

Assessment of this « significance » level can be modified at any time, notably in case of new events.

	Risks linked to the development of our drug candidates	Probability of occurrence	Estimated impact
3.1	Risks linked to the development of our drug candidates	Probability of occurrence	Estimated impact
3.1.1	Risks linked to product development	High	High
3.1.2	Risks linked to the completion of the clinical and preclinical phases of its products in development	High	High
3.1.3	Risks of default of subcontractors (and in particular those linked to the outsourcing of clinical trials in the manufacture of products)	High	High
3.1.4	Risk of dependency or operational delay in relation to programs under development	High	Moderate
3.1.5	Risks linked to immunotherapeutic approaches used by the Company	Moderate	High
3.2	Risks linked to the partnership strategy		
3.2.1	Risks linked to research and dependency with respect to current and future partnerships	High	High
3.2.2	Risks linked to potential conflicts that may affect the Company's relationship with its licensees	Weak	Moderate
3.3	Risks linked to marketing		
3.3.1	Risks linked to obtaining a Marketing Authorization (MA)	High	Moderate
3.3.2	Risks linked to the lack of commercial success of the products.	High	Moderate
3.3.3	Risks linked to changes in drug reimbursement policies	High	Moderate
3.4	Risks linked to intellectual property rights		
3.4.1	Risks linked to uncertain protection of patents and other intellectual property rights	Moderate	High
3.4.2	Risks associated with the introduction of liability, in particular product liability risks	Moderate	High
3.4.3	Risks linked to patents and intellectual property rights held by third parties	Weak	High
3.5	Risks linked to capital requirements		
3.5.1	Risks linked to the financing requirement of the business	High	Critical
3.5.2	Risks linked to access to public grants and to the research tax credit	Moderate	Moderate
3.5.3	Valuation of intangible assets and impairment tests	Moderate	Moderate

### 3.1 Risks linked to the development of our drug candidates

OSE Immunotherapeutics is active in the biotechnology sector and in particular in the field of immunotherapy. The Company develops neoepitopes that specifically stimulate T lymphocytes (small peptides of interest derived from tumor antigens - Tedopi®, CoVepiT) and biotherapies that are agonists or antagonists of immunological targets that block or activate immune responses. It thus combines research and development expertise in the fields of immunoregulation and immune-activation, with complementary teams developing projects at the start-up and later clinical stages.

### 3.1.1 Risks linked to product development

The Company's ability to make judicious strategic and scientific choices, such as the choice of an indication for a given drug, the choice of a partner or the choice of a drug at various stages of development, is essential to ensure the Company's continued operations. The organization of the various management bodies, as well as the use of external expertise, is designed to limit risk and thus optimize decision-making.

The Company has preclinical and clinical programs leading to the eventual marketing of therapeutic options in immuno-oncology and autoimmune diseases. Product development is a long and costly process that takes place in several phases with uncertain outcomes. The objective is to demonstrate the therapeutic benefit provided by the product with good tolerance for one or more given indications, compared to existing products or products in development.

Each clinical trial in human is subject to prior approval and/or post-approval and all development data is evaluated by the competent regulatory authorities, according to its development plan (in particular the EMA - European Medicines Agency, and the FDA - Food & Drug Administration).

These regulatory authorities could prevent the Company from undertaking clinical trials or pursuing clinical development if it is found that the data submitted have not been produced in compliance with applicable regulations or if they consider that the relationship between the expected benefits of the product and its potential risks is insufficient to justify the trial.

For example, the Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from health authorities, the Company will try to obtain a marketing authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.

In addition, the Company may elect, or the regulatory authorities may require the Company, to suspend or terminate clinical trials if patients are exposed to unexpected and serious risks. Deaths and other adverse events, whether or not related to the treatment under trial, could occur and require the Company to delay or stop the trial and thus prevent the Company from continuing the development of its product in the targeted indication or in other indications.

In addition, the conduct of clinical trials and the ability to recruit patients into these trials depend on many factors such as:

- The nature of the targeted indication;
- The number of patients affected by the targeted pathology and eligible for treatment;
- The evolution of the pathology of the patients included in the trial;
- The existence of other clinical trials involving the same population;
- The ability to convince clinical investigators to recruit patients into a trial;
- The ability to recruit and treat patients at a given clinical investigation center;
- Availability of sufficient quantities of the product under study.

The number of patients who can and want to participate in a clinical trial is limited and recruitment can be difficult and slow, leading to excessive delays in conducting clinical trials. In order to overcome this difficulty, the Company may have to increase the number of clinical centers or service providers, which increases the complexity of the follow-up and the cost of the trial.

In addition, the COVID-19 strain of coronavirus, which is spreading in many countries, including France, or an equivalent crisis, could lead to extend the duration of ongoing clinical trials or, more generally, disruptions that could have a material adverse effect on the Company's business and its clinical trials, in particular:

- Delays or difficulties in recruiting patients for its clinical trials;
- Delays or difficulties in launching clinical sites, including difficulties in recruiting investigators and clinical site staff;
- Diversion of healthcare resources from the conduct of clinical trials, including the diversion of hospitals used as sites for the Company's clinical trials and of hospital personnel supporting the conduct of such clinical trials;
- The interruption of key clinical trial-related activities, such as the monitoring of clinical trial sites, due to travel restrictions imposed or recommended by federal or state authorities, employers or others;

- Limitations of human resources that would normally be focused on conducting the Company's clinical trials, in particular due to disease amongst employees or members of their families or the desire of employees to avoid all contact with significant groups of persons.

This is what the Company had to undergo when, together with the Independent Data Monitoring Board (IDMC)\* and the trial Steering Committee, analyzed the potential impact of the Covid-19 pandemic on the Atalante 1 trial. Due to the increased risk of Covid-19 in patients with advanced lung cancer and the potential impact on the trial data, on the recommendation of the IDMC and the Atalante 1 Steering Committee, OSE Immunotherapeutics decided, in April 2020, to voluntarily and definitively stop the screening and inclusion of new patients in the step-2 initially planned in the trial and which was therefore not conducted.

Due to the Covid-19 pandemic, the screening and recruitment of new patients in TEDOPaM had to be temporarily suspended in March 2020.

*\* As provided for in the Atalante 1 trial protocol, an Independent Data Monitoring Committee (IDMC) is in charge of regularly reviewing the data collected throughout the trial. This independent committee of scientific experts, customary in large multicenter randomized clinical trials, is responsible for assessing study progress, tolerability data and key efficacy criteria in the interest of patients.*

In addition to the risks listed above, and in the context of clinical trials conducted by the Company in countries that are experiencing an increased impact from the COVID-19 coronavirus, the Company could also experience the following adverse impacts:

- Delays in obtaining authorizations from the administrative authorities necessary to launch the clinical trials planned by the Company;
- Delays in the receipt by clinical sites of supplies and equipment required to conduct the Company's clinical trials;
- The interruption of global maritime trade that could impact the transportation of clinical trial materials, such as investigational drugs and drugs used as the basis for comparison in the Company's clinical trials;
- Changes in local regulations as a result of the COVID-19 coronavirus outbreak, which could require the Company to modify the terms of its clinical trials, which could result in unforeseen costs or even the interruption of such trials;
- Delays in necessary interactions with local authorities, ethics committees or other key agencies and third-party contractors due to human resource limitations or forced leaves of absence of government employees;
- The refusal of regulatory authorities to accept data from clinical trials conducted in these affected geographic areas.

These same disruptions could materialize in the event of an outbreak of another contagious disease or another strain of a virus.

For trials for which all or part of the execution is entrusted to service providers, the Company depends on their ability to perform their services under the agreed conditions and within the agreed deadlines. The remoteness or geographical distribution of clinical investigation centers may raise operational and logistical difficulties, which could result in costs and delays. The disruptions related to the COVID-19 health crisis described above or an equivalent crisis could similarly affect the Company's service providers (see also 3.1.3 below).

Clinical trials are expensive. If the results of these tests are not satisfactory or conclusive, the Company may have to choose between abandoning the program, resulting in the loss of the financial investment and the corresponding time, or continuing it, with no guarantee that the additional expenses incurred will be successful.

Many pharmaceutical companies have experienced significant setbacks in clinical trials, including at an advanced stage or during the regulatory approval process, even after promising results.

The Company's inability to conduct and successfully complete clinical trials could have a material adverse effect on its business, outlook, financial position, income and development. Although these risks are common to all players in the pharmaceutical industry, they are all the more significant for the Company given its limited financial and human resources capacities.

In addition, the communication of erroneous interim or final results of clinical studies could have a significant impact on the Company's reputation with key audiences such as the scientific and medical world, pharmaceutical companies or financial markets. The definition and implementation of a communication plan that includes a process for reviewing outgoing data limits this risk.

### **3.1.2 Risks linked to the completion of the clinical and preclinical phases of its products in development**

The risks encountered are linked to the risks of research and development of innovative products - neoepitopes, agonist or antagonist monoclonal or bispecific antibodies, in immuno-oncology and in autoimmune diseases.

The development risks for these biotechnology products are linked to the development stages to be completed: humanization of the antibody and bioproduction - pharmaceutical development stages - pharmaco-toxicology stages - various clinical stages with a view to completing a registration dossier in a specific clinical indication.

#### **IN CLINICAL PHASE**

##### **VACCINES**

###### **TEDOPI®**

###### **Positive step-1 results of the Phase 3 clinical trial in non-small cell lung cancer**

Tedopi®, a therapeutic vaccine, is a patented combination of 10 neoepitopes selected and optimized from five tumor antigens (Memopi® technology). These 10 neoepitopes generate a specific cytotoxic T cell response directed against tumor cells that express at least one of these tumor antigens. The selected epitopes are chemically optimized and combined to avoid immune tolerance phenomena (known as "neoepitopes"). Tedopi® is a personalized treatment for HLA-A2+ patients, a key receptor for cytotoxic response.

Tedopi® has just validated step 1 of its Phase 3 clinical trial in non-small cell lung cancer (trial named Atalante 1), in invasive stage IIIB or metastatic stage IV in Europe, the United States and Israel. The study aimed to evaluate the benefits of the product in HLA-A2 positive patients in second- or third-line treatment after failure of checkpoint inhibitor therapy, a specific population for which no validated treatment is currently available and for which there is a strong medical need. The main assessment endpoint is overall survival.

The main endpoint of step-1 pursuant to the protocol of Phase 3 of the Atalante 1 trial was achieved with a survival rate at 12 months in the patients treated with Tedopi® and a difference of 10% in absolute difference in survival rate compared to chemotherapy. The results showed a clearly improved overall survival time with Tedopi® compared to the standard treatment, the significant increase in survival after progression, the maintenance of a good ECOG\* score reflecting the change in general health of the patient, and confirmation of a good tolerability profile.

\* The ECOG score is a performance scale used to assess the overall state of health of the patient. It is subdivided into 5 grades from 0 to 5, ranging from fully active (0) to completely disabled and then to death (5).

These results confirm the value and therapeutic interest of Tedopi® in a population of patients suffering from advanced lung cancer after failure of a checkpoint inhibitor treatment for which there is no confirmed treatment to date and which is awaiting new therapeutic options. The Company is continuing to collect additional clinical data and analyze all the results to identify and confirm a sub-group of patients of interest. At the same time, given that the positive Step-1 results significantly strengthened the value of Tedopi®, the Company is continuing to explore any potential partnering opportunities for the product.

Due to the global epidemic of COVID-19, the Company, in conjunction with the IDMC and the trial Steering Committee, analyzed the potential impact of this epidemic on the Atalante 1 trial. Due to the increased risk of COVID-19 in patients with advanced lung cancer and the potential impact on the trial data, as recommended by the IDMC and the Atalante 1 Trial Steering Committee, OSE Immunotherapeutics decided, in April 2020, to voluntarily and definitively suspend screening and recruitment of new patients in the step 2 initially planned in the trial and which was therefore not conducted.

Today, the Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from

health authorities, the Company will try to obtain a marketing authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.

### Pancreatic cancer

Tedopi® is currently undergoing a Phase 2 clinical trial in HLA-A2 positive patients with locally advanced pancreatic cancer (trial named TEDOPaM), in collaboration with the cooperative group in oncology GERCOR, the trial sponsor.

Due to the COVID-19 pandemic, screening and enrolment of new patients had been temporarily suspended in March 2020. After reviewing data collected until the end of March 2020 and based on the initial protocol (Tedopi® in combination with Opdivo® or alone versus chemotherapy by FOLFIRI) the trial's independent committee of scientific experts (IDMC, "Independent Data Monitoring Committee") recommended to stop the evaluation of treatment with Opdivo® in combination with Tedopi® and to integrate the chemotherapy (FOLFIRI) in combination with Tedopi®. GERCOR has consequently modified the treatment design and the new inclusions (subject to the COVID-19 pandemic impact) are expected in Q2 2021 with an amended protocol comparing Tedopi® in combination with FOLFIRI chemotherapy versus FOLFIRI, after treatment with FOLFIRINOX. The primary endpoint of the trial remains the one-year survival rate.

\**FOLFIRINOX: a combination chemotherapy with folinic acid, fluorouracil, irinotecan and oxaliplatin*

\*\**FOLFIRI: a combination chemotherapy with folinic acid, fluorouracil and irinotecan*

### Ovarian cancer

In March 2021, the French National Agency for Medicines and Health Products Safety (ANSM) and the French Central Ethic Committee (CPP) approved the initiation of a new Phase 2 clinical trial evaluating Tedopi® in patients with recurrent ovarian cancer (the TEDOVA trial). This clinical trial will be sponsored and conducted by the French oncology cooperative group ARCAGY-GINECO. Tedopi® will be evaluated alone and in combination with Merck's Keytruda® (pembrolizumab), an immune checkpoint inhibitor, as maintenance treatment in ovarian cancer patients after chemotherapy. The trial should enroll 180 patients and Phase 2 read-out is expected end of 2023.

The three-arm TEDOVA study will evaluate neo-epitope-based vaccine Tedopi® as a maintenance treatment, alone or in combination with anti-PD-1 Keytruda®, versus the best supportive care in platinum-sensitive recurrent ovarian cancer patients with controlled disease after platinum-based chemotherapy.

The main risk associated with Tedopi® is more specifically related to the Phase 3 trial which would not demonstrate a sufficient benefit/risk ratio and could lead to additional requests from the drug agencies in Europe and in the United States.

### COVEPI

#### In Phase 1 clinical trial

CoVepiT, a multi-target and long-term protection vaccine, was developed from neo-epitopes to fight infections caused by SARS-CoV-2, the virus responsible for COVID-19. The vaccine incorporates optimized peptide fragments (neoepitopes) improved using artificial intelligence algorithms to increase immune response and induce strong memory T cell responses.

CoVepiT is generated using OSE's proprietary Memopi® technology which has been validated for both safety and efficacy through the step-1 of Phase 3 clinical phase of neoepitope vaccine Tedopi® in patients with non-small lung cancer.

The results of preclinical and ex vivo studies in humans conducted with CoVepiT showed:

- Data support potential as novel and differentiated COVID-19 vaccine designed against multiple SARS-CoV-2 targets with technology known to induce memory T lymphocytes;
- Studies show that CoVepiT provides tissue-resident memory (Trm) sentinel T cell response with long-term protective immunity in barrier tissues such as the respiratory tract and the lung;
- The emergence of new mutated coronavirus variants strengthens the multi-epitope approach against 11 viral proteins to generate a T lymphocyte response.

These results from both preclinical and human ex vivo studies as well as the expected emergence of new SARS-CoV-2 variants build a strong basis for continuing the development of CoVepiT as a COVID-19 vaccine based on a vaccine technology that induces a sustained memory T lymphocyte response against multiple coronavirus targets.

On April 1<sup>st</sup>, 2021, OSE Immunotherapeutics announced the authorization from the Belgian Federal Agency for Medicines and Health Products and the Belgian Ethics Committee to initiate a Phase 1 clinical trial to evaluate the safety, reactogenicity and immunogenicity of CoVepiT in 48 healthy adult volunteers.

The main risk associated with CoVepiT is related to the results of its clinical development.

## IMMUNO-ONCOLOGY

### BI 765063 (OSE-172)

#### In Phase 1 clinical trials in advanced solid tumors, developed in partnership with Boehringer Ingelheim

BI 765063 (OSE-172) is a monoclonal antibody antagonistic to the SIRP $\alpha$  target, a receptor highly expressed by myeloid cells and suppressor macrophage cells present in the tumor microenvironment and promoting tumor growth. This checkpoint inhibitor is part of the transformation of cells described as TAMs (Tumor-Associated Macrophages), and MDSCs (Myeloid-Derived Suppressor Cells) to block these cells predictive of poor prognosis and transform them into good-prognosis cells. BI 765063 is in Phase 1 clinical trial in advanced solid tumors, with the first patient having been included in June 2019.

Results on Phase 1 escalation dose in monotherapy will be presented at the ASCO congress in early June 2021 with an abstract accepted and to be published by ASCO on May 20<sup>th</sup>, 2021 on its website. The Company will announce this abstract publication in a press release.

The risks associated with BI 765063 are linked to the results of its clinical development and its continued development within the framework of a partnership.

## AUTOIMMUNITY AND INFLAMMATION

### FR104

#### In Phase 1/2 clinical trial in renal transplantation and Phase 2 project in a niche indication for autoimmune diseases

FR104 is an immunomodulator consisting of an optimized monoclonal antibody fragment targeting the CD28 receptor, a key component of the destruction function of effector T lymphocytes which are deleterious in autoimmune diseases and transplantation.

The results of the Phase 1 clinical study of FR104 showed good clinical and biological tolerability of the product. Its immunosuppressive activity in humans has demonstrated that the product has the potential to show clinical activity in the treatment of transplantation and immune-mediated diseases.

In December 2020, the French National Medicines Safety Agency (Agence Nationale de Sécurité du Médicament) and the Committee for the Protection of People have given their authorization to start a Phase 1/2 clinical trial evaluating FR104, administered for the first time in patients who have received a kidney transplant. This study is being conducted under a collaboration agreement between OSE Immunotherapeutics and the Centre Hospitalier Universitaire de Nantes, which is the sponsor.

This Phase 1/2 clinical study aims to evaluate the safety, tolerance, pharmacokinetics, pharmacodynamics and efficacy of FR104 in patients who have received a de novo renal transplant.

At the same time, OSE Immunotherapeutics is planning a new Phase 2 clinical trial of FR104 in a niche autoimmune disease indication, a priori Graves disease, which affects the functions of the thyroid gland that secretes too many thyroid hormones, which can lead to hyperthyroidism, cardiological complications or osteoporosis.

The risks on FR104 are related to the results of its clinical development in renal transplantation and the implementation and results of a clinical development in an autoimmune disease.

### OSE-127/S95011

#### Undergoing a Phase 2 clinical trial in ulcerative colitis (OSE) and another planned Phase 2 study in Sjogren's Syndrome (Servier), developed in partnership with Servier

OSE-127/S95011 is an immunomodulatory monoclonal antibody that targets the CD127 receptor, the alpha chain of the Interleukin 7 receptor.

OSE-127/S95011 is subject to a two-step licensing option granted to Servier for its development and marketing in autoimmune diseases. This licensing option will allow the product to be developed until the completion of a Phase 2 clinical trial. After positive Phase 1 clinical results of OSE-127/S95011 and the exercise of option 1 in February 2019, a Phase 2 trial has been underway in ulcerative colitis since December 2020 sponsored by OSE Immunotherapeutics and another Phase 2 trial is planned in Sjögren's Syndrome sponsored by Servier. Option 2 is expected to be exercised upon completion of these two Phase 2 studies, with priority being given to the study in Sjögren's syndrome. Further development beyond Phase 2, if Phase 2 of this licensing option is validated, will be carried out by Servier.

The Phase 1 clinical trial results showed a good safety and tolerability profile for OSE-127/S95011. All pharmacokinetic and pharmacodynamic parameters were consistent and demonstrated dose-proportionality throughout the dose escalation to 10 mg/kg. Nevertheless, the efficacy of OSE-127/S95011 will have to be demonstrated in the continuation of clinical development: in Phase 2 underway in ulcerative colitis sponsored by OSE, and in the other Phase 2 in Sjögren's Syndrome, sponsored by Servier with first enrolled patient now expected by the end of Q2 / early Q3 2021. In addition, if Servier decides not to exercise Option 2 at the end of Phase 2 clinical development, the continued development of the product could be compromised for scientific (such as new data that cannot be predicted at this time) or non-scientific reasons (such as related to a new strategic orientation for Servier).

The risks associated with OSE-127/S95011 are linked to the results of its clinical development and its continued development within the framework of a partnership.

#### IN PRECLINICAL PHASE

##### IMMUNO-ONCOLOGY

**CLEC-1 (among CLR receptors-C-type lectin receptors)** is a myeloid checkpoint and a new therapeutic target of interest in immuno-oncology. Antagonistic monoclonal antibodies that block this new "Don't Eat Me" signal have been identified.

These CLEC-1 antagonistic monoclonal antibodies make it possible to remove new brakes on macrophage phagocytosis and dendritic cells and demonstrates synergistic anti-cancer effects, in particular when paired with chemotherapy.

This research program is conducted in collaboration with Dr Elise Chiffolleau (CRTI, Center for Research in Transplantation and Immunology, UMR1064 - INSERM, University of Nantes).

#### **BiCKI® is a new platform of bispecific inhibitors of checkpoints targeting the PD-1 receptor and other innovative targets.**

The novel bispecific fusion protein platform is built around a key backbone component anti-PD-1 (OSE-279), a new standard cancer treatment, merged with innovative immunotherapy targets, as yet undisclosed, with the exception of the first product from this platform: targeting IL-7. The BiCKI® platform aims to inhibit key immune checkpoint inhibitors while simultaneously delivering cytokines capable of modulating regulatory T cells, and/or increasing the responses of exhausted T cells within the tumor. It can also incorporate other therapeutic methods to modify the tumor microenvironment by delivering, for example, co-stimulation signals to restore the activity of anti-tumor T lymphocytes or restore phagocytic functions and macrophage polarization.

Based on an anti-PD-1 bifunctional antibody platform technology, BiCKI® is designed to expand the type of patients responding to immunotherapies. This is the second generation of PD-(L)1 inhibitors used to increase anti-tumor efficacy in hard-to-treat cancers by addressing untapped immune escape mechanisms.

**OSE-279 is a humanized anti-PD-1 monoclonal antibody.** It should enter Phase 1/2 clinical trial in 2021 for a niche indication in immuno-oncology. This would allow the Company to own a patented anti-PD-1 that it could subsequently develop in combination with other products in its portfolio.

#### AUTOIMMUNITY AND INFLAMMATION

**OSE-230 is an agonist antibody against ChemR23, also known as chemerin chemokine-like receptor 1 (CMKLR1), a G-protein coupled receptor (GPCR) expressed on myeloid immune cells known to modulate inflammation.** OSE-230 has the potential to activate the physiological pathways of chronic inflammation and restore the integrity of the pathological tissue.

Preclinical efficacy data have shown that OSE-230 is the first monoclonal antibody activator of specialized resolution receptors that restores the hemostasis of pathological tissue, its integrity and its functions. The product has a strong therapeutic potential in various chronic pathologies.

There is a risk that evaluation of these products in preclinical development will not allow their clinical development to be continued.

#### **RESEARCH & DEVELOPMENT**

In R&D, the Company is developing other agonist or antagonist monoclonal or bifunctional antibodies targeting new receptors of interest in immuno-oncology, autoimmune and inflammatory diseases.

The risks associated with these products are the usual risks of research and development.

To identify and validate new therapeutic targets, the Company works in close collaboration with academic and university research centers.

The risks associated with this academic collaboration are the usual risks associated with research.

#### **3.1.3 Risks of sub-contractor default (in particular those linked to clinical study outsourcing and product manufacturing)**

The Company uses subcontracting in the conduct of activities and in particular in ongoing clinical trials: the monitoring of patients already included in Phase 3 trials with Tedopi® for lung cancer, whose Step-1 was positive, the Phase 2 trial with Tedopi® in therapeutic combination in pancreatic cancer, the Phase 2 trial with Tedopi® in combination in ovarian cancer, the planned Phase 1/2 trial of CoVepiT against COVID-19, the Phase 2 trial of SE-127/S95011 for ulcerative colitis, the Phase 1 trial of BI 765063 (OSE-172) for advanced solid tumors, or for the production of clinical lots of these products currently in clinical development.

The Company utilizes subcontractors to perform certain tasks including the management of these clinical trials or the manufacturing of clinical slots and development of complex procedures that must be highly monitored. If these subcontractors fail to carry out their tasks, deliver inadequate performance, or are slower than required or usual, the Company will not be able to successfully produce, develop, or market its products.

The main subcontractors in charge of managing the clinical trials or in charge of the manufacturing of clinical slots are the followings:

- Phase 3 with Tedopi® in Non-Small Cell Lung Cancer (with step-1 positive results):  
CRO (Clinical Research Organization): Linica (international with headquarters in Japan)  
Manufacturing of drug substance: Polypeptide (United States)  
Manufacturing of final product: Baccinex (Switzerland)
  
- Phase 1 with CoVepiT against COVID-19:  
CRO (Clinical Research Organization): ICTA (France)  
Manufacturing of drug substance: Polypeptide (United States and Strasbourg/France)  
Manufacturing of final product: Baccinex (Switzerland)
  
- Phase 2 with OSE-127/S95011 in ulcerative colitis:  
CRO (Clinical Research Organization): Pharm-Olam (United States)  
Manufacturing of drug substance: LFB (France)  
Manufacturing of final product: Baccinex (Switzerland)
  
- Phase 1 with BI 765063 (OSE-172) in solid advanced tumors:  
CRO (Clinical Research Organization): MedPace (international with headquarters in the United States)

Manufacturing of drug substance and final product: managed by the partner Boehringer Ingelheim (Merck in France and Lonza in Switzerland)

- Phase 1 / 2 with FR104 in renal transplant:  
Manufacturing of drug substance: KBY (United States)  
Manufacturing of final product: Baccinex (Switzerland)

In addition, dependency on respect to third-party manufacturers presents additional risks that the Company would not face if it manufactured its own products, i.e.:

- Non-compliance of these third parties with regulatory standards and quality control;
- Breach of agreements by these third parties;
- Termination or non-renewal of these agreements for reasons beyond its control;
- Bankruptcy of subcontractors, resulting in suspension of services, not allowing the Company the time to find an alternative solution.

If the products manufactured by third-party suppliers are non-compliant with regulatory standards, sanctions could be imposed on the Company. These sanctions could include fines, injunctions, civil penalties, refusal by regulatory organizations to grant marketing authorization for its products, delays, suspension or withdrawal of authorizations, license revocations, seizures or product recalls, operating restrictions and legal proceedings, all of which could have a considerable adverse impact on the Company's business.

Moreover, the agreements entered into with subcontractors usually contain clauses that limit their liability, which means that the Company could possibly not obtain full compensation for any damages that it could suffer as a result of the violation of these commitments by the subcontractors in question.

In the event that the Company changes manufacturers for its products, it would be required to undergo re-approval of the new manufacturer's processes and procedures in accordance with applicable Good Manufacturing Practices ("GMP") standards. This re-approval could be costly, time-consuming and require the attention of its most qualified staff. If re-approval is not successful, the Company could be forced to look for another supplier, which could delay the production, development, and marketing of its products and increase their manufacturing costs.

Such events could have a material adverse impact on the Company's business, prospects, financial position, results, and development. In order to limit these risks, the Company pays the greatest attention to the importance of its relationships and communications with its subcontractors. Sub-contractors are evaluated and must undergo strict audits by regulatory agencies and by the Company.

In addition, the Company depends on third parties to supply it with certain biological products (including peptides/adjuvants) needed to manufacture its drugs.

Even if the Company's policy is to build long-term contractual relationships with its strategic suppliers, and rely on large suppliers in the pharmaceutical industry, its provisioning of certain biological products could be limited, interrupted, or restricted. In addition, in such a case, the Company might not be able to find acceptable quality laboratory products from other suppliers, in the necessary volumes or at an acceptable cost. If its key suppliers or manufacturers are unreliable or its supply of products or materials is reduced or interrupted, it might be unable to develop, produce, and then market its products in a timely and competitive manner.

If the Company encounters difficulties in the provisioning of its biological products or is unable to maintain its subcontracting agreements, sign new agreements, or obtain the biological products necessary for the development and manufacturing of its products in the future, its business, prospects, financial position, results, and development could be materially impacted.

Finally, the current COVID-19 health crisis, the appearance of another contagious disease or strain of virus could also create disturbances among the Company's subcontractors that could have a material adverse impact on the Company's business, and clinical trials, in particular:

- Delays or difficulties in provisioning, manufacturing, or transport of biological products, supplies, or materials necessary to conduct the Company's clinical trials;
- Diversion of resources to produce complex procedures;
- Changes in regulatory and quality-control standards applicable to subcontractors, making their services more time-consuming, costly or even impossible; and

- Limitations of human resources that would normally be the Company's responsibility, in particular due to diseased employees or members of their families or the desire of employees to avoid all contact with significant groups of persons.

It is difficult to predict the evolution of the epidemic and how restrictions on individuals or additional government measures might impact future patient recruitment at sites participating in ongoing studies.

For patients who are already participating in the various clinical trials, there is a risk that some participants may not be able to attend the follow-up visits prescribed by the study protocol due to government or local restrictions. The Company seeks to mitigate this risk by using teleconferences and videoconferences as part of the monitoring of clinical studies with, in particular, clinical investigators. In addition, the pandemic could cause delays in preclinical studies. In order to minimize the overload of care services, ensure the safety of new patients, avoid major deviations related to missed follow-up visits and minimize contacts between patients and clinical investigation teams, recruitment of new patients in the TEDOPaM clinical trial has been temporarily suspended and the time to initiate Phases 2 OSE-127 / S95011 may be impacted in the coming months.

### **3.1.4 Risk of dependency or operational delay in relation to programs under development**

OSE Immunotherapeutics is a biotechnology company focused on developing innovative immunotherapies acting on activator or suppressor cells to stimulate or inhibit the immune response for immuno-oncology and autoimmune diseases and transplantation. It develops next generation products optimized to better target the key receptors of the immune response's activation or regulation, allowing the therapeutic effect to be sustained over time. The Company aims to become a leading international player in the field of immunotherapy with an innovative technology base and expertise in the selection and optimization of receptor targeting that will lead to significant therapeutic advances.

It masters the technologies of immunoregulation and immuno-activation of the immune system with complementary international teams and expertise involved in the research and optimization of drug candidates, pharmaceutical development, clinical development and registration.

The Company has a diversified portfolio of advanced immunotherapy products ranging from Phase 3 to Phase 1 clinical and preclinical development. These next generation products have independent development risks and could be attractive to different players in the pharmaceutical industry. They may be subject to early or late licensing for specific regions and/or with pharmaceutical partners interested in one of the clinical areas targeted by the Company (immuno-oncology, autoimmune diseases, transplantation).

Research and development programs aimed at identifying new candidate products require significant technical, financial and human resources. While research programs may initially show promise in identifying potential candidate products, there can be no assurance that such programs will be successful in generating products suitable for clinical development that could attract the interest of potential partners, in particular because of the following factors:

The research method used may not identify potential candidate products;

Or the candidate products could, as a result of new studies or clinical trials, be difficult to produce, ineffective, unstable, have dangerous side effects, undifferentiated properties, or other characteristics suggesting their likely ineffectiveness or potential harm.

If the Company were unable to develop these innovative products for the various immunological targets identified in its research and development programs, it would encounter difficulties in finding new partners, and its business, financial position, income, development and medium- and long-term outlook would be significantly impacted.

The development of a drug requires the involvement of highly qualified personnel. The departure of research and development experts could present a risk to the Company with a possible delay in development before the recruitment of key complementary skills.

The future success of the Company and its ability to generate long-term revenues will depend on the successful development as well as the commercial success of its activating or regulatory immunotherapy products developed against cancer or autoimmune diseases, and in particular on the occurrence of numerous factors, such as:

- **Tedopi®:** validation by the health authorities of the first step of Phase 3 completed in March 2020, in lung cancer after failure of a checkpoint inhibitor; the success of the ongoing Phase 2 clinical trial of Tedopi® in combination in pancreatic cancer (this Phase 2 trial being conducted under GERCOR sponsorship); the success of the Phase 2 clinical trial of as a maintenance treatment, alone or in combination with anti-PD-1 Keytruda®, versus the best supportive care in platinum-sensitive recurrent ovarian cancer patients with controlled disease after platinum-based chemotherapy (this Phase 2 trial being conducted under ARGAGY-GINECO sponsorship).
- **CoVepiT:** this COVID-19 vaccine program, in clinical Phase 1 following the approval from Belgian regulatory authorities received on April 1<sup>st</sup>, 2021, will have to successfully pass this clinical phase to continue its further clinical development;
- **BI 765063 (OSE-172):** this program, developed under an exclusive worldwide collaboration and licensing agreement with Boehringer Ingelheim Internal GmbH, will have to successfully complete its ongoing Phase 1 clinical trial in advanced solid tumors and the subsequent steps of its clinical development in immuno-oncology;
- **CLEC-1, BiCKI®, OSE-279** The continuation or not of the clinical development of these products will depend on the results of their preclinical development steps to lead them to a clinical program in immuno-oncology.
- **OSE-127/S95011:** this program, developed under the 2-step licensing option with Servier, after successfully completing its Phase 1 clinical trial to evaluate its potential in autoimmune inflammatory diseases, will have to successfully complete the Phase 2 clinical trial step, with priority in Sjögren's Syndrome (Phase 2a led by Servier), or in ulcerative colitis (Phase 2 led by OSE Immunotherapeutics), before this program can be supported by Servier;
- **FR104:** after positive Phase 1 clinical trial results, this program will have to successfully complete the ongoing Phase 2 in renal transplantation and that of the implementation and results of a Phase 2 clinical trial in a niche autoimmune indication, a priori in Graves disease.
- **OSE-230** the continuation or not of the preclinical development will depend on the results of the preclinical development steps to lead OSE-230 towards a clinical program in the resolution of the inflammation;
- For research and development programs on other products developed by the Company, the establishment of partnerships and/or licensing agreements;
- Marketing authorization ("MA") granted or not by the regulatory authorities;
- Production on an industrial scale and in sufficient quantities of pharmaceutical batches of constant and reproducible quality;
- The acceptance or non-acceptance of the Company's products by the medical community, healthcare prescribers and third-party payers (such as social security systems), and their effective commercial success.

Thus the most common risks encountered are the following:

- In general, as with any new drug development, there is a significant risk if the lack of efficacy of the product is proven, or if serious adverse events occur, which would have a negative impact on the outcome of the study. Similarly, the project may not succeed if the number of patients admitted to the clinical studies is insufficient to conclude efficacy. In addition, unforeseen risks of intolerance, or changes in applicable regulatory requirements could affect the timing and nature of clinical development activities, the relative costs and the timing of payments contingent upon completion of the various phases and the reimbursement of expenses.
- If the Company's products were to prove ineffective or have unacceptable side effects, it would be impossible to market them, which could have a material adverse effect on the Company's business or outlook, financial position, income and development.

- The risk linked to the failure to develop its products is highly related to the stage of maturity of the drug and is necessarily inherent to the Company's business. For the development of the drug in Phase 3 in lung cancer, the Company believes that there is a lower risk in Phase 3 (compared to Phase 2 projects) of not reaching the marketing authorization stage.
- For Tedopi®, regulatory approvals may not be obtained, may be delayed pending new clinical trials, or may only be obtained under more restrictive conditions. The Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from health authorities, the Company will try to obtain a marketing authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.
- The current COVID-19 health crisis, the appearance of another contagious disease or another strain of a virus leading to quarantine, the total or partial paralysis of the economy and/or the hospital system in any form whatsoever, particularly in the countries in which the Company is conducting or planning to conduct clinical trials, could lead to a suspension or even a complete halt in recruitment, which could jeopardize the initial development strategy of the product; or delay the conduct of clinical trials as such or a delay in the regulatory review by the competent authorities.
- Existing signed pharmaceutical partners may decide not to complete the development and marketing of candidate drugs due to internal priorities or may not have adequate resources to complete them.
- The exclusive property rights of third parties could prevent the Company and its partners from marketing the candidate drugs.
- Authorized products may not find their place on the market and/or be limited in their selling price.
- In such a case, the estimates made on the business outlook offered by the market could turn out to be too optimistic.
- In the absence of successful development, marketing authorization or commercialization of its drugs, the Company would be unable to generate significant revenue. If development programs are delayed, the Company may be required to raise additional capital or to reduce or discontinue, in whole or in part, its operations, research projects or development programs.

### **3.1.5 Risks linked to the immuno-therapeutic approaches selected by the company**

The Company develops agonist or antagonist immunotherapy products used to activate or regulate the immune system, fight against cancer and immune diseases linked to autoimmune diseases and transplantation.

#### **IN IMMUNO-ONCOLOGY**

As of the date of this Universal Registration Document, there are several registered anti-cancer immunotherapy products on the market.

The first immunotherapy products against cancer are checkpoint inhibitors acting on T cells (Yervoy® BMS, Opdivo® BMS, Keytruda® Merck, Tecentriq® Roche, Imfinzi® AstraZeneca, Pfizer/Merck Serono, Bavencio® Merck, and others registered or being registered), and a therapeutic vaccine, Provenge®.

Provenge®, the first immune activation product on the market in this area, is a cell therapy product to combat prostate cancer that was licensed in the United States in 2010 (Provenge® or sipuleucel-T, developed by the US company, Dendreon, subsequently acquired by the pharmaceutical company, Valeant).

#### **Checkpoint inhibitors acting on T lymphocytes**

A new class of products called checkpoint inhibitors (non-specifically removing the blocking of cytotoxic T cells) has also entered the market. Checkpoint inhibitors were first registered for melanoma since 2011, then for lung cancer from 2014 to 2018 and for other indications.

**Yervoy®** (ipilimumab, BMS and ONO): this first entry is a monoclonal antibody (preventing the immunosuppressive inhibition of T lymphocytes called CTLA4). It has been registered worldwide for metastatic melanoma since 2011. A combination of Yervoy® and Opdivo® was authorized for a special type of melanoma (compared with BRAF); these two products were already registered for this indication. In 2018, the product was registered in combination with nivolumab (Opdivo®) in metastatic colorectal cancer and in 1st-line treatment of renal cancer.

**Opdivo®** (nivolumab, BMS and ONO): a monoclonal antibody/checkpoint inhibitor acting on as a brake on other T lymphocytes called PD-1. First marketing authorization: December 2014 (metastatic melanoma). Since then, Opdivo® has been registered in metastatic non-small cell lung cancer (NSCLC) (2015), renal cancer (2015), Hodgkin's lymphoma (2016), head and neck cancer (2016), bladder cancer or urothelial carcinoma (2017), metastatic colorectal cancer (MSH-H or dMMR) (2017), hepatocellular carcinoma (2017). In 2018, the product was registered in combination with ipilimumab (Yervoy®) in metastatic colorectal cancer and in first-line therapy in renal cancer.

**Keytruda®** (pembrolizumab, Merck & Co.): second monoclonal antibody targeting the same PD-1 inhibitor. First marketing authorization: in 2014 in metastatic melanoma. Since then, Keytruda® has been registered in non-small cell lung cancer (NSCLC) (2015), head and neck cancer (2016), Hodgkin's lymphoma (2017), bladder cancer or urothelial carcinoma (2017), gastric cancer or gastro esophageal junction cancer (2017), cervical cancer (2018), diffuse large B cell lymphoma (June 2018), hepatocellular carcinoma or liver cancer (2018), Merkel cell carcinoma (an aggressive skin tumor) (2018), renal cancer (2019), esophageal cancer (2019) and endometrial cancer (2019).

After registration in 2015 as a 2nd-line therapy for patients suffering from metastatic non-small cell lung cancer (NSCLC) with a PD-1 biomarker expression, in October 2016, Keytruda® was registered in 1st-line therapy in NSCLC for patients expressing the PD-1 marker (PD-L1 expression over 50% at tumor level). In May 2017, Keytruda® obtained its conditional registration in 1st-line therapy (in combination with pemetrexed and carboplatin) in NSCLC, whatever the PD-L1 expression. In August 2018, Keytruda® was registered in 1st-line therapy (in combination with pemetrexed and platinum-based chemotherapy) in metastatic non-epithelial NSCLC without tumor-genomic aberration of the EGFR or ALK gene. In October of the same year, it was registered in 1st-line therapy (in combination with carboplatin and paclitaxel) in NSCLC, whatever the PD-L1 expression. In April 2019, the product was registered in 1st-line monotherapy for stage III NSCLC (PD-L1 proportion expressed at over 1% at the tumor level).

**Tecentriq®** (atezolizumab, Genentech - Roche): designed to target the PD-L1 protein (a PD-1 ligand acting on the same pathway as T lymphocyte inhibitors), was approved in the United States for bladder cancer in May 2016, with a companion test to identify PD-L1 positive patients (Ventana PD-L1-SP 142 assay). In October 2016, this product was registered for the treatment of lung cancer as a second-line therapy for patients suffering from metastatic non-small cell lung cancer (NSCLC) whose disease has progressed during or after platinum-based chemotherapy, and during an appropriate targeted treatment in the presence of a tumor with EGFR or ALK gene mutation. In December 2018, Tecentriq® obtained its registration as a first-line therapy for metastatic non-epithelial NSCLC in combination with Avastin® and chemotherapy. In March 2019, the product was registered in metastatic triple negative breast cancer and in 1st-line therapy of small cell lung cancer. In 2020, it was registered in combination with Avastin® for hepatocellular carcinoma.

**Bavencio®** (avelumab, Merck Darmstadt or EMD Serono in collaboration with Pfizer - Javelin program) is a monoclonal antibody targeting the anti-PD-L1 target. This antibody is an IgG1, a cytotoxic antibody. Bavencio® was registered in March 2017 for Merkel cell carcinoma (an aggressive skin tumor), and in May 2017 for bladder cancer or urothelial carcinoma.

**Imfinzi®** (durvalumab, AstraZeneca) is a humanized monoclonal antibody targeting the PD-L1 ligand. It was registered for bladder cancer (May 2017) and for unresectable non-small cell lung cancer (February 2018) in patients whose cancer has not progressed after chemo and radiotherapy. Tremelimumab, an anti-CTLA-4 drug (Astra), was developed in combination with durvalumab, from the same company, for various indications.

Many monoclonal antibodies targeting PD-1 or its PD-L1 ligand are being developed in the United States, Europe and especially in China.

Third-line treatments for advanced lung cancer are offered but are essentially palliative. To date there is no approved treatment available for patients who are unresponsive to checkpoint inhibitors.

The Company is developing, in partnership with Boehringer Ingelheim International, a new generation checkpoint inhibitor called BI 765063 (OSE-172), that acts on suppressor myeloid cells and macrophages. The Company received licenses from French and Belgian health authorities in March 2019 for Phase 1 clinical trials of the product for different types of solid cancer but does not yet have any results. Presently, there is no certainty that appropriate clinical results will be obtained for the remainder of the development with competitive advantages that remain to be demonstrated clinically.

The products developed by the Company are immunotherapies for which preclinical and clinical data on their safety and efficacy are still limited. Many uncertainties therefore weigh on the prospects for the development and profitability of products resulting from these technologies as long as their safety, efficacy, and acceptance by patients, medical doctors and healthcare payers have not been established.

If the Company has success in the Phase 2 trial of Tedopi® for the treatment of lung cancer (positive results obtained on a limited number of patients), the results might not be confirmed in subsequent phases on a greater number of patients (Phase 3 trials include a greater number of patients than Phase 2 trials). The positive results in Step-1 of the Phase 3 clinical trial (N=99 patients), conducted for non-small cell lung cancer following failure of checkpoint inhibitor treatment, demonstrated that the main criterion of this step had been reached with a 12-month survival rate in patients treated with Tedopi® and a 10% absolute difference in the survival rate compared with chemotherapy. These results confirm the therapeutic interest of Tedopi®. The Company is continuing additional analyses of the Step-1 data.

Moreover, due to the worldwide COVID-19 epidemic, on the recommendation of the IDMC and the Steering Committee of the study, the Company decided to voluntarily and definitively suspend screening and recruitment of new patients in the Step-2 initially planned in the trial that will thus not be conducted.

Today, the Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from health authorities, the Company will try to obtain a marketing authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.

The clinical trials data could be strongly impacted by the worldwide COVID-19 pandemic and by the increased risk for patients with advanced lung cancer, as COVID-19 can cause serious pulmonary complications in this immunocompromised patient population. Moreover, for patient safety, several scientific and medical societies currently recommend the voluntary suspension of new patient recruiting in clinical trials in oncology.

Moreover, as more and more frequently in oncology, the Company's products must be administered in combination with other therapies. Many uncertainties therefore weigh on the prospects for the development and profitability of products resulting from these technologies as long as their safety, efficacy, and acceptance by patients, medical doctors and healthcare payers have not been established.

## IN AUTOIMMUNE DISEASES

The immunological treatment of autoimmune diseases is based on three approaches:

Eliminate pathogenic autoantibodies (plasmapheresis method), modulate activation of lymphocytes and synthesis of cytokines (immunosuppressors such as corticosteroids, cyclosporin A, the molecules interfering with purine metabolism such as azathioprine (Imurel®) or mycophenolate mofetil (Cellcept®) and, in a more targeted fashion, modify the immune response to make it non-pathogenic (immunomodulation, for example, by inhibiting the cytotoxic action of TNFα by anti-TNFα antibodies by blocking B lymphocytes by anti-CD20s).

The key players in the autoimmune disease market are pharmaceutical groups Johnson & Johnson (J&J), AbbVie, Amgen, Genentech/Roche, Astellas, UCB, Eli Lilly, Sanofi, AstraZeneca, Novartis and Biogen.

The Company's products are developed for new targets:

FR104 finalized the Phase 1 trial with positive results; however the first results may not be confirmed by the subsequent clinical phases.

OSE-127/S95011 showed positive Phase 1 results (evaluated in healthy volunteers) with a good safety and tolerability profile and a dosing and administration schedule defined for the Phase 2 clinical trial which must demonstrate product efficacy in patients with Sjögren's Syndrome or ulcerative colitis; no certainty currently exists that appropriate clinical results will be obtained for the rest of their development with competitive advantages that remain to be clinically demonstrated.

In such cases, product development might not be continued, which would have a significant impact on the business, results, financial position, and development of the Company.

## 3.2 Risks linked to the partnership strategy

### 3.2.1 Risks linked to research and dependency on current and future partnerships

#### 3.2.1.1 Licensing and license option agreements

To develop and market products, the Company seeks to enter into agreements for collaboration and licensing with pharmaceutical companies that can assist it in drug development and financing. As of the date of this Universal Registration Document, the Company has four licensing and license option agreements.

A first licensing and distribution agreement for Tedopi® in Israel was signed in May 2015 with Rafa Laboratories, a pharmaceutical company specializing in oncology and rare lung diseases, long established on this market promoting innovation.

This exclusive long-term agreement includes the license, distribution and sales of Tedopi® in Israel. Under the terms of this agreement, commercialization and distribution will be carried out in the territory over the long term. Rafa Laboratories made a cash upfront payment of 100,000 euros upon signing. Milestone payments are expected as the product is developed, steps that have not been completed to date. RAFA will share equally with OSE Immunotherapeutics profits from Tedopi® sales in Israel.

According to the initial agreement signed in December 2016, OSE Immunotherapeutics granted Servier a two-step license option to acquire the exclusive world rights for development and marketing of OSE-127/S95011 until the finalization of a Phase 2 study planned for ulcerative colitis, an autoimmune bowel disease. This agreement, in a total amount that could reach €272 million including an upfront payment of €10.25 million (received in early 2017) and a payment of €30 million upon exercise of a two-step license option (including €10 million on Option 1 - exercised in February 2019 and paid in March 2019 - and €20 million upon exercise of Option 2). A March 2020 amendment changes the procedures of the potential exercise of Step 2 of the license option. OSE Immunotherapeutics could receive a milestone payment of €5 million from Servier upon inclusion of the first patient in a Phase 2a clinical study (sponsored by Servier) in Sjögren's Syndrome, with first enrolled patient now expected by the end of Q2 / early Q3 2021. Sjögren's syndrome is a systemic autoimmune disease characterized by an exocrine gland condition affecting the tear and salivary glands. An additional payment of €15 million is expected upon exercise of the option, at the end of the two Phase 2 studies planned, and in priority at the end of the trial focusing on Sjögren's Syndrome.

Subsequent payments will be linked to clinical development milestones, registration in multiple indications, then sales-related milestones with double-digit royalties.

An exclusive worldwide collaboration and licensing agreement was entered into in April 2018 with Boehringer Ingelheim International for the joint development of BI 765063 (OSE-172) for the treatment of advanced solid tumors. Boehringer Ingelheim acquired worldwide rights for the development, registration, and marketing of BI 765063 (OSE-172). According to the terms of the agreement, OSE Immunotherapeutics received an upfront payment from Boehringer Ingelheim in the amount of €15 million, and a total of €15 million in milestone payments following regulatory approval to launch Phase 1 in March 2019 and on inclusion of the first patient in the study.

Overall, the agreement provides for a potential amount of more than €1.1 billion according to predefined development steps, marketing authorization, and sales, plus royalties on net worldwide sales of the product.

Finally, a fourth licensing and distribution agreement for Tedopi® in Korea was signed in November 2019 with Chong Kun Dang Pharmaceutical Corporation (CKD), a pharmaceutical company long established in this market promoting innovation.

Under the terms of the agreement, OSE Immunotherapeutics will receive milestone payments totalling €4.3 million, including €1.2 million upon signature (€700,000) and positive results from Step-1 of Atalante Phase 3 trial (€500,000) plus royalties on product sales and a transfer price margin at a level slightly below around thirty percent. The agreement covers the development and license of Tedopi® in the Korean market, which represents approximately 1% of the global oncology market.

The Company, however, cannot guarantee that these agreements will lead to the registration of these products currently in clinical development phases.

Moreover, in the current COVID-19 health crisis, the appearance of another contagious disease or another strain of a virus leading to an equivalent situation (quarantine, total or partial paralysis of the economy and/or the hospital system in any form whatsoever) the Company cannot guarantee that the projections of key clinical steps will be effective, and consequently that the milestone payments will be paid according to the schedule planned by the Company. Likewise, such events could seriously disrupt the activity of current and future partners, and prevent them from using all or a major part of their essential infrastructures, jeopardize their desire to continue their agreements with the Company, suspend developments or co-developments, redirect or limit the resources assigned to conducting the clinical trials to other research programs or delay the progress of clinical trials that they must provide in order for the Company to receive the milestone payments and royalties.

Such events could seriously disrupt the activity of the Company and have a material adverse impact on its business including its ongoing clinical trials, its schedule for obtaining marketing authorizations, its financial position, and its prospects. It should be noted that on December 31, 2018, OSE regained the worldwide rights for FR104 from Janssen Biotech as part of a worldwide licensing agreement entered into in 2013 followed by the exercise of a license option in July 2016. Janssen Biotech's decision to return the FR104 program to OSE was motivated by an internal strategy review and prioritization of its own product portfolio. Since then, the Company has been evaluating the best options for the next steps of development of the product, ready to enter the planned Phase 2 clinical trial in autoimmune diseases or transplantation, including worldwide partnership opportunities.

When the Company conducts research products and markets its product as part of collaboration agreements, some key tasks or functions are under the responsibility of its partners. Consequently, the Company runs the risk that they will not perform as expected. In addition, the decisions may be under the control of its partners, or subject to their approval. The Company and its partners may also have diverging views on certain matters. Failures in the development process or disagreements in terms of priority could arise and harm the activities conducted under these collaboration agreements. The Company could also encounter conflicts or possible difficulties with its partners during the term of the agreements or when they are renewed or renegotiated. The relationships with its partners could also experience ups and downs.

In addition, if a current or future partner encounters difficulty obtaining its own laboratory products necessary to develop and manufacture its own products or difficulty obtaining the licenses required to this effect (for example for the BI 754091 checkpoint inhibitor from Boehringer Ingelheim), there could be a delay, suspension, or re-orientation of the partnership that could significantly impact the business, prospects, the financial position, the results and the growth of OSE Immunotherapeutics.

All these events could impact the development, the launch and/or the marketing of some of its products or its candidate products and could cause a decline in its revenue and adversely impact its operating income.

In addition, the Company faces standard commercial risks inherent in the biopharmaceutical industry, including, without limitation:

- Competition resulting from existing therapies and/or new drugs;
- Size of the market of the indications of the leading product;
- Pricing of the products and reimbursement policies;
- Interests of partners and potential investors;
- Development time for new clinical trials;
- Protection afforded by patents and the capacity to prevent counterfeits.

More broadly, the Company could fail to adequately estimate the scientific and medical results of the development operations at the time it enters into a partnership agreement, and therefore the compensation linked to these partnerships, or not have the resources or access to all the necessary information to fully assess them, in particular concerning the potential of research and development portfolios, the difficulties linked to production, questions of compliance, and monitoring the outcome of ongoing disputes.

### **3.2.1.2 Consortium agreements**

In order to obtain financial support and public-private scientific collaboration to develop its research programs, the Company seeks to take part in collaborative programs in consortium agreements. As of the date of this Universal Registration Document, several programs have been developed as part of French consortium agreements.

- **OSE-127/S95011** in the EFFIMab consortium, a preclinical and clinical program of €20 million aiming to establish the clinical proof of concept of the product in ulcerative colitis, an autoimmune disease of the colon. EFFIMab is financed in part by the public investment bank Bpifrance in the Industrial-Strategic-Innovation (ISI) program. The consortium is composed of several private and public partners. The failure of one of the partners without possible alternative in spite of the best efforts of the other partners could lead to the failure of the program overall.

In January 2021, new funding of €1.3 million was triggered by the completion of several key milestones of the OSE-127 / S95011 product including the strengthening of preclinical and translational data in the indication ulcerative colitis (UC), the completion of the phase 1 clinical study, the first regulatory authorization for a phase 2 clinical study in UC and specific steps in the manufacturing of the product.

- **BI 765063 (OSE-172)** in the EFFI-CLIN consortium (July 2017), a program with funding of €9.2 million, whose aim is to study the tolerability and clinical efficacy of BI 765063 (OSE-172), a new immunotherapy for cancer that will be evaluated as a monotherapy or in combination in various indications where the presence of myeloid cells is a poor prognostic factor. This collaborative project is financed by the French General Investment Commission (CGI) and managed by Bpifrance. The consortium is composed of private and public partners.
- **OSE-703** obtained funding of €386,000 (December 2017) as part of a call for projects of the French Single Interministry Fund (FUI) - Regions, dedicated to financing projects from competitiveness centers, to identify new monoclonal antibodies and new therapeutic targets in a collaborative program to develop an innovative test enabling the exploration and measurement of the cytotoxicity of monoclonal antibodies. This research project, called HybridADCC, with a total cost of €2.4 million, is financed by the FUI at €1.2 million and was labeled by the Atlanpole Biotherapies center.
- **Immunomonitor** (Treatment Response Monitoring for Cancer Immunotherapies Using Immune Repertoire Analysis), a research project with €435,000 in funding from Bpifrance (July 2018) as part of a European call for projects, Eurostars was conducted in a European consortium with five partners. The objective of this collaborative project is to clinically validate a platform for analysis of immune repertoire sequencing data (TCR, T receptor), of patients treated with Tedopi® immunotherapy.
- **CoVepiT:** €5.2 million was granted to the Company in December 2020 as part of the PSPC-COVID call for projects, operated on behalf of the French State by Bpifrance as part of the Future Investments Program (PIA). Funding from the French State, totaling €5.8 million for the entire consortium, including €5.2 million for OSE Immunotherapeutics to support the CoVepiT 1 study, the production of a clinical batch according to Good Manufacturing Practices and the planned clinical Phase 1/2 which will assess the safety and immunogenicity of CoVepiT in high-risk patients.

As part of the consortium agreements, the failure of one of the partners without possible alternative in spite of the best efforts of the other partners could lead to the failure of the program overall.

The Company might not be able to find partners or not find good partners to develop its products. If it finds these partners, they could decide to withdraw from the agreements. The Company might also not be successful in entering into new agreements on its other drugs. In addition, its current and future collaboration and licensing agreements might not bear fruit.

If the Company is unable to maintain its existing collaboration and licensing agreements or enter into new agreements, it may need to study alternative development conditions, including the complete abandonment or sale of some programs, which could hinder, even limit its growth.

The Company might not be able to control either the amount or the schedule of the resources that its existing or future partners will dedicate to the development, manufacturing, and marketing of its products. These partners may not meet their obligations as anticipated by the Company. This is why it could face significant delays or not be successful in introducing its products on certain markets.

Moreover, in the current COVID-19 health crisis, of the appearance of another contagious disease or another virus strain leading to an equivalent situation (quarantine, total or partial paralysis of the economy and/or hospital system in any form whatsoever), the business activity of the partners could be seriously disrupted, which would prevent them from using all or a large part of their essential infrastructures, jeopardize their desire to continue the agreements reached with the Company, suspend developments or co-developments, redirect or limit the resources allocated to clinical trials to other research

programs or delay the progress of clinical trials that they must provide in order for the Company to receive the milestone payments and royalties.

Moreover, even though it seeks to include non-compete clauses in its collaboration and licensing agreements, these restrictions might not be able to offer adequate protection to the Company. Its partners could decide to pursue alternative competing technologies with others.

To successfully complete certain tasks in product development, the Company relies on a network of scientific experts intervening as outside consultants, including researchers attached to academic institutions. To build and maintain such a network in acceptable conditions, the Company faces intense competition. These external advisers can end their commitments at any time. The Company has only limited control over their activities. Most of these scientific advisers, however, are also shareholders of the Company, or benefit from equity incentives in the form of share subscription warrants (BSAs), founders' warrants (BSPCEs) or consulting agreements, thereby enhancing their interest in the success of the Company. On the other hand, the Company considers that its development programs in the cancer immunotherapy segment, its experience in transplantation, autoimmune diseases, its product optimization platforms, its experience, and the professional network of its management are the means of attracting and retaining high quality scientific partners.

The occurrence of one or more of these risks could have a material adverse impact on the business, prospects, financial position, results, and development of the Company. In order to limit the risks linked to current and future partnerships, partnership strategies, strategies for growth and acquisition of new candidates are maintained.

### **3.2.1.3 Initial partnerships**

#### **Risks linked to the off-balance sheet commitments generated by the acquisition of rights with Takeda for Memopi® and the INSERM for FR104 and MD707**

As part of the initial transaction for the acquisition of the Tedopi® (Memopi® technology) assets from the pharmaceutical company Takeda, the Company made a commitment to pay an earn-out at the time its product was registered, then no more than single-digit royalties on future sales (see Section 20 – Major Agreements).

In addition, OSE Immunotherapeutics researchers are working in close collaboration with INSERM researchers. Sometimes, the result of their work leads to patents jointly owned by Effimune/OSE and INSERM, subject to operating agreements.

Two operating agreements have been established with the INSERM for research conducted in collaboration with patents filed as co-property on behalf of Effimune and the INSERM. These agreements grant worldwide operating rights on the patent licenses for each of the agreements:

In October 2011, an operating agreement was signed with the INSERM for the monoclonal antibody project from the MD707 clone targeting the Interleukin-7 alpha receptor. These joint research projects resulted in the filing of a jointly owned patent. This 2011 patent and the antibodies resulting from the patent were studied in various autoimmune disease models, but in view of the results, were not retained for final development. This 2011 patent was thus not used as part of the EFFIMab consortium for development of the OSE-127/S95011 product in autoimmune diseases.

In March 2013, an operating agreement was signed with the INSERM for the FR104 antibody including the filing of a jointly owned patent. For the FR104 product, the exercise of the license by Janssen Biotech in July 2016 led to financial settlements with the INSERM.

Depending on the results and advances of different jointly owned products, diverging views and distributions could arise, leading to conflicts or possible difficulties with these entities during the term of its agreements or when they are renewed or renegotiated. The relationships with these entities could also experience ups and downs. More broadly, the Company could fail to adequately estimate the scientific and medical results of the development operations at the time it enters into an operating agreement, and therefore the compensation linked to these agreements, or not have the resources or the access to all the necessary information to fully assess them, in particular concerning the potential of the research and development portfolios, the difficulties linked to production, questions of compliance, and monitoring the outcome of ongoing disputes.

### **3.2.2 Risks linked to potential conflicts could affect the Company's relationship with its licensees**

The Company's strategy for some of its development products, in particular OSE-127/S95011 (2 step license option agreement with Servier) and BI 765063 (OSE-172) (collaboration and licensing agreement with Boehringer Ingelheim International) is to license these latter to pharmaceutical laboratories. The signing of licensing agreements and their outcomes is thus important for the Company.

Conflicts could arise, moreover, between licensees during execution of agreements binding on the Company, that could affect their continuation and consequently the manufacturing or marketing of the products developed by the Company. These could be conflicts concerning the conditions of the signing of the agreements or their proper execution, by either of the parties, of their obligations pursuant to those agreements. For example, some agreements entered into with licensees typically contain clauses on which a party will pay costs and fees, and such clauses could be subject to interpretation or dispute, thereby endangering the profits that the Company could expect from that partnership. Such conflicts could materially impact the business, the financial position, the results, the development, and the prospects of the Company.

### **3.3 Risks linked to marketing**

#### **3.3.1 Risks linked to obtaining a Marketing Authorization (MA)**

To obtain a marketing authorization for one or more of its products, the Company, or its partners, must demonstrate to the regulatory authorities their pharmaceutical quality, their safety of use, and their efficacy for the targeted indications.

The Company's ability to obtain a marketing authorization for its products depends on several factors, in particular:

- The possibility of continuing development of its products (manufacturing of lots and tests), and firstly for the drug Tedopi®, that validated the step-1 of its Phase 3 trial, the last clinical study phase before registration;
- The fact that the Company or its partners are able to carry out clinical trials, in the designated time frames with the initially planned human, technical, and financial resources;
- The fact that its products have already been approved or not for another indication that has already received a marketing authorization; and
- The fact that its competitors have not announced clinical results likely to change the evaluation criteria used by the regulatory authorities.

If the Company does not obtain any marketing authorization, it will not be able to market its products. In addition, its products might not obtain marketing authorization for a given geographical region, which could significantly limit the marketing of the product in question.

The occurrence of one or more of these risks could have a material adverse impact on the business, prospects, financial position, results, and development of the Company.

#### **3.3.2 Risks linked to the lack of commercial success of the products**

##### **3.3.2.1 Risks linked to market penetration difficulties**

If the Company is able to obtain a marketing authorization or find developing commercial partners allowing it to market its products in the future, it would need time to obtain the support of the medical community, healthcare providers, and third-party payers. The degree of market acceptance depends on several factors, in particular:

- Healthcare providers' perception of the product's therapeutic benefit;
- Clinical developments made after the marketing authorization;
- Occurrence of unwanted impacts after obtaining marketing authorization;
- Existence of alternative therapeutic options;

- Ease of the product's use, especially the method of administration;
- Cost of treatment;
- Reimbursement policies of governments and other third parties;
- Effective implementation of a scientific publication strategy; and
- Support of recognized experts;

Poor market penetration resulting from one of these factors could have a material adverse effect on the business, prospects, financial position, results, and development of the Company.

This risk will only be present, however, when the Company's products are registered and marketed or are close to being marketed.

### **3.3.2.2 Risks linked to the competitive environment and technological changes**

The pharmaceutical market is characterized by rapidly evolving technologies, the predominance of products protected by intellectual property rights, and intense competition. Numerous entities, including pharmaceutical laboratories, biotechnology companies, academic institutions and other research organizations, are actively engaged in the discovery, research, development, and marketing of drugs, including immunotherapy and other products to treat cancer and autoimmune diseases (see paragraph 6.2.2, Targeted pathologies and immuno-oncology treatments) Should the Company obtain marketing authorization for one of its immunotherapy products, it would compete against a number of established therapies. This product could also compete with a certain number of innovative therapies being developed or recently introduced on the market, such as targeted therapies, monoclonal antibodies, cell therapy, gene therapy, and checkpoint inhibitors.

FR104, OSE-127/S95011 and BI 765063 (OSE-172) are first-in-class drugs, that currently do not have an equivalent on the market. Other companies, in particular, large pharmaceutical laboratories, are also developing first-in-class drugs, some of which target the immune system in a similar manner and thus have the potential to compete with the Company in the targeted markets.

Many of the Company's competitors that are actively developing anti-cancer therapies have much greater resources and experience in management, research, patient access in clinical trials, manufacturing, and marketing than those of the Company. In particular, the big pharmaceutical laboratories have significantly more experience than the Company in conducting clinical trials and obtaining regulatory authorizations. Smaller or early-stage companies, especially in immunotherapy, could also be significant competitors. These companies are also likely to compete with the Company to acquire rights to promising products and other complementary technologies.

The Tedopi® product, via neo-epitopes selected and optimized from five tumor antigens, targets other cancers expressing the same tumor antigens that can benefit from this T specific immunotherapy product. Tedopi® thus will not necessarily hinder other existing techniques or those in development by other players in the pharmaceutical industry (such as checkpoint inhibitors), but in some cases, could be used in relevant therapeutic combinations in this innovative domain of immunotherapy.

Finally, the Company cannot guarantee that its products will:

- Obtain the necessary licenses or receive marketing authorization more rapidly than its competitors;
- Remain competitive with other products developed by its competitors that could be safer, effective, or less costly;
- Remain competitive faced with the products of its competitors who are more effective in their production and their marketing;
- Be a commercial success; or
- Not be rendered obsolete or unprofitable by technological progress or other therapies developed by competitors.

Such events could have a material adverse impact on the Company's business, prospects, financial position, results, and development.

The Company believes that the competition risk is relatively high for its business, in particular taking into account the size of some of its potential competitors. The competitive issue is integrated in the Company's development choices, and why it is closely monitoring the development of competing drugs. The fact for example that oncology treatments can be combined with others (checkpoint inhibitors, combinations of checkpoints inhibitors, chemotherapy, targeted therapies,

immunotherapies acting on different targets or different cell types) helps limit the risk of competition because the development of one drug does not necessarily make another drug less interesting.

### **3.3.3 Risks linked to changes in drug reimbursement policies**

Once marketed, market acceptance of the Company's products will depend, in part, on the reimbursement rates offered by the public health insurance funds and private insurance companies. The primary health insurance funds and other third-party payers will seek to limit the cost of care by restricting or refusing to cover reimbursement of costly products and treatment protocols. This risk is actually greater in Europe due to the budget crisis in certain countries and more generally due to weak economic growth.

The Company's ability to successfully market its products will depend in part on obtaining adequate reimbursement rates for its drugs and related therapies from the public authorities, private insurers and other organizations in Europe and the United States. The third-party payers more and more frequently question the prices of therapeutic products and medical services. Cost control measures implemented by healthcare service providers and reimbursement organizations and the effect of any healthcare system reforms could adversely impact the Company's operating income. It might therefore not obtain satisfactory reimbursement rates for its products, which could harm their market acceptance, in which case the Company would be unable to receive an adequate return on its investments.

The occurrence of one or more of these risks could have a material adverse impact on the business, prospects, financial position, results, and development of the Company.

## **3.4 Risks linked to intellectual property rights**

### **3.4.1 Risks linked to uncertain protection of patents and other intellectual property rights**

OSE Immunotherapeutics holds, directly and indirectly through its wholly owned subsidiary OSE Pharma International, the worldwide rights on its anti-cancer T-specific immunotherapy technology.

The Company obtained orphan drug status for Tedopi® in the United States in 2013 for so-called "non-small cell" lung cancer in patients positive for the HLA-A2 marker. This technology directed against five tumor antigens benefits from extended protection under United States orphan drug status that gives seven years of additional protection after the marketing authorization. As the tumor antigens that it covers are present in other cancers, the clinical applications of the Company's technology allow different developments in these types of cancer or according to different combinations with other products.

The Company directly holds intellectual property rights over five patent families concerning FR104, two patent families for OSE-127/S95011, five patent families for BI 765063 (OSE-172), and three patent families for OSE-703. These latter are presented in paragraph 5.5 of this Universal Registration Document.

The ability to protect oneself in a patent lawsuit represents a significant risk, in cases in which the intellectual property is not adequately protected or if the products harm the intellectual property rights of a competitor. The Company will therefore strive to file all patent applications necessary to best protect the products and technologies that it develops. In addition, it will ensure that it maintains very strict confidentiality standards and enforce application of confidentiality agreements among its employees and all collaborating parties to protect the secrets inherent in its business.

It is important for the success of the Company's business, that the Company and its licensees and licensors are able to obtain, maintain and enforce its patents and its intellectual property rights in Europe, United States and other countries. It cannot be ruled out that:

- The patents granted or licensed to its partners or itself could be challenged, or held invalid, or be unenforceable by the Company;
- The extent of any patent protection may be inadequate to protect the Company from its competitors; or
- Third parties could claim rights on patents or other intellectual property rights owned by the Company.

The grant of a patent does not guarantee its validity or enforceability and third parties could challenge these two aspects. The grant and enforceability of a biotechnology patent are highly uncertain and raise complex legal and scientific issues. So far, no uniform worldwide policy has emerged in terms of the content of patents granted in the area of biotechnology and the scope of allowable claims. Litigation may be necessary to enforce the Company's intellectual property rights, protect its trade secrets or determine the validity and scope of its intellectual property rights. Any litigation could result in considerable expenses, reduce its profits and fail to offer it adequate protection. Its competitors could successfully dispute patents granted or licensed to the Company in court or other proceedings, which could ultimately reduce the scope of its patents. In addition, these patents could be successfully counterfeited or infringed due to innovations.

In addition, some countries could try to grant mandatory licenses to third parties on patents protecting the originator products, which would limit the value of the patent protection given to these products.

The occurrence of any of these events concerning one of its patents or intellectual property rights could have a material adverse effect on its business, prospects, financial position, results, and development. These risks are even greater for the Company in view of its limited financing and human resources capacities. In order to mitigate this risk, the process for managing patents and the Company's rights was created and organized.

### **3.4.2 Risks linked to legal liability, in particular product liability risks**

The Company is exposed to potential liability, including product liability, intrinsic to conducting clinical trials, manufacturing and marketing therapeutic products in humans. It could also be held liable in connection with clinical trials, including the preparation of therapeutic products tested and unexpected side effects resulting from the administration of these products. Claims or legal proceedings could be filed or brought against the Company by patients, regulatory agencies, pharmaceutical companies, or other third parties using or selling its products. These legal proceedings could include claims arising from the actions of its partners, licensees, and subcontractors, over whom the Company exercises little or no control. The Company cannot ensure that its current insurance coverage is adequate to protect it against lawsuits that could arise or in response to an exceptional or unexpected situation. If the Company, its partners, licensees, and subcontractors are found liable in a legal proceeding and are unable to obtain and maintain appropriate insurance coverage at an acceptable price, or to protect themselves by whatever means against product liability claims, it could seriously affect the marketing of its products and more generally harm its business, prospects, financial position, results, and development. The Company could also be subject to civil or criminal proceedings and its image would be harmed. To limit this risk, the Company has subscribed to the insurance policies detailed in the section and will obtain additional insurance coverage as necessary as its products are developed.

The Company's activity is subject to a more and more restrictive regulatory framework. This regulatory framework itself could be impacted due to measures taken with respect to the COVID-19 epidemic or any equivalent epidemic, that could require the Company to modify its clinical trial procedures, delay the necessary interactions with the local authorities, ethics committees, or other important agencies and third-party co-contractors or change the criteria used by health authorities to accept the data from clinical trials conducted in these affected geographical regions.

The pharmaceutical industry worldwide faces constant changes in its legal and regulatory environment and increased monitoring by authorities and the public that require ever more guarantees on the safety and efficacy of drugs or the conduct of its business. In addition, incentives for research are reduced.

The health authorities and, in particular, the United States Food and Drug Administration (FDA), have imposed heavier and heavier requirements concerning the amount of data needed to demonstrate product efficacy and safety. These conditions have reduced the number of products authorized. The products marketed, moreover, are subject to regular re-evaluation of the benefit/risk ratio following their authorization. Late discovery of issues not identified at the research stage can lead to restrictions on marketing, product suspension, or withdrawal as well as the risk of legal proceedings.

To the extent that new regulations could lead to additional constraints on the conduct of business and increase the cost of obtaining and maintaining the marketing authorizations of products or limit the economic value of new products for the inventors, the prospects for growth of the pharmaceutical and medical industry and of the Company could be reduced.

In addition, all clinical studies must receive prior approval by the health authorities and ethics committees in the countries in which the studies will be conducted; a negative opinion could hinder or stop the Company's clinical development program. Likewise, in conducting its studies, the Company monitors data and safety, and it could decide to end a study early, definitively or not, and discontinue the development of certain products.

In addition, health authorities could decide to suspend or terminate prematurely an ongoing clinical trial depending on the information that it receives during a study, in particular on the occurrence of serious adverse events.

The occurrence of one or more of these risks could have a material adverse impact on the business, prospects, financial position, results, and development of the Company.

### **3.4.3 Risks linked to patents and intellectual property rights held by third parties**

The expansion of the biotechnology industry and the growing number of patents granted increase the risk that third parties could maintain that their own intellectual property rights are infringed by the Company's products or technologies. In general, patent applications are only published 18 months after the date of priority applications. In the United States, some patent applications are not published prior to the grant of the patent itself. Also, in the United States, patents can be granted on the basis of their invention date, under the "first-to-invent, first-to-file" rule, which does not always result in a patent being granted to the party who first filed the application. Discoveries are sometimes published or patented months or even years later. The Company cannot be sure that third parties were not the first to invent products or file patent applications on inventions also covered by its pending patent applications or those of its partners. In such instances, the Company may need to obtain licenses from those third parties holding the patents (licenses which may not be obtained under reasonable terms, if at all), or cease production and sale of certain products or develop alternative technologies.

Any litigation or claim against the Company, regardless of its outcome, could result in substantial costs and could compromise its reputation. Some of its competitors with greater resources may be better able to bear the costs of complex legal proceedings. Any litigation of this type could severely impact the Company's ability to continue its activities. Specifically, intellectual property litigation could force the Company to:

- Cease selling or using any of its products that are part of the disputed intellectual property, which would reduce its revenue;
- Obtain a license from the holder of the intellectual property rights, which may not be obtainable in reasonable terms, if at all.

Active monitoring of intellectual property matters helps limit this risk.

## **3.5 Risks linked to capital requirements**

### **3.5.1 Risks linked to uncertain additional funding**

The Company has the cash needed to continue its activities in the twelve months following the publication of the financial statements for the fiscal year ended on December 31, 2020 (29,368 K€ at December 31, 2020), enabling it to finance the continuation of its clinical and preclinical programs (Tedopi®; CoVepiT, whose development is supported by financing obtained as part of the PSPC-COVID call for projects, operated on behalf of the French State by Bpifrance under its Investments for the Future Program; OSE-279, whose development will be supported by the first tranche of the loan granted by the European Investment Bank in early 2021; OSE-230; CLEC-1; FR104; OSE-127/S95011 whose development is partially funded up to Phase 2 under the licensing and license option agreement with Servier and the EFFIMAB consortium; BI 765063

(OSE-172), whose development is funded under the collaboration and license agreement with Boehringer Ingelheim (April 2018) and the EFFI-CLIN consortium supporting several development stages and a clinical program planned up to Phase 2).

The financing as well as the repayment schedule for the loans and repayable advances available to the Company are detailed in note 5 to the consolidated financial statements.

Beyond its products in preclinical or clinical phase, the Company considers that, in view of its activity, in the future it might need to obtain new sources of funding for its clinical trials and long-term growth, in particular through possible agreements including milestone payments related to its development programs that could be licensed to partners, the signing of industrial and commercial partnerships and any new capital increases.

The potential payments to be received include €5 million from Servier upon enrolment of the first patient in the Phase 2 study in the Sjögren syndrome and the first €10 million tranche from the European Investment Bank which will result in the publication of a prospectus.

As of the date of this Universal Registration Document, none of Company's products have been marketed and thus have not generated any sales revenue. The Company's ability to generate profit will come from its ability to quickly obtain international marketing authorizations, in order to successfully market its products alone or in partnerships.

The Company foresees the following revenue sources for the next four years:

- Exercise of options
- Revenue linked to achieving milestones
- Payments made by future partners under certain agreements
- Public grants and reimbursements of research tax credits

The Company cannot guarantee that it will generate revenue from the sale of products enabling it to become profitable in the near future. The interruption of one of these sources of revenue, or a worldwide health crisis, could have a material adverse impact on its business, prospects, financial position, results, and development. This would have a significant impact on the business, results, financial position, and development of the Company.

In order to face this, the Company could sign partnership agreements more upstream according to the development, results, and prospects of its various projects. These partnerships would allow the Company to generate additional revenue to finalize its preclinical and clinical trials or lead to redefining the allocation of its financing needs depending on the potential of the products in clinical development.

OSE Immunotherapeutics could also call on investors and the market according to its development needs and depending on favorable economic circumstances. It could also receive public aid as part of consortia for business innovation, for example the EFFIMab consortium for the OSE-127/S95011 program, the EFFI-CLIN consortium for the BI 765063 (OSE-172) program, or the HybridADCC financing program for the OSE-703 program.

Future capital needs will depend on many factors that are largely beyond the control of the Company, for example:

- Higher costs and slower progress than expected for its research and development programs.
- Higher costs and longer delays than expected in obtaining regulatory approvals, including the time to prepare submissions to regulatory agencies.
- Costs for preparing, filing, defending, and maintaining its patents and other intellectual property rights.
- Costs for responding to technological and market developments, establishing and maintaining collaboration agreements, and ensuring the efficient manufacturing and marketing of its products.
- Additional costs for marketing its own products, should the Company decide to undertake this marketing itself; and
- New opportunities for developing promising new products or opportunities to acquire technologies, products, or companies.

The Company cannot guarantee that additional funds will be available to it when it will need them and, as the case may be, that the funds will be available in acceptable conditions. If the necessary funds are not available, the Company could find it necessary to:

- Delay, reduce, or even eliminate development programs.
- Obtain funding through partnership agreements that might require it to give up rights to technologies or products, that it would have continued holding under different circumstances.

- Acquire licenses or enter into new collaboration agreements that could be less attractive to it than those it would have been able to obtain under different circumstances, or
- Consider selling assets, or even merging with another company.

The Company's ease in securing additional funding depends to great extent on its past, present and future financial position. In this regard, since its founding until 2017, the Company has mostly experienced operating losses.

As of December 31, 2020, the Company had operational losses of €19 million, and it anticipates potential operational losses in upcoming years, in connection with its development activities, and in particular due to its ongoing investments in drug development (manufacturing of batches and conducting clinical trials).

In addition, to the extent that the Company could raise capital by issuing new shares or other financial instruments that could later become convertible to capital of the Company, the investors' investment could be diluted.

In this respect, the Company carried out a capital increase on November 18, 2020, with cancellation of preferential subscription rights through a private placement with 25 qualified French and international investors, a large majority of which were new shareholders, and by the accelerated construction of an order book, for €18.6 million. Thanks to this fundraising, the Company strengthened its financial visibility until the first quarter of 2022. The total amount of this capital increase corresponds to the issuance of 2,517,589 new ordinary shares at a subscription price of €7.40 per new common share (issue premium included), i.e. a dilution rate of 16.3% of the share capital before the transaction on an undiluted basis and 14.0% after the transaction. The subscription price for the New Shares was set at €7.40, i.e. a discount of 18.7% to the last closing price (as of Friday, November 13, 2020)<sup>1</sup>.

The Company does not rule out new fundraising from qualified investors or more broadly from the market, depending on market opportunities.

Debt financing, to the extent it is available, could also include restrictive conditions.

For example, on February 15, 2021, the Company signed a financing agreement with the European Investment Bank for a maximum amount of €25 million. The first tranche of €10 million, not subject to conditions and for which OSE Immunotherapeutics will request payment before the end of May 2021, will enable the expansion of the clinical development of Tedopi® to new cancer indications by evaluating it in combination with a checkpoint inhibitor. The loan agreement also contains an agreement to issue share subscription warrants to EIB for the first two tranches of the financing, in particular the issue of 850,000 share subscription warrants with respect to the drawdown of the first tranche, which will have a dilutive effect for shareholders.

The occurrence of one or more of these risks could have a material adverse impact on the business, prospects, financial position, results, and development of the Company, as well as the position of shareholders.

The Company includes financing risk in its management issues. The signing of partnerships that includes upfront payments, payments during product development, and royalties on sales, aims to decrease, with time, the financing risk and the need to use capital financing. The Company, however, considers that its exposure to the economic and market environment remains substantial.

The Company conducted a specific review of its liquidity risk and taking into account the capital increase of November 2020, the new public aid received and the loan of the BEI, OSE Immunotherapeutics considers that its available cash, as of the recording date of this Universal Registration Document, allows it to finance its current operating expenses in the upcoming 12 months.

Available cash at February 28, 2021, is €20.7 million and does not take into account the 2020 research tax credit receivable of €5.1 million and the first €10 million tranche to be received from the BEI.

The Company, moreover, has estimated the impact of the COVID-19 crisis on its cash position. Even though certain milestones could be shifted by several months following the slowing of clinical trials, the expenses should also be delayed.

Thus, the Company believes that its current cash position should enable it to finance both ongoing and future clinical trials, in particular to continue clinical and preclinical development related to Tedopi®, CoVepiT, BI 765063 (OSE-172), CLEC-1, OSE-

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1. <sup>1</sup> The subscription price of €7.40 per New Ordinary Share represents a discount of 19.9% compared to the volume -weighted average of the Company's share prices for the last three (3) trading sessions preceding the setting of the issue price, i.e., on 11, 12 and 13 November 2020.

279, OSE-127/S95011, FR104, OSE-230 and ongoing R&D over the 12 months following the filing date of this Universal Registration Document.

The Company intends, moreover, to take advantage of existing public aids in the form of research tax credits or from the EFFIMab and EIFFI-CLIN consortia. Concerning the EFFIMab program, the fifth milestone occurred in 2020, and the report was submitted during the 3<sup>rd</sup> quarter of 2020, which triggered a €1,326,000 payment by Bpifrance in January 2021. An agreement was signed with the BPI to finance the development of our Covipit vaccine in December 2020 which should, on the achievement of certain criteria, trigger payments totaling €5.2 million during 2021.

Although the Company for the first time recently substantially used a bank loan (EIB financing of €25 million, the first tranche of which will be drawn by the end of May 2021), it intends to finance itself mainly by issuing new shares until its profitability allows debt financing, unless grants and subsidies put in place by the French Government and available through banks are available and attractive in terms of cost. In this regard, it should be noted that the Company benefited from three loans totaling €7 million in May 2020 under the French Government-Guaranteed loan program.

Under these conditions, as a result of the EIB loan, the Company is exposed to liquidity risks in the event of the occurrence of a usual event of default in such a matter, leading to the early repayment of this bank loan and interest.

To cover the financing that the Company might need in order to accelerate the clinical development of its products or develop new products, the Combined General Shareholders' Meeting of June 17, 2020, delegated powers to the Board of Directors to carry out primary or secondary fundraising transactions.

The Company could call upon various sources of financing, either from investors in a transaction on financial markets, through public aid, or through new industrial agreements on the portfolio products. This additional source of financing would be used to finance the Company's growth, new projects, or new indications for its current products.

### **3.5.2 Risks linked to the availability of public grants and research tax credits**

Since it was founded, the Company has received public funding for research expenses (see Note 5 to the 2020 financial statements), to finance its activities. OSE Pharma, that became OSE Immunotherapeutics, received a research tax credit of €675,000 for 2015, €2,645,000 for 2016, and €2,940,000 for 2017, €4,487,000 for 2018, €3,059,000 for fiscal year 2019 and should receive €5,120,000 for fiscal year 2020.

The research tax credit is one source of funding. The Company has no assurance that it will have access to this source of funding, or that the funding will be maintained in the future. This source of funding could in fact be threatened by regulatory changes or by an audit by tax authorities that could lead to a reduction in the amount received or to be received even if the Company meets the requirements for documentation and eligibility of expenses. Taking into account the advanced status of the Company's development programs, and the limited portion that this aid represents and will represent, compared with the overall budget of the Company, this risk is limited.

### **3.5.3 Valuation of intangible assets and impairment tests**

The Company OSE Immunotherapeutics, following the merger of OSE Pharma with Effimune, recognized intangible assets in its statement of financial position. In the Company's upcoming accounting statements, adverse changes in its activities, business forecasts, and discounted cash flow assumptions could result in the recognition of impairment losses that could have significant impacts on the results of OSE Immunotherapeutics. These tests will be conducted when events or circumstances indicate that a reduction in value is likely to have occurred and at least once per year.

These tests were performed at the close of the 2020 fiscal year and did not result in any recognition of impairment.

### 3.6 Insurance and risk coverage

The Company believes that its internal procedures governing risk prevention and safeguarding, as well as the insurance policies it holds, are adequate to cover the main insurable risks that it has identified.

The Company has implemented a coverage policy for the principal insurable risks with coverage amounts that it considers compatible with its cash flow requirements. The total premiums paid for all insurance policies amounted to €45,000 during fiscal year 2020.

Taking into account the specificity of its activities - concentrated on development at this stage - and on the innovative character of its approach, the quantification of any risks in the absence of a direct damage rate, or damage indicators in its sector of activity, makes it difficult to determine a coverage amount, in particular for civil liability. The Company, however, believes that the insurance policies mentioned below adequately cover the risks inherent in its activities and its insurance policy is consistent with the practices in its sector of business. The Company does not foresee any particular difficulties in keeping adequate levels of insurance in the future limited by the conditions and capacities of the market. The insurance policies are held with insurance companies that have good financial ratings and were chosen for their ability to contribute to the growth of the Company. OSE Immunotherapeutics deems that its insurance coverage and the limitations of its coverage are reasonable and prudent taking into account its activities and the associated risks.

The Company has subscribed to several insurance policies, including the following:

- A "business and professional civil liability" insurance policy with CNA (€4,000 paid in 2020).
- A "managers' liability" policy with AIG that covers the civil liability of the legal and factual executive corporate executives of the Company and its subsidiary, when such liability is incurred in the execution of their duties (€11,000 paid in 2020).
- A "professional multi-risk" policy for its premises, with Generali (€3,400 paid in 2020).
- In view of its investments made in laboratory equipment during 2018, 2019 and 2020, the Company now has a specific insurance policy covering this equipment (€4,500 paid in 2020)
- Taking into account the progress of the development of its product Tedopi®, the Company has subscribed to specific insurance coverage for clinical trials with I4CT, to cover the liability of OSE Immunotherapeutics with respect to patients in the countries involved.
- The Company has also subscribed to insurance policies for the Phase 1 trials of OSE-127/S95011 (€7,000 recognized for 2020) and BI 765063 (OSE-172) (€6,000 recognized for 2020) and €8,600 for the Phase 3 trial of Tedopi®.

The rates and coverage amounts depend on local regulations applicable to the clinical investigation centers concerned, such as in France, where the Public Health Code specifies an insurance obligation for clinical trial sponsors as well as the conditions of that insurance.

These agreements do not provide coverage against operating losses. The Company deems that the cost/benefit ratio of covering losses from operations in the event of an accident at its stage of development, particularly given the lack of revenue on sales of its products, does not justify subscribing to such coverage. The Company's liability in clinical trials will be covered by specific agreements, whose rates and coverage amounts depend on local regulations applicable to the clinical investigation centers concerned, such as in France, where the Public Health Code sets out an insurance obligation for clinical trial sponsors as well as the conditions of that insurance. The overall amount of insurance premiums paid, and coverages held for clinical trials depends therefore on the number of trials, their location, and the predicted number of patients included in the trial.

The Company has also subscribed to an insurance policy for the civil liability of its executive corporate managers when such liability is incurred in the exercise of their duties.

The Company cannot guarantee that it will always be able to maintain or obtain similar insurance coverage at an acceptable price, which could lead it to accept more costly insurance policies and assume a higher level of risk. This will be important as the Company's business activity grows. Moreover, the occurrence of one or more major accidents, even if covered by insurance, could seriously impact the Company's business and financial position due to the interruption of its activities, the time for repayment by the insurance companies, should policy coverage limits be exceeded and, finally, due to premium increases resulting from such an accident.

The occurrence of one or more of these risks could have a material adverse impact on the business, prospects, financial position, results, and development of the Company.

Taking into account the Company's prospects and, in particular, as it initiates a greater number of clinical trials, the Company anticipates that its insurance premium expenses will continue to rise while remaining relatively low compared with the costs of its research and development, its annual losses, and the value of its assets.

### **3.7 Exceptional events and litigation**

During the 2020 fiscal year and up to the registration date of this Universal Registration Document, the Company has not been involved in any administrative, criminal, legal, or arbitration procedure that could have a material adverse impact not reflected in the financial statements of the Company, on its activity, financial position, results, or development.

## 4 Information about the issuer

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### 4.1 Company name

The name of the Company is "OSE Immunotherapeutics" and its trade name is "OSE Immunotherapeutics".

### 4.2 Place of registration and registration number

The Company is listed in the Nantes Trade and Companies Register under ID number 479 457 715.

The Company's activity code is 7211Z. This corresponds to biotechnology research and development.

The Company's LEI is 969500HIUWVGY6NZSM05.

### 4.3 Date and term of incorporation

Initially formed as a limited liability company ("Société À Responsabilité Limitée") on November 17, 2004, it was converted into a public limited company ("Société Anonyme") with a Board of Directors by decision of the General Shareholders' Meeting of April 27, 2012.

The Company was formed for a period of 99 years from the date of its listing in the Trade and Companies Register, unless the term is extended or the Company is dissolved early.

The reporting date was set at December 31, every year from the Company's date of incorporation.

### 4.4 Registered office, legal form and legislation

The Company's registered office is at 22 boulevard Benoni Goullin, 44200 Nantes, France.

The Company is a public limited company (société anonyme) with a Board of Directors, governed by French law. It is governed by current and future legislation and regulations, in particular the French Commercial Code and amendments thereto, as well as by its bylaws.

Telephone: +33 (0)2 28 29 10 10

The Company website is: [www.ose-immuno.com](http://www.ose-immuno.com).

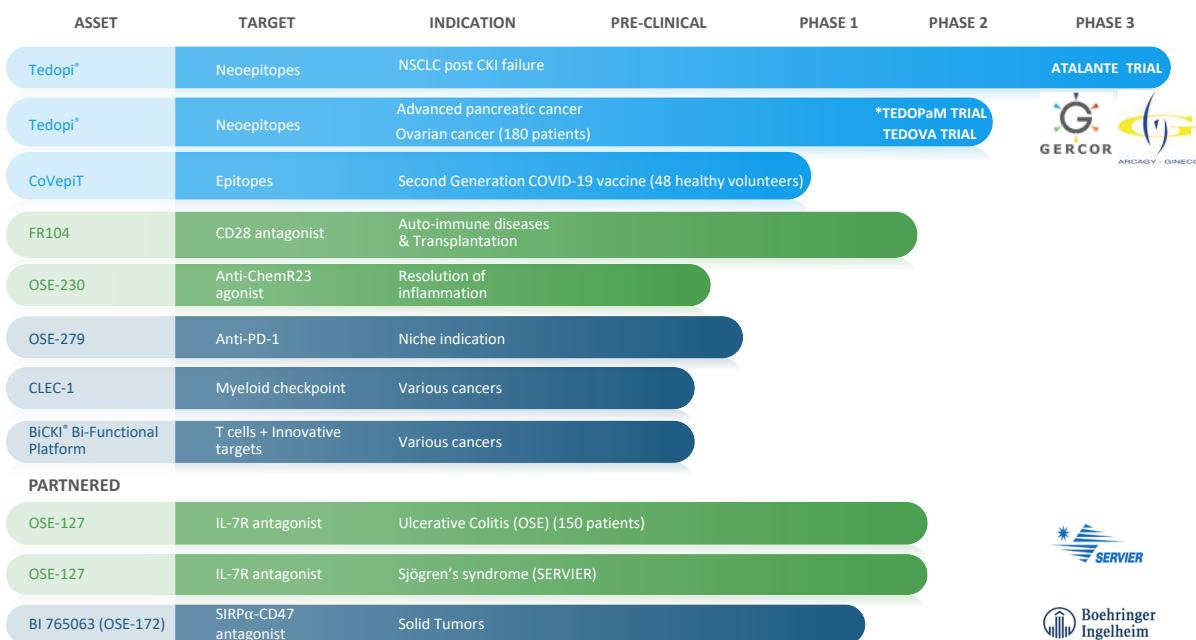
The reader's attention is drawn to the fact that, unless otherwise stated in this Universal Registration Document, the information appearing on this website does not form part of this document.

## 5 Business overview

### 5.1 Principal activities

OSE Immunotherapeutics is a biotechnology company focused on developing innovative immunotherapies, directly or through partnerships, to control and regulate the immune system for immuno-oncology and autoimmune diseases. The company's immunology research and development platform is focused on three areas: T-cell-based vaccination, Immuno-Oncology (focus on myeloid targets), Auto-immunity & Inflammation.

The OSE Immunotherapeutics clinical portfolio has a diversified risk profile, with development programs ranging from research to Phase 3 clinical trials with independent risks. Four products are in the clinical phase.



\* Due to the COVID-19 crisis, accrual of new patients in TEDOPaM should restart in 2021.

NB: To date, no product in the portfolio has been the subject for a Marketing Authorization application

### 5.1.1 T cell vaccines

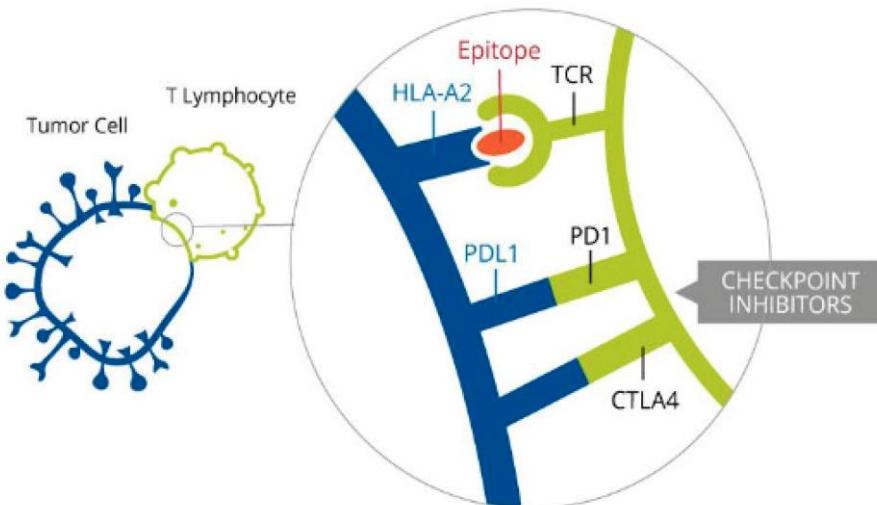
#### 5.1.1.1 Clinical development

##### TEDOPI®, therapeutic vaccine developed for non-small cell lung cancer

Tedopi® is a combination of 10 neopeptides (small peptides) selected and optimized from five tumor antigens present in several cancers that generate a specific cytotoxic T cell response directed against tumor cells that express at least one of those tumor antigens and an associated T helper response.

These five tumor antigens (CEA, p53, HER-2/neu, MAGE-2 and MAGE-3) were selected because their presence represents a poor prognostic factor in several types of cancers. Ninety percent of invasive tumors express at least one of these five tumor antigens. The 10 selected epitopes trigger a synergistic increased T lymphocyte response with no immunodominance (i.e., no preferential response to one or two epitopes). These strong cytotoxic T cell-specific responses cause the immune system to destroy tumor cells that express HLA-A2 and one of the targeted tumor antigens.

This product has been granted orphan status in the United States for lung cancer patients who are HLA-A2 positive, representing 45% of that population (under 200,000 people). This special status allows accelerated product development.



*Tedopi®: mechanism of action*

#### POSITIVE RESULTS FROM STEP-1 OF PHASE 3 CLINICAL TRIAL IN NON-SMALL CELL LUNG CANCER: THE MOST ADVANCED CLINICAL APPLICATION

The international Phase 3 clinical trial of Tedopi®, Atalante 1, was designed to evaluate the benefits of the product in HLA-A2 positive patients in second- or third-line therapy versus second- or third-line chemotherapy (docetaxel or pemetrexed) in invasive stage IIIB or metastatic stage IV non-small cell lung cancer after failure of treatment with anti-PD-1 and anti-PD-L1 checkpoint inhibitors. The main assessment endpoint is overall survival.

The post checkpoint inhibitor patient population, to which the Atalante 1 study is addressed, is currently growing, since anti-PD-1 and anti-PD-(L)1 T checkpoint inhibitors are recognized as standard treatment as maintenance (at an earlier stage of stage III disease), as first-line therapy for invasive stage IIIB and metastatic stage IV (instead of or in combination with chemotherapy) and as second-line treatment (after failure of first-line platinum-based therapy).

The positive step-1 results of the Phase 3 Atalante 1 trial were presented at the European Society for Medical Oncology (ESMO) virtual annual congress in September 2020.

These results showed a clearly improved overall survival time with Tedopi® compared to the standard treatment, the significant increase in survival after progression, the maintenance of a good ECOG\* score reflecting the change in general health of the patient, and confirmation of a good tolerability profile.

The primary endpoint, the overall survival rate at one year in the population in mITT \*\*, was achieved: overall survival rate at one year of 46% for patients treated with Tedopi® [95 % CI: 33 % -59 %], above the upper limit pursuant to the protocol (predefined futility limit H0 <25% = to be rejected; alternative hypothesis of predefined efficacy H1> 40% = considered clinically significant). This overall survival rate of 46% is 10% higher than that of standard chemotherapy of 36% [95% CI: 21% -54%].

- The overall survival rate at one year of 47.5% is confirmed in the modified protocol population \*\*\* (major deviations excluded), considered as the target population for this indication [95% CI: 34.3% -60.9%], compared to the standard treatment at 34.4% [95% CI: 18.6% - 53.2%].
- The median overall survival is longer in the ITT population: 9.8 months in the Tedopi® group versus 8.7 months in the standard treatment group, hazard ratio (HR): 0.71 [95% CI: 0.44 - 1.16]; p = 0.17.
- The difference in median overall survival was statistically significant in the target population per protocol at 11.1 months in the Tedopi® group versus 8.7 months in the standard treatment group, p = 0.037; HR: 0.57 [95% CI: 0.34 - 0.97].
- In the other main secondary endpoints, the disease control rate at 6 months and 12 months is comparable in the two treatment groups.
- The time to deterioration in ECOG status was significantly longer in the Tedopi® group (8.4 months versus 4.4 months; p = 0.002). Similarly, the survival time after progression was significantly longer in the Tedopi® group (7.5 months versus 4.4 months; p = 0.022).

- Good tolerability profile of Tedopi® with significantly fewer severe adverse effects attributable to the treatment (14% Tedopi® versus 43% standard treatment, p <0.001).

Overall, the benefit/risk ratio is favorable to Tedopi® and better than that of standard treatment in these patients previously treated with checkpoint inhibitors.

\* *The ECOG score is a performance scale used to assess the overall state of health of the patient. It is subdivided into 5 grades from 0 to 5, ranging from fully active (0) to completely disabled and then to death (5).*

\*\* *Multiple Intention-To-Treat (mITT) population: all evaluable randomized patients (survival data ≥ 12 months) who received at least one dose of the study treatment.*

\*\*\* *PP (Per Protocol) Population: ITT population without major deviations from the protocol, defined after a blind review by non-small cell lung cancer experts.*

These results confirm the value and therapeutic interest of Tedopi® in a population of patients suffering from advanced lung cancer after failure of a checkpoint inhibitor treatment for which there is no confirmed treatment to date, and which is awaiting new therapeutic options. The Company is continuing to collect additional clinical data and analyze all the results to identify and confirm a sub-group of patients of interest. At the same time, given that the positive Step-1 results significantly strengthened the value of Tedopi®, the Company is continuing to explore any potential partnering opportunities for the product.

In April 2020, due to the global epidemic of COVID-19, the Company, in conjunction with the Independent Data Monitoring Committee (IDMC) and the Trial Steering Committee, analyzed the potential impact of this epidemic on the Atalante 1 trial. The clinical trials data risked being strongly impacted by the worldwide COVID-19 pandemic and by the increased risk for patients with advanced lung cancer, as COVID-19 can cause serious pulmonary complications in this immunocompromised patient population. Moreover, for patient safety, several scientific and medical societies currently recommended the voluntary suspension of new patient recruiting in clinical trials in oncology.

The Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from health authorities, the Company will try to obtain a marketing authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.

Consequently, following the recommendation from both IDMC and Atalante 1 Steering Committee, OSE Immunotherapeutics voluntarily decided to terminate patient screening and recruitment in the Step-2 initially planned for the trial and therefore now cancelled.

Today, the Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from health authorities, the Company will try to obtain a marketing authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.

## PHASE 1/2 CLINICAL TRIALS

**TWO PHASE 1/2 CLINICAL TRIALS** were conducted in the United States in patients with mildly aggressive cancers expressing HLA-A2 positively. The objective was to measure the tolerability of the product administered via repeated subcutaneous injections (5mg/peptide/dose) with six injections spaced three weeks apart. The efficacy criterion for the treatment sought was to quantify and assess the specific cytotoxic T cell response induced with respect to natural epitopes and chemically modified optimized epitopes.

A positive cytotoxic T immune response was obtained in 93% of the patients in whom it was measured (16 patients who received six injections). Eight out of 15 patients responded to more than five epitopes, and on average, each patient induced a cytotoxic T cell response against four epitopes.

The effector activity of T lymphocytes from treated patients was also measured in their ability to destroy tumor cells presented to them if those tumor cells have the required receptors (ex vivo results). This T lymphocyte effector activity has been significantly established in human tumor cells that express HLA-A2 versus human tumors that do not express HLA-A2.

The tumors studied also express one of the tumor antigens targeted by the epitopes (fresh human tumor lines and reference human colon or breast tumor lines).

The results of these Phase 1/2 trials showed that the product was generally well tolerated by patients. In addition, the regimen and doses were validated in these trials. This regimen was subsequently used in the Phase 2 trial with an initial induction period during the first six injections (three weeks apart) followed by a period of consolidation of the response through a subcutaneous injection every two to three months. This mode of administration was also the one used in the Phase 3 trial in non-small cell lung cancer.

## PHASE 2 CLINICAL TRIAL

A Phase 2 clinical trial of Tedopi® was conducted in the United States in Stage IIIB invasive or IV metastatic non-small cell lung cancer (NSCLC) in HLA-A2 positive patients after failure of at least one first line of therapy. The purpose of the study was to evaluate the tolerability, efficacy (tumor response and survival), and cytotoxic T immunogenicity of the product.

The results of this study showed the efficacy of the treatment, with an increase in survival associated with good tolerability. The median survival of patients treated with Tedopi® was 17.3 months compared to 12 months for the control group (composed of HLA-A2 negative patients).

135 patients enrolled in this trial; 64 patients were HLA-A2 positive; 72 patients were HLA-A2 negative with information available only on one-year survival for this observation group.

A large majority of patients were metastatic at inclusion (67% of patients). 31% of patients had received at least one prior first line of therapy; 28% received two prior lines, and 37.5% of patients received three or more therapeutic lines (up to six therapeutic lines). 92% had received prior platinum therapy and 34% had received prior targeted therapy (gefitinib or erlotinib).

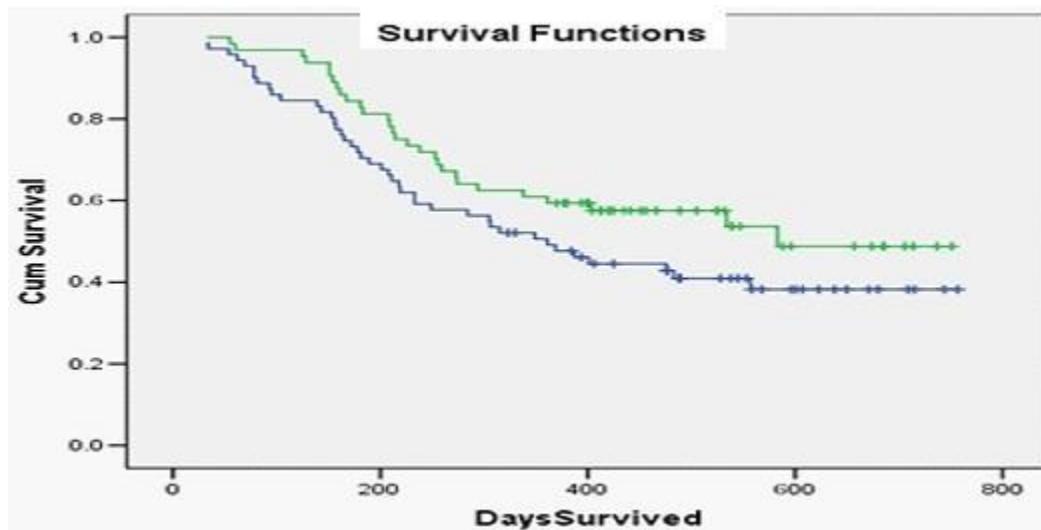
The group of 72 HLA-A2 negative patients was monitored only for one-year survival data, as the trial was designed to assess the one-year survival rate.

## SURVIVAL RESULTS

The median survival was 17.3 months in the Tedopi®-treated group and 12 months in the HLA-A2 negative group not treated with immunotherapy (observation group receiving standard therapy). This median survival of 17 months is especially important in this trial population, with 67% of patients metastatic. In addition, this population was previously heavily pre-treated with different therapeutic lines (65% of patients received more than two lines - patients receiving third-line therapy, and 92% received at least one platinum-based chemotherapy).

The one-year survival rate was 59% in the HLA-A2 positive group compared to 49% in the HLA-A2 negative group. This difference in efficacy in favor of the treatment under study, although not significant, is very interesting because the HLA-A2 negative control group has a better prognosis for survival (Nagata et al. 2009, Bulut et al. 2009). The two-year and three-year survival rates for the immunotherapy group were 39% and 27%, respectively. At four years, the long-term survival rate was maintained for 25% of patients (see curve).

Figure 1: Survival curve



Green = HLA-A2+: Patients treated with Tedopi® (n= 64 - 29 deaths)

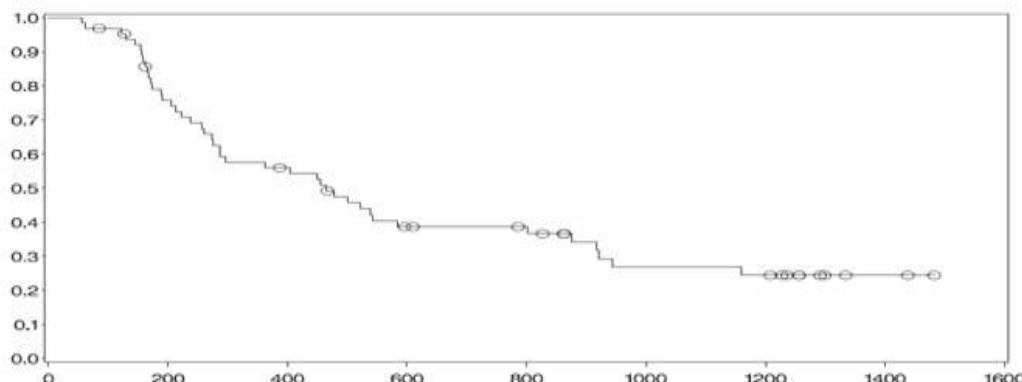
Blue = HLA-A2-: Control group (n = 71 - 42 deaths)

One-year survival rate: p = 0.063; 59% survival (HLA-A2+ treated group); 49% survival (HLA-A2- control group)

Median survival (days): p = 0.086:17.3 months (HLA-A2+ treated group); 12 months (HLA-A2- control group)

Figure 2: Long-term survival curve

Long-term survival curve: 25% of patients present at four years



The long-term survival curve is all the more interesting since the majority of patients included were metastatic and heavily pre-treated previously.

Evaluation of progression-free time: at the same time, the median progression-free time for patients treated with Tedopi® was estimated at 9.4 months, with 47% of patients still progression-free at one year.

Evaluation of tumor response: stabilization of tumor response was observed in 89% of the population.

#### Cytotoxic T cell immune response correlated with observed survival

With Tedopi® a T cell immune response (measured in Elispot) for at least one epitope is observed in 91% of this population most often at a metastatic stage. The immune response is positive for three epitopes in 64% of the population.

The correlation between survival and the number of epitope responses was established to a significant degree (log Rank test). Longer survival was correlated to a significant degree with the number of positive responses to the various epitopes ( $p<0.001$ ).

From 0 to 1 epitope:  $406 \pm 58$  days of survival

From 2 to 3 epitopes:  $778 \pm 72$  days of survival

From 4 to 5 epitopes:  $875 \pm 67$  days of survival

New exploratory data from a translational analysis were presented in a poster session entitled: “*Survival is improved by antigen-specific cytotoxic T lymphocytes (CTL) responses after treatment with the neoepitope-based vaccine Tedopi® in HLA-A2 positive advanced non-small cell lung cancer (NSCLC) patients*” \*, at the Society for Immunotherapy of Cancer (SITC) conference held in National Harbor, Maryland, USA, November 6-10, 2019. This poster session described the results of immunogenicity assays to explore the predictive effect of neo-epitopes on overall survival by type and number. The results presented demonstrated that in advanced non-small cell lung cancer (NSCLC) patients, survival was significantly prolonged in patients immunized with the combination of neoepitopes used in Tedopi®.

## OUTCOMES FOR HIGH-RISK PATIENTS

Patients with brain metastases were eligible for the Phase 2 trial. The spontaneous prognosis of these patients is a few months and this type of metastasis is a proven severity criterion in lung cancer.

A survival analysis was performed in a subgroup of six patients with brain metastases (9% of the trial population) who were already heavily pre-treated with brain radiotherapy and 1-3 prior lines of chemotherapy. The Tedopi® survival study showed a median survival of 13.75 months with extremes ranging from 7 months to over 41 months, a particularly interesting result for this usually poor prognosis group. The immune response study showed that five out of six patients developed a cytotoxic T cell response to at least one epitope and up to five of the tested epitopes included in Tedopi®.

The long-term survival observed at four years is accompanied by a favorable tolerability profile.

(M. Barve et al. JCO 2008 - J. Clin Oncol 26 : 2008 (May 20 suppl; abst 8057) (Janus et al. 2012)

(J. Nemunaitis et al., Denver IASLC 2015).

## PHASE 2 CLINICAL TRIAL IN PANCREATIC CANCER

The Phase 2 clinical trial, TEDOPaM, is being sponsored by the oncology cooperative group GERCOR and aims to evaluate Tedopi® in locally advanced or metastatic pancreatic cancer.

Due to the COVID-19 pandemic, accrual of new patients had been temporarily suspended in March 2020. After reviewing data collected until the end of March 2020 and based on the initial protocol (Tedopi® in combination with Opdivo® or alone versus chemotherapy by FOLFIRI) trial’s independent committee of scientific experts (IDMC, “Independent Data Monitoring Committee”) recommended to stop the evaluation of treatment with Opdivo® in combination with Tedopi® and to integrate the chemotherapy (FOLFIRI) in combination with Tedopi®. GERCOR has consequently modified the treatment design and the new inclusions (subject to the COVID-19 pandemic impact) are expected in Q2 2021 with an amended protocol comparing Tedopi® in combination with FOLFIRI chemotherapy versus FOLFIRI, after treatment with FOLFIRINOX. The primary endpoint of the trial remains the one-year survival rate.

## PHASE 2 CLINICAL TRIAL IN OVARIAN CANCER

In March 2021, the French National Agency for Medicines and Health Products Safety (ANSM) and the French Central Ethic Committee (CPP) approved the initiation of a new Phase 2 clinical trial evaluating Tedopi® in patients with recurrent ovarian cancer (the TEDOVA trial). Tedopi® will be evaluated alone and in combination with Merck’s Keytruda® (pembrolizumab), an immune checkpoint inhibitor, as maintenance treatment in ovarian cancer patients after chemotherapy. The study will include 180 patients and Phase 2 read-out is expected end of 2023.

The three arm TEDOVA study will evaluate neo-epitope-based vaccine Tedopi® as a maintenance treatment, alone or in combination with anti-PD-1 Keytruda®, versus the best supportive care in platinum-sensitive recurrent ovarian cancer patients with controlled disease after platinum-based chemotherapy.

As part of its partnership strategy, the Company is exploring partnership opportunities for Tedopi®, its most advanced product in its development stage.

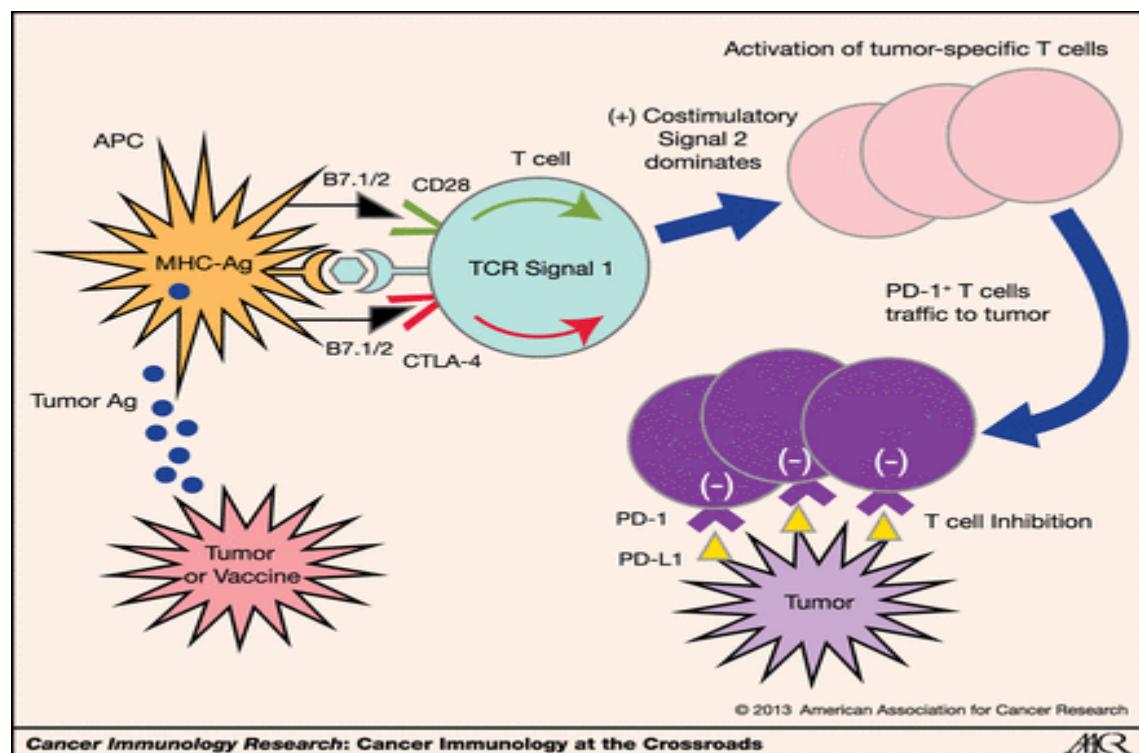
## OTHER INDICATIONS ENVISAGED FOR TEDOPI®, IN PARTICULAR IN COMBINATION WITH A CHECKPOINT INHIBITOR

In 2021, the Company plans to expand the clinical development of Tedopi® to new cancer indications by combining it with a checkpoint inhibitor.

Blocking checkpoint inhibitors is the most advanced approach in cancer immunotherapy to activate anti-tumor immunity, with two products registered, for example, in lung cancer (NSCLC) or melanoma (nivolumab and pembrolizumab). Even though this clinical activity is very promising, with an observed difference in survival compared to chemotherapy, other strategies are expected to increase the results in terms of survival, progression-free survival time, quality of life and control of observed autoimmune reactions. Effective tumor clearance requires coordinated immune mechanisms involving both the activation of immune effector cells and the blocking of suppressor mechanisms. Therefore, there is a strong rationale for combining “T specific therapeutic vaccines” with T lymphocyte-specific activation action, with non-specific checkpoint inhibitors that act as a brake on T lymphocytes.

To counter the immune system's attack, cancer cells use a wide variety of mechanisms, including low expression of histocompatibility molecules or MHC (MHC receptors are essential when they partner with peptides in the form of epitopes or neoepitopes to trigger a T lymphocyte response). Tumor cells also use the expression of T cell inhibitory molecules on which checkpoint inhibitors act, such as certain members of the family of molecules called B7, and where the PD-L1 ligand of PD-1 (also PD-L2, B7-H3, VISTA) is found.

Combinations of specific cancer therapies with non-specific checkpoint inhibitors have been successfully tested in certain tumors, as already explained in pancreatic cancer (Le D.T. et al., 2013), and in prostate cancer [Jochems C. et al., 2014] and melanoma [Hodi F.S. et al., 2010].



The distinct roles of control points such as CTLA-4 and PD-1 in the regulation of anti-tumor T response effector cells are described in the tumor microenvironment by J. R. Brahmer and D. M. Pardoll in the diagram above.

Interlocking mechanisms between specific and non-specific immunity:

**MHC/epitope/TCR:** this is the first signal for specific activation of T lymphocytes, it occurs via the epitope presented by the major histocompatibility complex (MHC) at the T lymphocyte receptor (TCR - signal 1). The interaction between the TCR and the peptide-MHC complex must be prolonged and of high intensity to be effective in the activation of the T lymphocyte. The affinity between the TCR receptor and the presented peptide in the groove of the MHC molecule plays a major role in the stability of this bond.

The tumor cell (or a “tumor” vaccine in the diagram) is the source of tumor antigens that must be processed and presented as epitopes by the MHC major histocompatibility complex to activate the T lymphocyte cells.

Tumor-specific T cell activation leads to T cell proliferation and effector function, but also to overexpression of PD-1. In the tumor microenvironment, PD-1-expressing T cells may encounter PD-L1 ligands, which may prevent them from expressing their cytotoxic killing function. The PD-1 (programmed cell death-1) molecule is expressed after CTLA-4 and is recognized by two ligands (PDL-1 and PDL-2).

Currently, the checkpoint inhibitors that are the most advanced or registered in multiple clinical indications target CTLA4, PD-1, PD-L1, all of which are expressed on T lymphocytes. The PD-1/PD-L1 axis is the main target of the checkpoint inhibitors that act on lymphocyte brakes in the tumor microenvironment.

However, there is a significant initial immunological escape from these biotherapies (response rate limited to a small number of treatment-naïve patients expressing the PD-L1 marker). For those patients who did respond, secondary immunological escape (after an initial response to treatment) became an emerging problem. Combining treatments that act on multiple targets is one way to combat that escape and overcome immune resistance, but these combinations must ensure manageable safety and tolerability. The elements that favor this type of combination are many:

- High expression of HLA and CD8 at the tumor level is a good prognostic factor (SD Brown et al.; *Genome Research* 2014);
- The increase of IFN- $\gamma$  in tumor cells linked to the effect of therapeutic vaccines or neoepitopes facilitates immune recognition with an increase in Major Histocompatibility Complex or MHC-I receptors. This is observed at the same time as the increased expression of PD-L1 (Grenga I et al; *Journal for ImmunoTherapy of Cancer* 2014);
- Tumor neoantigens with a high tumor level are associated with longer overall survival (N McGranahan et al, *Science* 2016 - Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade).

Other actors in the tumor microenvironment are also involved with the generation of an immunosuppressive tumor microenvironment that include regulatory T lymphocytes (called Treg, identified as CD4+ CD25+ foxp3+) and the differentiation of suppressive lines of myeloid origin (MDSC) that inhibit T effectors (via secretion of mediators such as TGF beta and IL-10). Tregs are T lymphocytes that suppress T immune responses. Tregs accumulate in the tumor, also preventing the killing functions. The interaction of CTLA-4, PD-1 and PDL-1 molecules with their ligand is necessary for the suppressive function of the Tregs while the activating signals that pass through CD28 inhibit this suppressive function. Checkpoint inhibitors therefore also promote inhibition of the suppressive activity of the Tregs.

Suppressive myeloid cells may also accumulate in tumors and disrupt the function of cytotoxic lymphocytes. There are currently no treatments to eliminate them.

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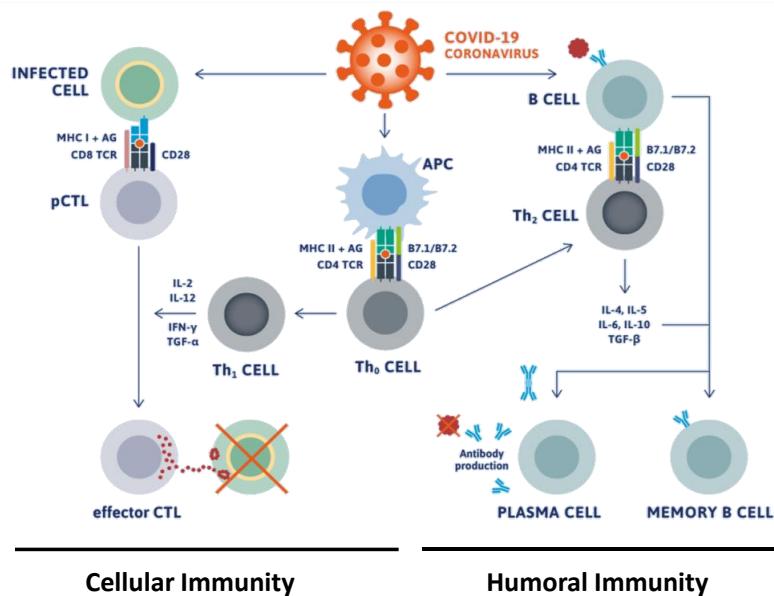
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### 5.1.1.2 Preclinical Development

#### CoVepiT, multi-target and long-term protective vaccine against COVID-19

CoVepiT was developed from neo-epitopes to fight infections caused by SARS-CoV-2, the virus responsible for COVID-19. The vaccine incorporates optimized peptide fragments (neoepitopes) improved using artificial intelligence algorithms to increase immune response and induce strong memory T cell responses.

CoVepiT is generated using OSE's proprietary Memopi® technology which has been validated for both safety and efficacy through the step-1 of Phase 3 clinical phase of neoepitope vaccine Tedopi® in patients with non-small lung cancer.



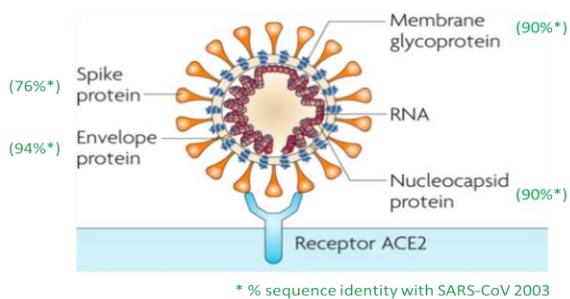
#### POSITIVE RESULTS IN PRECLINICAL AND EX VIVO IN HUMANS

- Data support potential as novel and differentiated COVID-19 vaccine designed against multiple SARS-CoV-2 targets with technology known to induce memory T lymphocytes.
- Studies show that CoVepiT provides tissue-resident memory (Trm) sentinel T cell response with long-term protective immunity in barrier tissues such as the respiratory tract and the lung.
- The emergence of new mutated coronavirus variants strengthens the multi-epitope approach against 11 viral proteins to generate a T lymphocyte response.

The human ex vivo clinical study, named CoVepiT 1, was conducted in 120 convalescent COVID-19 subjects versus unexposed subjects. It aimed at assessing the memory T cell immune response at a distance from a resolving infection with SARS-CoV-2 adults. The main objective of the study was achieved: the identification of T memory immuno-dominant epitopes after infection with COVID-19 and incorporation in the vaccine composition.

Scientists warn of new SARS-CoV-2 variants spreading rapidly across Europe and bearing mutation in some key targets of the virus, in particular the Spike protein and Nucleoprotein. On the basis of new analyses on nearly 167,000 different virus sequences isolated on a global scale, the OSE bioinformatics team confirmed no mutations had occurred in the very stable region of the viral genome of the 11 targets selected by OSE. The CoVepiT vaccine therefore covers both initial and new SARS-CoV-2 strains and variants.

These results from both preclinical and human ex vivo studies as well as the expected emergence of new SARS-CoV-2 variants build a strong basis for supporting the development of CoVepiT as a novel and differentiated COVID-19 vaccine designed against multiple coronavirus targets with vaccinal technology known to induce long-lasting memory T lymphocytes.



These results were published in **BioRxiv** in August 2020 in an article entitled: “*Tissue-resident memory CD8 T-cell responses elicited by single injection of a multi-target COVID-19 vaccine*”.

In parallel, OSE Immunotherapeutics gave an overview on the development of this multi-target vaccine at the World Immunotherapy Congress, or Festival of Biologics, held virtually November 2-9, 2020. This is the first presentation on a second-generation memory T cell COVID-19 vaccine at a scientific congress.

## INITIATION OF A PHASE 1 CLINICAL TRIAL

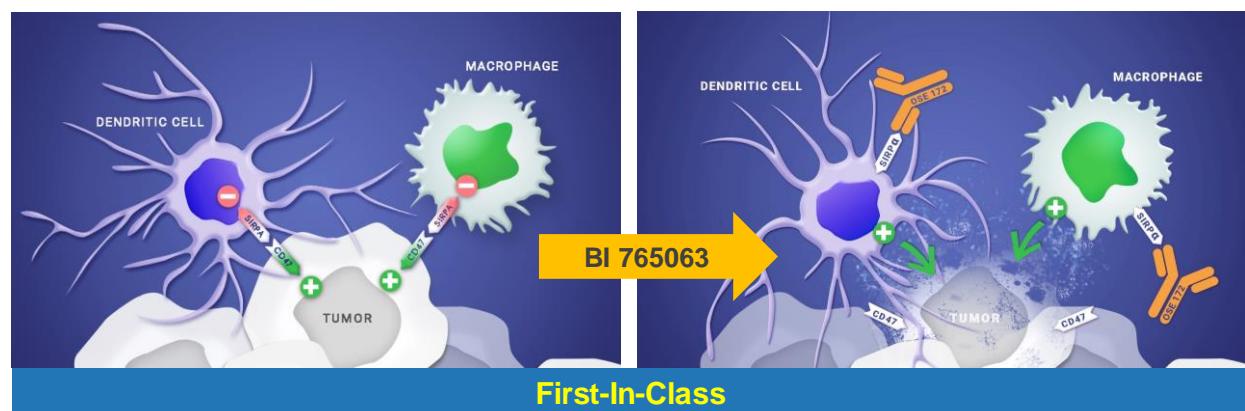
On April 1<sup>st</sup>, 2021, OSE Immunotherapeutics announced the authorization from the Belgian Federal Agency for Medicines and Health Products and the Belgian Ethics Committee to initiate a Phase 1 clinical trial to evaluate the safety, reactogenicity and immunogenicity of CoVepiT in healthy adult volunteers. Professor Isabel Leroux-Roels, at the Center for Vaccinology, Ghent University and Hospital, Ghent, Belgium, will serve as the trial’s Principal Investigator.

### 5.1.2 Immuno-oncology

#### 5.1.2.1 Clinical development

##### BI 765063 (OSE-172), selective monoclonal antibody antagonist targeting the SIRP $\alpha$ myeloid receptor

BI 765063 selectively blocks the SIRP $\alpha$ /CD47 interaction and thus increases the function of myeloid cells: phagocytosis of tumor cells and presentation of tumor antigens by dendritic cells. BI 765063 is also a selective inhibitor of SIRP $\alpha$  which, due to this property and the absence of binding and blocking by SIRP $\gamma$ , a very similar receptor, guarantees the maintenance of a T lymphocyte response and the destruction of the T cell-mediated tumor.



SIRP $\alpha$  is expressed by Myeloid-Derived Suppressor Cells (MDSCs) and Tumor Associated Macrophages (TAMs) and controls their differentiation.

## PHASE 1 CLINICAL TRIAL IN ADVANCED SOLID TUMORS

BI 765063 has been in Phase 1 clinical trial in patients with advanced solid tumors since June 2019. This first-in-human Phase 1 trial is a dose finding study of BI 765063 administered as a single agent and in combination with Boehringer Ingelheim's monoclonal antibody PD-1 antagonist BI 754,091, a T-lymphocyte checkpoint inhibitor. The trial aims to characterize safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of the immunotherapy in patients with advanced solid tumors.

The study is being conducted by OSE Immunotherapeutics under its license and collaboration agreement with Boehringer Ingelheim, which acquired the exclusive rights to BI 765063 in April 2018.

## BI 765063 (OSE-172), MYELOID CHECKPOINT INHIBITOR DESIGNED FOR IMMUNO-ONCOLOGY

The generation of an immunosuppressive tumor microenvironment is regularly observed in cancer progression and involves several cell lines with suppressive functions. Regulatory T lymphocytes (called Tregs) exert suppressive activity, and the first generation of checkpoint inhibitors acts on these regulatory T cells or Tregs (via the ligands of the CTLA-4, PD-1 and PDL-1 molecules).

At the same time, differentiation of Myeloid-Derived Suppressor Cells that inhibit the functions of effector T lymphocytes (via secretion of mediators such as TGF beta and IL-10) can be seen. These MDSC myeloid cells can be widely observed in the tumor microenvironment. In parallel, tumor-associated macrophages (TAMs) also accumulate locally with suppressive functions that promote tumor growth.

There is currently no treatment to reduce or eliminate these myeloid suppressor cells or tumor-associated macrophages. A second generation of checkpoint inhibitors can be created by acting on these new suppressive immune cell targets.

## TARGET

OSE Immunotherapeutics has identified the SIRP $\alpha$  (Signal Regulatory Protein alpha) target as a major checkpoint for myeloid cells. The Company has developed a selective SIRP $\alpha$  antagonist antibody, the checkpoint inhibitor BI 765063 (OSE-172), which transforms the tumor microenvironment by blocking suppressor cells and activating anti-tumor effector cells.

The optimization carried out on this product is the subject of three families of patents filed by the Company, the first of which was published on April 24, 2016.

## MECHANISM OF ACTION

BI 765063 (OSE-172) is a monoclonal antibody. A new-generation checkpoint inhibitor, it specifically blocks a function of tumor-associated myeloid/monocyte/macrophage suppressor cells (TAMs). These suppressor cells are very numerous in the tumor microenvironment and have a poor prognosis in aggressive cancers because they promote tumor growth (Chanmee T et al., Cancers 2014).

BI 765063 (OSE-172) blocks SIRP $\alpha$ , a receptor that is highly expressed by myeloid cells and suppressor macrophage cells. BI 765063 (OSE-172) restores the effector functions of these suppressor cells, and this activity encourages the restoration of immunosurveillance (Hanna R.N. et al.; Science 2015). It is also used in combination with other immunological therapies, in particular checkpoint inhibitors that act on T lymphocytes, such as those targeting the PD-1/PD-L1 axis or products that stimulate the immune system.

This innovative product is part of the transformation of cells described as tumor-associated macrophages (TAMs) and suppressive myeloid suppressor cells (MDSCs) to block these poor-prognosis cells and transform them into good-prognosis effector cells.

Data from preclinical and translational studies, recently published (October 2020) in the Journal of Clinical Investigation (JCI), show, in vivo models in rodents and ex vivo in humans, the efficacy and mechanism of action of BI 765063 (OSE-172), the first selective antagonist of the "Don't Eat" signal mediated by SIRP $\alpha$ . For the first time, the OSE R&D team has identified the "Don't Find Me" signal, a complementary mechanism mediated by SIRP $\alpha$  whereby cancer cells evade immune detection by preventing T lymphocytes from entering the heart of the tumor.

The article entitled: “*Selective SIRP $\alpha$  blockade reverses tumor T cell exclusion and overcomes cancer immunotherapy resistance*” (<https://www.jci.org/articles/view/135528/ga>) relates to the work of the OSE R&D team, which discovered that the anti-SIRP $\alpha$  strategy reversed a major resistance and escape mechanism to immunotherapy. According to this mechanism, called “T lymphocyte exclusion”, activated T lymphocytes cannot enter the site of the tumor and remain blocked at the periphery. Studies carried out in vivo models of resistance to anti-PD-1, PD-L1 or co-stimulation activators 4-1BB, have shown that the T lymphocytes initially blocked at the periphery of the tumor could effectively penetrate within the tumor when, in parallel, the SIRP $\alpha$  brake was blocked. Crossing this barrier is associated with a positive modulation of the expression of macrophages and the secretion of chemokines, allowing the penetration of T lymphocytes into the heart of the tumor.

## PROOFS OF CONCEPT OBTAINED IN IN VIVO MODELS

They have been obtained in aggressive cancer models such as primary liver cancer (HCC “Hepato Cell Carcinoma”), melanoma and breast cancer. These experiments have confirmed a therapeutic effect whenever BI 765063 (OSE-172) is used as monotherapy or in therapeutic combination with either another checkpoint inhibitor or an immune system stimulator, which may be long-lasting. The therapeutic effect is described as long-lasting because it was not possible to re-implant a tumor in animals treated with BI 765063 (OSE-172) that had developed anti-tumor immunization. Treatment with BI 765063 (OSE-172) as a monotherapy and in combination with other immunotherapy treatments induces a powerful and long-lasting anti-tumor action.

The main preclinical results of BI 765063 (OSE-172) have been presented at international conferences in the form of poster sessions and oral presentations (1-5) and have shown that this checkpoint inhibitor:

- Transforms the immunosuppressive tumor microenvironment in vivo and decreases tumor growth in a triple-negative breast cancer model;
- Slows the spread of metastases in a triple-negative breast cancer model;
- In combination with an anti-PD-1/PD-L1 antibody, synergy for survival in hepatocellular carcinoma (HCC), which strengthens the rationale for combination therapy;
- In combination with other immunotherapies, BI 765063 (OSE-172) induces a strong memory anti-tumor T immune response, which protects against tumor relapse.
- Modifies suppressive myeloid cells from ovarian cancer ascites to make them stimulative;
- BI 765063 (OSE-172) selectively binds to SIRP $\alpha$ , not to SIRPy, a costimulatory receptor necessary for human T cell response.

(1) *Dual targeting of adaptive and innate checkpoints induces potent memory anti-tumor response*, Gauttier V. et al., EACR poster 2016

(2) *Selective targeting of the SIRP $\alpha$  immune checkpoints, but not CD47, controls the polarization of macrophages*, Gauttier V. et al., EACR poster 2016

(4) *Control of immune tolerance by the SIRP $\alpha$  -CD47 pathway and Myeloid-Derived Suppressor Cells*, Poirier N. et al., EACR poster ICI 2016

(4) *Selective Targeting of the SIRP- $\alpha$  Immune Checkpoints to Dampen Suppression By Myeloid-Derived Suppressor Cells And Control Polarization Of Human Macrophages*, Vanhove B et al. 2016.

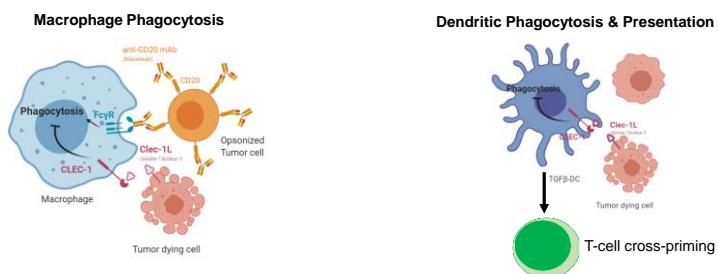
(5) *Selective targeting of SIRP $\alpha$  induces potent memory anti-tumor immune responses without presenting haematological toxicity*, Gauttier V et al., AACR poster 2017

The diseases for which BI 765063 (OSE-172) could be developed concern all cancers in which TAM and MDSC cells are involved. These TAM (tumor-associated macrophages) cells or MDSCs (myeloid-derived suppressive cells) are key cells in the progression of inflammatory cancers. The cytokines secreted by these suppressor cells promote this climate (IL-10, IL-1 $\beta$ , TGF $\beta$ ). Cancers related to chronic inflammation (primary liver cancer/colon cancer) could be, as an example, cancers of interest for such a strategy (Zamarron B.F. and 2011) (Mallmann MR et al. 2012).

### 5.1.2.2 Preclinical development

#### CLEC-1, NEW IMMUNE MYELOID CHECKPOINT THAT REGULATES THE ANTI-TUMOR RESPONSE

The OSE Immunotherapeutics teams have characterized a new myeloid checkpoint target CLEC-1 (among CLR receptors-C-type lectin receptors) and have identified antagonistic monoclonal antibodies that block this new signal "Don't Eat Me". They increase both the phagocytosis of cancer cells by macrophages and the uptake of antigens by dendritic cells. The identification of CLEC-1 and its antagonists constitute an exciting innovative step in cancer immunotherapy.



Similar to the SIRPa/CD47 axis, the CLEC-1/CLEC-1 ligand pathway inhibits macrophage phagocytosis and the presentation of antigens by dendritic cells. The CLEC-1 ligand differs from CD47 because it is expressed by tumor cells under stress conditions, in particular when it is exposed to chemotherapy or radiotherapy. The new CLEC-1 monoclonal antibody antagonists developed by OSE Immunotherapeutics overcome this inhibition and act in synergy with the antibodies targeting tumor antigens currently on the market.

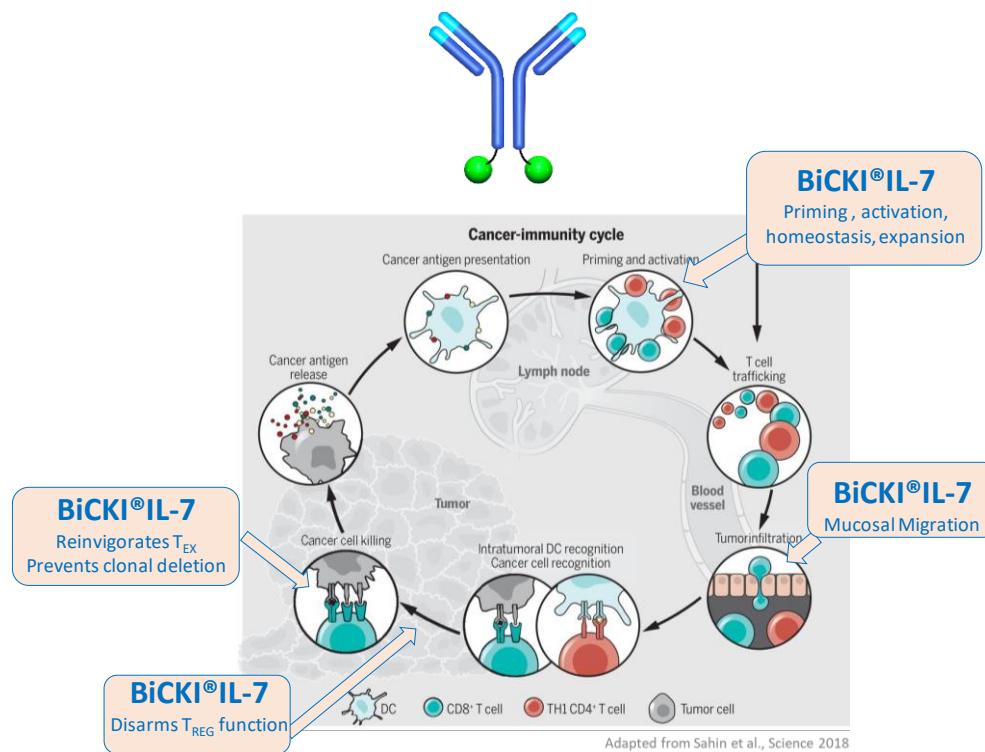
The CLEC-1 research program is conducted in collaboration with Dr Elise Chiffolleau (CRTI, Center for Research in Transplantation and Immunology) and teams from UMR1064, INSERM, Nantes University at Nantes University Hospital.

CLEC-1 monoclonal antibody antagonists identified as new myeloid checkpoint inhibitors for immuno-oncology were presented in June 2020 at the annual virtual congress of the American Association of Cancer Research (AACR) and in November 2020 at the SITC (Society for Immunotherapy of Cancer) annual conference.

### **BiCKI®, new platform of bispecific checkpoint inhibitors**

The BiCKI® platform targets the PD-1 receptor and other innovative targets. A bispecific fusion protein platform, it is built around a key backbone component anti-PD-1 (OSE-279), chosen for its bioproduction ability, merged with innovative immunotherapy targets. The BiCKI® platform aims to inhibit key immune checkpoint inhibitors while simultaneously delivering cytokines capable of modulating regulatory T cells, and/or increasing the responses of exhausted T cells within the tumor. It can also incorporate other therapeutic methods to modify the tumor microenvironment by delivering, for example, costimulation signals to restore the activity of anti-tumor T lymphocytes or restore phagocytic functions and macrophage polarization.

Based on an anti-PD-1 bifunctional antibody platform technology, BiCKI® is designed to expand the type of patients responding to immunotherapies. This is the second generation of PD-(L)1 inhibitor used to increase anti-tumor efficacy in hard-to-treat cancers by addressing untapped immune escape mechanisms.



The first cytokine selected to be paired with the anti-PD-1 in the bispecific antibody is Interleukin-7 (IL-7), which has been shown to improve immune functions and cancer immunotherapy efficacy. The bifunctional anti-PD-1/IL-7 is a bispecific therapy developed to combat primary and secondary resistance mechanisms to treatment with checkpoint inhibitors. The preclinical data showed that BiCKI®/IL-7 altered the immune balance in favor of effector T cells by stimulating the functions of those cells and disarming regulatory T-cells.

**OSE-279**, the backbone of the BiCKI® bispecific fusion protein platform, is a humanized anti-PD-1 monoclonal antibody. It should enter Phase 1/2 clinical trial in 2021 for a niche indication in immuno-oncology. This will enable the Company to own a patented anti-PD-1 that it may subsequently develop in combination with other products in its portfolio.

### 5.1.3 Auto-Immunity & Inflammation

#### 5.1.3.1 Clinical development

**OSE-127/S95011, An immunomodulatory monoclonal antibody that targets the Interleukin-7 receptor alpha chain (IL-7R-alpha or CD127 receptor).**

OSE-127/S95011 has an innovative mechanism of action that blocks Interleukin-7 and internalization of the receptor, inducing a powerful antagonist effect on pathogenic T lymphocytes involved in autoimmune diseases. This mechanism has been confirmed in *in vivo* models of autoimmune diseases that mimic human ulcerative colitis.



*OSE-127/S95011, IL-7 receptor antagonist*

Interleukin-7 (IL-7) is an interleukin involved in T cell survival, development and homeostasis. T lymphocyte proliferation requires the presence of Interleukin 7. IL-7 is the fuel for many autoimmune diseases. A major challenge in the treatment of inflammatory diseases could be the presence of pathogenic memory T lymphocytes in the tissues, likely to be resistant to conventional immunomodulatory therapy.

OSE-127/S95011 inhibits and blocks the IL-7 pathway. This interleukin plays an important role in the pathophysiology of autoimmune diseases such as ulcerative colitis, an inflammatory bowel disease in which T lymphocytes have a deleterious role destroying the lining of the colon.

OSE-127/S95011 is being developed under a two-step license option agreement with Servier until the completion of two Phase 2 clinical trials, with a priority focus on the completion of the planned Phase 2a trial in Sjögren's Syndrome, a systemic autoimmune disease characterized by damage to the exocrine glands, in particular lacrimal and salivary glands (Servier is the sponsor). The other Phase 2 study is being conducted in ulcerative colitis, an autoimmune bowel disease. It started in December 2020, sponsored by OSE Immunotherapeutics.

In February 2019, Servier validated the first step of this agreement with the exercise of the first option after the validation of a previously defined development stage. Furthermore, this clinical development is currently being conducted as part of the EFFIMab consortium funded by Bpifrance, of which OSE Immunotherapeutics is the leader and which includes public and private partners. Continued development after this Phase 2 will be fully ensured by Servier.

## PHASE 1 CLINICAL TRIAL IN HEALTHY VOLUNTEERS

OSE-127/S95011 entered the clinical trial phase at the end of 2018, following the authorization granted by the Agence Fédérale des Médicaments et des Produits de Santé (AFMPS) and the Belgian Ethics Committee in November.

The purpose of the Phase 1 dose-escalation clinical study, the first administration to human, was to evaluate the safety and tolerability of single- and multiple-doses of OSE-127/S95011 through intravenous and subcutaneous administration. This randomized, double-blind, placebo-controlled trial was conducted in 63 healthy volunteers. Secondary endpoints included measures of pharmacokinetics, pharmacodynamics and immunogenicity to help assess and understand how the drug is absorbed and metabolized. In addition, exploratory biomarkers were used to assess the product's potential to treat inflammatory autoimmune diseases.

This Phase 1 clinical study of OSE-127/S95011 showed positive results, with a good safety and tolerability profile for the product. All pharmacokinetic and pharmacodynamic parameters were consistent and demonstrated dose-proportionality throughout the dose escalation to 10 mg/kg. These data made it possible to determine the dosing and administration schedule for the two independent Phase 2 clinical trials, one in ulcerative colitis (OSE-sponsored) and one in Sjögren's Syndrome (Servier-sponsored).

## ONGOING PHASE 2 CLINICAL TRIAL IN MODERATE TO SEVERE ACTIVE ULCERATIVE COLITIS.

The Phase 2 clinical trial is underway sponsored by OSE Immunotherapeutics, which announced the enrolment of a first patient on December 21, 2020.

This randomized, double-blind, placebo-controlled Phase 2 trial aims to assess the efficacy and safety of OSE-127/S95011 in 150 patients suffering from moderate to severe active ulcerative colitis after failure, loss of response or intolerance to previous treatment(s).

The patient population (with moderate to severe ulcerative colitis, failure or intolerance to immunosuppressants, anti-TNF $\alpha$ , anti-integrins, ustekinumab and/or corticosteroids) was selected because of these patients' need for new treatment options to avoid disease-related complications for as long as possible and in which the safety profile of OSE-127/S95011 can be reliably assessed.

## TARGET

The Interleukin-7 receptor is composed of two subunits, the alpha (or CD127) chain and the gamma (or CD132) chain, which is common to other interleukin receptors (IL-2, IL-4, IL-7, IL-9, IL-15 receptor). A mutation on the alpha chain of the Interleukin-7 receptor leads to immunodeficiency. The blocking of the Interleukin-7 receptor therefore represents a therapeutic target with multiple applications, particularly in autoimmune diseases. This cytokine is different from IL-2 and IL-15 because its presence is necessary and crucial for the generation and maintenance of memory T lymphocytes, as well as for IL-17 secreting cells (special helper T-cells). Consequently, IL-7 is considered the "fuel" for pathogenic T responses related to autoimmune and chronic inflammatory diseases (2) (Dooms, H. et al. 2013). Almost all T lymphocytes express IL-7R, with a major exception for regulatory T cells (Tregs) (3-5) (Michel, L. et al. 2008; Powell, N. et al. 2012), and this therapeutic approach provides an opportunity to selectively target effector T (eff T) while sparing regulatory T cells.

## MECHANISM OF ACTION

OSE-127/S95011 has an innovative mechanism of action that blocks Interleukin-7 and internalization of the receptor, thus inducing a powerful antagonist effect on pathogenic T lymphocytes involved in autoimmune diseases. This mechanism has been confirmed in in vivo models of autoimmune diseases that mimic human ulcerative colitis.

## PROOF OF CONCEPT CONFIRMED IN RELEVANT IN VITRO AND IN VIVO MODELS

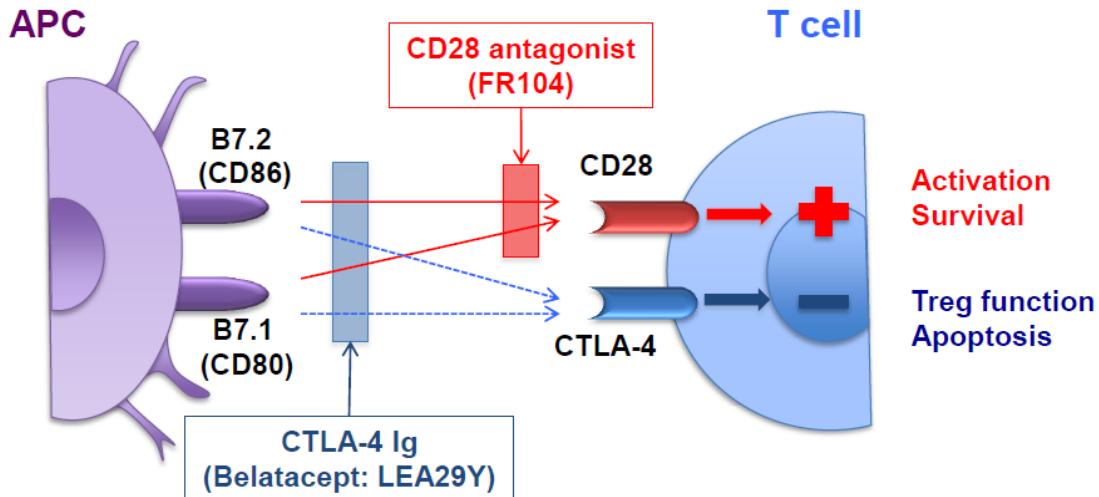
OSE-127/S95011 has demonstrated its efficacy in preclinical inflammation models mediated by T cells, with both immediate and long-term effects, giving it a very novel mechanism of action.

This strategy, which differs from conventional or newer anti-inflammatory drugs used in the clinic, has demonstrated its efficacy in several preclinical models to restore altered immune balance in inflammatory bowel diseases (Powell, N. et al. 2012; Yamazaki, M. et al. 2003), type 1 diabetes, multiple sclerosis, and rheumatoid arthritis.

## **FR104, monoclonal antibody, CD28 antagonist**

This pegylated monovalent antibody selectively inhibits the CD28 receptor for potential clinical applications in autoimmune pathologies and transplantation.

The blocking of CD28 by FR104 makes it possible to control the effector T functions while maximizing the regulatory T cells. This novel control of immune synapses potentially offers new therapeutic options in many inflammatory and autoimmune diseases in which T cells are involved and where there is a significant medical need.



*CD 28 delivers stimulation signals to the CTLA-4 and PDL-1 T cells and deliver inhibition signals to T-cells*

Normally, the immune system defends the body against external aggression and tolerates its own constituents. An autoimmune disease occurs when the self-tolerance mechanisms fail, allowing auto-reactive lymphocytes to attack the body's constituents. The immune system then becomes pathogenic and induces tissue or cell damage. These diseases evolve chronically throughout life, with relapse and remission phases. Costimulatory signals are necessary to continue the harmful activation of the T lymphocyte. Blocking these costimulation signals is a new therapeutic pathway in which FR104 is involved.

In transplants and grafts, the immune system seeks to eliminate what it regards as foreign. In bone marrow transplants, the immunocompetent cells in the graft are able to recognize alloantigens in the host as foreign and reject them. This is called Graft Versus Host Disease (GVHD). Alloreactivity (antigens from an individual of the same species but with a different genetic and tissue structure) remains a major obstacle to organ and tissue transplantation because immunological rejection leads to relatively rapid graft loss without immunosuppressive treatment. Alloreactive lymphocytes are at the heart of these rejections and develop high-intensity immune responses one seeks to block.

## PHASE 1 CLINICAL TRIAL: POSITIVE RESULTS

An initial Phase 1 trial with FR104 showed positive clinical results. The clinical and biological tolerability profile of this new product was very satisfactory in 64 healthy volunteers who received increasing doses of the product in single or repeated administrations. In addition, initial clinical activity data from this trial, using a KLH test, clearly showed a dose-dependent inhibition of the antibody response to KLH.

The results of the Phase 1 clinical study of FR104 showed good clinical and biological tolerability of the product. Its immunosuppressive activity in humans has demonstrated that the product has the potential to show clinical activity in the treatment of transplantation and immune-mediated diseases.

## ONGOING PHASE 2 CLINICAL TRIAL IN RENAL TRANSPLANTATION

In December 2020, the French National Medicines Safety Agency (Agence Nationale de Sécurité du Médicament) and the Committee for the Protection of People have given their authorization to start a Phase 1/2 clinical trial evaluating FR104, administered for the first time in patients who have received a kidney transplant. This study is being conducted under a collaboration agreement between OSE Immunotherapeutics and the Centre Hospitalier Universitaire de Nantes, which is the sponsor.

Professor Gilles Blancho, who heads the Institut de Transplantation Urologie-Néphrologie (ITUN) at the University Hospital Center, is the coordinating investigator.

The Phase 1/2 clinical trial aims to evaluate the safety, tolerance, pharmacokinetics, pharmacodynamics and efficacy of FR104 in patients who have received a renal transplant.

Long-term monitoring will be provided for one year after the end of the trial. The efficacy and long-term safety of the product will be measured according to criteria of renal function, incidence of rejection and adverse effects of FR104.

## PROJECT FOR A PHASE 2 CLINICAL TRIAL IN A NICHE INDICATION IN AUTOIMMUNE DISEASES

At the same time, OSE Immunotherapeutics is planning a new Phase 2 clinical trial of FR104 in an indication for autoimmune diseases, a priori the Graves' disease.

### TARGET

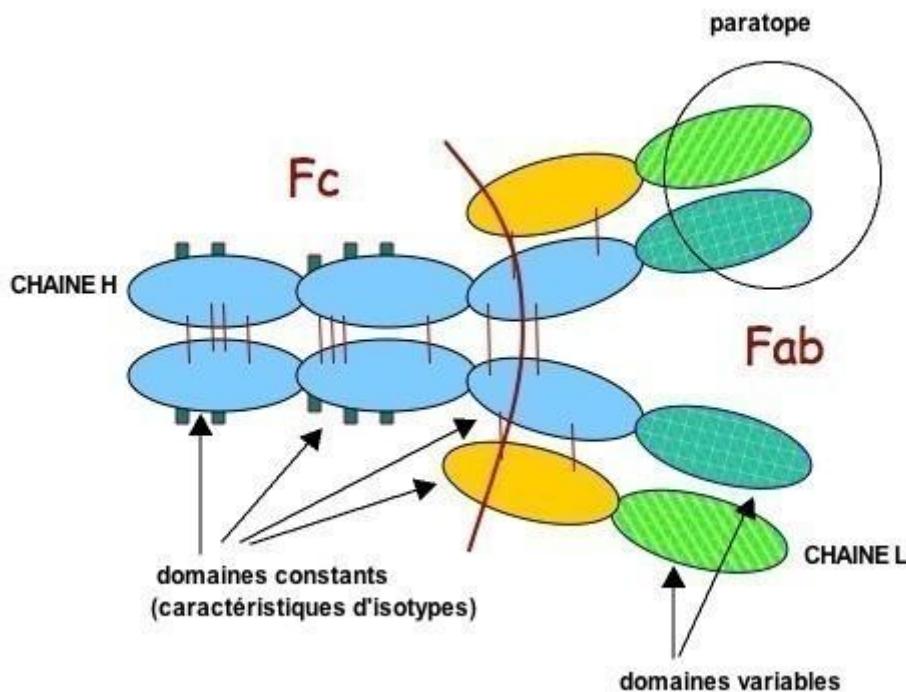
The binding of CD28, expressed on the surface of a lymphocyte, to B7-1 (also known as CD80) or B7-2 (also known as CD86) ligands, expressed on the surface of an antigen-presenting cell, provides the T lymphocyte with a costimulatory signal for it to become fully activated. Costimulatory signals regulate lymphocyte responses. The pharmacological effect on the costimulatory signal is a new therapeutic approach for modulating immune responses, in this present case to fight autoimmune reactions by reducing undesirable immune responses, and to prevent transplant rejection.



FR104 is an anti-CD28 monoclonal antibody, a pegylated humanized Fab' fragment in monovalent heterodimeric form.

It neutralizes CD28 interaction with its CD80/CD86 ligands (and also with CD275/ICOS-L). Due to its monovalent form, FR104 blocks CD28-CD80/86 interactions without activating T lymphocytes (see above Figure).

Unlike CD80/86 antagonists, FR104 does not prevent the powerful regulatory activity from CTLA4-CD80/86 interactions. These interactions are essential for the suppressive activity of regulatory T lymphocyte cells (Treg) [1]. FR104 thus reinforces the CTLA4-dependent suppressive activity while inhibiting effector T cells (Teff) [15]. FR104 is a bi-branched pegylated product; it is a chemical modification amplifying its pharmacokinetics to allow for an increased presence of the product at blood level. This addition is done on its C-terminal end (C-terminal cysteine 2). As a result of the chemical modification, the pegylated product leads to stable blood rate over time.



Overall dosing and administration schedule of an antibody with an Fc fragment and two Fab' fragments

#### IN VITRO MECHANISM OF ACTION

- FR104 selectively inhibits CD28-CD80/86 and CD28-CD275 interactions.
- It inhibits T-cell proliferation and cytokine synthesis (Interferon-gamma and Interleukin-2).
- It inhibits the responses of special effector T cells (memory effector T cells).
- It induces a response of CTLA-4-dependent regulatory T cells resulting in T-suppressive activity.
- It will not induce spontaneous activation of CD28-dependent T cells.

#### PROOF-OF CONCEPT CONFIRMED IN MANY RELEVANT IN VIVO MODELS.

In *in vivo* transplantation models (heart graft [3–5], liver graft [6] and kidney graft [1,7, 8]), CD28 antagonists act in synergy with other products, such as monoclonal antibodies and calcineurin inhibitors (CNIs). This class of CNI drugs is one of the reference treatments with cyclosporine as leading drug, often associated with corticosteroids. Alloreactivity or graft rejection is inhibited by FR104. Regulatory T cells are induced both in the periphery and in the graft, guaranteeing long-term conclusive graft outcomes. FR104, associated with calcineurin inhibitors (CNIs without added corticosteroids, or low-dose CNIs), is able to prevent graft rejection, inhibit the development of alloantibodies and extend graft survival [13] over the long term.

Other *in vivo* models of autoimmune pathologies have clearly proved the efficacy of FR104 (encephalomyelitis [14], rheumatoid arthritis (Vierboom et al., 2016), uveitis [10] and psoriasis [11]).

They have confirmed the significant therapeutic potential of this anti-CD28 monoclonal antibody.

The FP7-HEALTH-2011 European program supported the preclinical development of FR104 in T dependent autoimmune diseases (TRIAD program: Tolerance Restoration In Autoimmune Diseases).

The major assets of FR104, one of the first products of this class, are:

- It is an immunomodulator and CD28 antagonist,
- The selection and patented optimization of this product candidate are key to ensure its efficacy and safety with the choice of developing a monovalent fragment (Fab'),

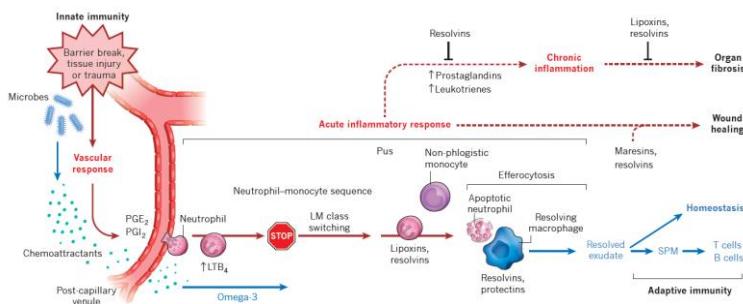
- The related humanization and pegylation processes, which increase its pharmacokinetic properties, also contribute to greater efficacy and good tolerability,
- It causes a decrease in effector T cells directly involved in the pathology of autoimmune diseases,
- It acts in synergy with suppressive regulatory T cells,
- It draws on a strong patent portfolio.

### 5.1.3.2 Preclinical development

#### **OSE-230, an antibody agonist of ChemR23, a therapy that triggers the resolution of chronic inflammation**

OSE-230 is an agonist antibody against ChemR23, also known as chemerin chemokine-like receptor 1 (CMKLR1), a G-protein coupled receptor (GPCR) expressed on myeloid immune cells known to modulate inflammation.

Persistent inflammation is a hallmark of all chronic inflammatory and autoimmune diseases. If it is not controlled or resolved, it can lead to worsening tissue damage and cause tissue fibrosis, possibly associated with the loss of organ function. Most anti-inflammatory agents act using a mechanism that blocks pro-inflammation pathways. In contrast, OSE Immunotherapeutics is developing OSE-230 as a first-in-class therapeutic agent with the potential to resolve chronic inflammation by driving affected tissues to complete the inflammation program and restore tissue integrity. The product has a strong therapeutic potential in various chronic pathologies.



Preclinical efficacy data for OSE-230 were presented at the annual FOCIS (Federation of Clinical Immunology Societies) meeting on October 29, 2020 in an oral presentation entitled: *"Agonist anti-ChemR23 mAb blunts tissue neutrophil accumulation and triggers chronic colitis inflammation resolution"*. The data show that OSE-230 is the first monoclonal antibody triggering the activation of specialized receptors of resolution to restore tissue homeostasis, integrity and functions. The main results show that:

- OSE-230 induces inflammation resolution acceleration *in vivo* in acute inflammatory preclinical models by triggering pro-resolutive programs in macrophages and neutrophils at the site of inflammation.
- More importantly, OSE-230 triggers efficient resolution of inflammation in chronic colitis models which spontaneously do not resolve, with a significant decrease in leukocyte infiltrates, tissue lesions, fibrosis and inflammation-driven tumors.
- Preclinical studies also demonstrated resolution of inflammation in type 1 diabetes and multiple sclerosis models.

These results were based on OSE's key findings:

- Natural resolution of inflammation is elicited by pro-resolving lipids which activate GPCRs to induce neutrophil apoptosis, reduce neutrophil tissue recruitment and promote macrophage efferocytosis.
- Using transcriptional analyses of up to 300 chronic colitis patients, OSE's R&D team identified ChemR23 as a GPCR receptor of the resolution program overexpressed in the inflamed tissues of patients unresponsive to anti-TNF $\alpha$  or anti- $\alpha 4\beta 7$  therapies. In these patients, treatment resistance was strongly associated with bowel mucosal neutrophil accumulation.
- The ChemR23 receptor is mainly expressed by resident tissue macrophages and neutrophils only under inflammatory (TNF, IL-6, LPS) conditions.

#### 5.1.4 Research and Development

The Company continues to identify new targets and optimize product candidates selected for immuno-oncology and autoimmune diseases. In particular, other checkpoint inhibitors and immunomodulators will be selected and optimized, based on proof-of-concept substantiated during research and development, to enter the development phase.

The Company plans to add new products to its portfolio, continue to develop its pre-clinical research programs and move them to the clinical trial phase, either by its own resources, or in co-development as part of a partnership, for broad indications or niche indications.

## 5.2 Principal markets

### 5.2.1 Immuno-oncology market

#### **IMMUNO-ONCOLOGY: ASSESSMENT OF THE CANCER IMMUNOTHERAPY MARKET AND ASSESSMENT OF THE MARKET FOR TEDOPI® IN LUNG CANCER**

In June 2017, “GBI Research” forecast a rise in the global oncology market from \$118.6 billion in 2016 to \$241 billion in 2023. In January 2020, the “**Immuno -Oncology Market - Global Forecast to 2022**” estimated the global immuno-oncology market at more than \$100 billion in 2022.

The first cancer immunotherapy products registered were checkpoint inhibitors acting on T cells (Opdivo® BMS, Keytruda® Merck, Tecentriq® Roche, Yervoy® BMS, Bavencio® Merck Serono/Pfizer, Imfinzi® AstraZeneca), and a therapeutic vaccine, Provenge®.

The first immune activation product, Provenge®, to have entered the market in this field is a cell therapy product to combat prostate cancer which was licensed in the United States in 2010 (Provenge® or sipuleucel-T, developed by the US company Dendreon, since acquired by the pharmaceutical company Valeant).

**Opdivo®** (nivolumab, monoclonal antibody, anti-PD-1 checkpoint inhibitor from BMS)/First marketing authorization: December 2014 (metastatic melanoma). Since then, Opdivo® has been registered in metastatic non-small cell lung cancer (NSCLC) (2015), renal cancer (2015), Hodgkin's lymphoma (2016), head and neck cancer (2016), bladder cancer or urothelial carcinoma (2017), metastatic colorectal cancer (MSH-H or dMMR) (2017), hepatocellular carcinoma (2017). In 2018, the product was registered in combination with ipilimumab (Yervoy®) in metastatic colorectal cancer and in first-line therapy in renal cancer.

Revenue (based on data published by the companies)

2016 = \$3.8 billion; 2017 = \$4.9 billion; 2018 = \$6.7 billion; 2019 = \$7.2 billion; 2020 = \$6.99 billion.

**Keytruda®** (pembrolizumab, monoclonal antibody, anti-PD-1 checkpoint inhibitor from Merck MSD)

First marketing authorization: in 2014 in metastatic melanoma. Since then, Keytruda® has been registered in non-small cell lung cancer (NSCLC) (2015), head and neck cancer (2016), Hodgkin's lymphoma (2017), bladder cancer or urothelial carcinoma (2017), gastric cancer or gastro esophageal junction cancer (2017), cervical cancer (2018), diffuse large B cell lymphoma (June 2018), hepatocellular carcinoma or liver cancer (2018), Merkel cell carcinoma (an aggressive skin tumor) (2018), renal cancer (2019), esophageal cancer (2019) and endometrial cancer (2019).

After registration in 2015 as a 2nd-line therapy for patients suffering from metastatic non-small cell lung cancer (NSCLC) with a PD-1 biomarker expression, in October 2016, Keytruda® was registered in 1st-line therapy in NSCLC for patients expressing the PD-1 marker (PD-L1 expression over 50% at tumor level). In May 2017, Keytruda® obtained its conditional registration in 1st-line therapy (in combination with pemetrexed and carboplatin) in NSCLC, whatever the PD-L1 expression. In August 2018, Keytruda® was registered in 1st-line therapy (in combination with pemetrexed and platinum-based chemotherapy) in metastatic non-epithelial NSCLC without tumor-genomic aberration of the EGFR or ALK gene. In October of the same year, it was registered in 1st-line therapy (in combination with carboplatin and paclitaxel) in NSCLC, whatever the PD-L1 expression.

In April 2019, the product was registered in 1st-line monotherapy for stage III NSCLC (PD-L1 proportion expressed at over 1% at the tumor level).

Revenue: 2015 = \$566 million; 2016 = \$1.4 billion; 2017 = \$3.8 billion; 2018 = \$7.1 billion; 2019 = \$11.1 billion; 2020 = \$14.38 billion.

#### **Tecentriq® (atezolizumab, anti-PD-L1 checkpoint inhibitor from Roche)**

First marketing authorization: in May 2016 in urothelial bladder cancer, with a companion test to identify PD-L1 positive patients (Ventana PD-L1-SO 142 assay). Then in October 2016, Tecentriq® was registered in the treatment of lung cancer as a second-line therapy for patients suffering from metastatic non-small cell lung cancer (NSCLC) whose disease has progressed during, or after, platinum-based chemotherapy and during an appropriate targeted treatment in the presence of a tumor with EGFR or ALK gene mutation. In December 2018, Tecentriq® obtained its registration in 1st-line therapy for non-epithelial metastatic NSCLC in combination with Avastin® and chemotherapy. In March 2019, the product was registered in metastatic triple negative breast cancer and in 1st-line therapy of small cell lung cancer. In 2020, it was registered in combination with Avastin® for hepatocellular carcinoma.

Revenue: 2016 = \$168 million; 2017 = \$508 million; 2018 = \$765 million; 2019 = \$1.9 billion. 2020 = CHF 2.7 billion (+55%). A strong increase in sales of Tecentriq® in 2020 is due to its indication for new pathologies (certain lung cancers, breast cancer and hepatocellular carcinoma).

#### **Yervoy® (ipilimumab, monoclonal antibody targeting CTLA-4, from BMS)**

First marketing authorization in 2011 in melanoma. In 2018, the product was registered in combination with nivolumab (Opdivo®) in metastatic colorectal cancer and in 1st-line treatment of renal cancer.

Revenue: 2018 = \$1.3 billion; 2019 = \$1.5 billion; 2020 = \$1.6 billion.

**Bavencio® (avelumab, monoclonal antibody targeting anti-PD-L1, from Merck Darmstadt or EMD Serono in collaboration with Pfizer-Javelin program):** this antibody is an IgG1, a cytotoxic antibody. Two registrations were obtained in 2017: in Merkel cell carcinoma (an aggressive skin tumor) and in bladder cancer or urothelial carcinoma.

Revenue: 2019 = €103 million; 2020 = €153 million.

#### **Imfinzi® (durvalimab, humanized monoclonal antibody targeting the PD-L1 ligand, checkpoint inhibitor MEDI 4736d)**

Then, in 2018, registration in inoperable non-small cell lung cancer (NSCLC) in patients who have not progressed after chemo or radiotherapy.

Revenue: 2019 = \$1.5 billion dollars (AstraZeneca estimated that the market would peak at over \$6 billion). 2020 = \$2.04 billion (AstraZeneca estimated that the market would peak at over \$6 billion).

As an indicator, products generating significant revenue in the cancer market in 2019 included, among others (from data published by the companies) the following products and pharmaceutical companies:

**Avastin® (bevacizumab, Roche):** an anti-angiogenic indicated for a number of cancers (lung, breast, ovarian, colon and kidney)

Revenue: 2019 = \$7.4 billion; 2020 = \$5 billion.

**Herceptin® (trastuzumab, Roche):** an HER2 mutation-targeted therapy for breast cancer

Revenue: 2019 = \$6.3 billion; 2020 = \$3.7 billion.

**Alimta® (pemetrexed, Eli Lilly):** chemotherapy for NSCLC

Revenue: 2019 = \$2.1 billion; 2020 = \$2.3 billion.

List prices for these products are as follows:

In the United States, a year's treatment with Yervoy® costs \$120,000.

Recently registered products targeting ALK mutations in lung cancer, such as Xalkori® (crizotinib - Pfizer) cost \$138,000 a year; ceritinib or Zykadia® from Novartis (indicated following the failure of Xalkori®) costs \$158,400 a year.

Checkpoint inhibitors registered for NSCLC: nivolumab (Opdivo® - BMS), pembrolizumab (Keytruda® - Merck & Co), atezolizumab (Tecentriq® - Roche), durvalumab (Imfinzi® AstraZeneca) all cost \$150,000 a year.

In Europe, the price of Opdivo® ranges between €5,000 and €6,000 a month (i.e. around €72,000 a year). The treatment price for a man weighing 75 kg would exceed €7,000 per month for Keytruda®, the product of Merck & Co. This price is also the same for Yervoy® in melanoma.

## ASSESSMENT OF THE MARKET FOR TEDOPI® IN LUNG CANCER

Every year, more deaths are recorded from lung cancer than from colon, breast and prostate cancers put together.

Risk factors are cigarettes, air pollution and family history.

In 2020, 2.2 million new cases (incidence) were recorded worldwide (11.4% of the total number of new cancers) and 1.8 million deaths (mortality) (18% of the total). The global mortality-to-incidence ratio was high at 0.82. The number of new cases is estimated at 3.6 million in 2040, with a rise in the average annual incidence rate of 2.51% \*.

Non-small cell lung cancer (NSCLC) accounts for around 85 to 88% of lung cancers. The 5-year overall survival rate was 23% according to cancer.net 2019 (Doctor Approved Patient Information from ASCO®). For the vast majority of patients, this cancer is discovered at an advanced stage (Yang et al., 2005) (Govindan et al., 2006) (American Cancer Society, 2012). NSCLC is considered to be a major public health issue due to its poor prognosis.

The HLA-A2 population accounts for 45% of the population suffering from NSCLC (similar figures in Asia, the United States and the European Union). The presence of the HLA-A2 marker is considered an aggravating risk factor at an advanced stage and the majority of patients are already at an advanced stage when they are diagnosed (stage III invasive or stage IV metastatic) with high risk.

In the United States in 2020, the incidence of lung cancer was 253,537 patients with 159,641 deaths. This impact included 212,000 patients with NSCLC, of which 89,000 were non-respondent to checkpoint inhibitors, and out of these, 44,000 were HLA-A2 positive\*.

In Europe in 2020, the incidence of lung cancer was 475,534 patients with 384,176 deaths. This impact included 400,000 patients with NSCLC, of which 168,000 were non-respondent to checkpoint inhibitors, and out of these, 84,000 were HLA-A2 positive\*.

In total, a potential of 130,000 patients are candidates for treatment with Tedopi® in the United States and Europe.

\* Source: WHO International Agency for Research on Cancer - 2020 Lung Fact Sheet

OSE Immunotherapeutics' internal assessment for Tedopi® is based on the epidemiology of HLA-A2 positive lung cancer with HLA-A2+ patients accounting for 45% of the non-small cell bronchial carcinoma population (88% of the lung cancer population).

The current estimate of potential sales of Tedopi® for lung cancer are based on an estimated market share of 15% at the 4-year peak and a price of around €50,000 (price estimated in the United States and Europe based on the price of comparable cancer research, personalized medicine, or "orphan" status products).

Estimated potential sales for lung cancer are around €2 billion worldwide.

The majority of patients are already at an advanced stage when they are diagnosed (Stage III invasive or Stage IV metastatic) and have a high risk of mortality. Despite the new treatments, 5-year survival rates are around 6% (American Cancer Society, 2019) for cancer patients.

Checkpoint inhibitors are becoming a standard treatment and are increasingly used in different lines of early through to late treatment. Tedopi's® positioning as a post-checkpoint inhibitor is not a restriction on its potential market. By focusing exclusively on patients whose treatment with PD-1/PD-L1 immune checkpoint inhibitors has failed, Tedopi® meets a very high therapeutic need since no product has, to date, been registered for this population in immune escape.

At this stage, no estimates have been made for any other clinical applications in other cancers or therapeutic combinations with other products.

## ASSESSMENT OF THE MARKET FOR TEDOPI® IN PANCREATIC CANCER

The incidence of pancreatic ductal adenocarcinoma is steadily increasing in Western countries and is likely to become the 2nd greatest cause of death by cancer in 2030, after lung cancer and before liver cancer (Rahib L et al: Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. *Cancer Res* 2014). The prognosis for this disease is very poor with a 5-year survival rate of less than 5%. As to the prognosis, most patients have metastases (50%) or a locally advanced cancer (one third). If the disease is operable, surgical resection followed by adjunctive chemotherapy can be used to treat a minority of patients, with 80% of cases relapsing during the follow-up period.

Standard treatment for metastatic pancreatic adenocarcinoma is still gemcitabine monotherapy for up to 15 years. For more than 10 years, dozens of Phase 3 randomized clinical trials assessed combinations of cytotoxics, or cytotoxics with targeted therapies, without managing to demonstrate that these treatments were in any way superior to gemcitabine alone. Since 2011, treatments with folfirinox (Conroy T et al: FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med* 2011) and then by nab-paclitaxel + gemcitabine demonstrated their superiority over gemcitabine alone in terms of response rate, progression-free survival and overall survival. Progression-free survival rates at 6, 12 and 18 months were 52.8%, 12.1% and 3.3%, respectively, in the folfiriinox group.

Preliminary results for therapeutic vaccines targeting tumor antigens directly (telomerase, KRAS proteins or mesothelin) and GVAX (granulocyte-macrophage colony-stimulating factor - secreting allogeneic pancreatic tumor cells) showed moderate clinical activity and a good tolerance profile [Middleton G et al. Gemcitabine and capecitabine with or without telomerase peptide vaccine GV1001 in patients with locally advanced or metastatic pancreatic cancer (TeloVac): An open-label, randomized, phase 3 trial. *Lancet Oncol* 2014; DT et al. A live-attenuated Listeria vaccine (ANZ-100) and a live-attenuated vaccine expressing mesothelin (CRS-207) for advanced cancers: phase I studies of safety and immune induction. *Clin Cancer Res* 2012]. DT et al. Safety and survival with GVAX pancreas prime and Listeria Monocytogenes-expressing mesothelin (CRS-207) boost vaccines for metastatic pancreatic cancer. *J Clin Oncol* 2015]

Pancreatic adenocarcinoma is associated with significant number of neoantigens which justify the use of immunotherapy. The somewhat moderate outcomes reported with the checkpoint inhibitors or therapeutic vaccines used in this type of cancer can be explained by the pivotal role played by the tumor microenvironment (the stroma) in the development and progression of this type of cancer. A dense, fibrous stroma combined with a pancreatic adenocarcinoma forms a physical and chemical double barrier, involved in immunosuppression. To reverse this immunosuppression, induction chemotherapy is an interesting option. Cytotoxics may reduce the tumor load and activate the immune system by destroying tumor cells. The activation of tumor neoantigens and pro-inflammatory cytokines is also a promising means of awakening the immune defenses.

## ASSESSMENT OF THE MARKET FOR TEDOPI® IN OVARIAN CANCER

Ovarian cancer is the 7<sup>th</sup> most common cancer in the world, and the 8<sup>th</sup> leading cause of cancer mortality in women. Globally, the five-year survival rate for ovarian cancer is 30 to 40%. In 2018, nearly 300,000 new cases were diagnosed. After the first relapse, ovarian cancer is treated as a chronic disease, requiring repeated courses of platinum-based chemotherapy. Chemotherapy is stopped after six cycles. One of the major priorities is to extend the time intervals without chemotherapy by offering patients a maintenance strategy using targeted therapy (PARP inhibitors or bevacizumab). At THEIR first or second relapse, the patients received both a PARP inhibitor and bevacizumab. Those who progress after PARP inhibitors and bevacizumab represent an unmet medical need: they are then offered chemotherapy alone, with no maintenance strategy: the TEDOVA trial is aimed at these women.

### 5.2.2 Anti-COVID vaccine market

While the global market for all vaccines is \$24 billion per year (nearly €20 billion), several sources agree that annual revenue from the COVID-19 vaccine should reach \$10 billion dollars (€8.3 billion), at least for the duration of the pandemic (<https://fr.statista.com/infographie/21717/entreprises-pharmaceutiques-laboratoires-chiffre-affaires-production-vente-vaccins/>).

Analysts (Morgan Stanley, Credit Suisse) base this calculation on an annual vaccination against COVID-19 (just like the flu vaccine) and on the cost per dose around \$20 per dose. With a conservative approach whereby only people who get

vaccinated against the flu will get vaccinated against COVID-19, the market could reach \$10 billion. <https://www.ft.com/content/7961437d-33cd-4f47-b190-2be3b571c8e5>).

These market size forecasts will be affected by a number of as yet unknown factors, including the size and duration of the COVID-19 pandemic, the endemic nature of the disease, possible mutations in the virus, the efficacy of a single dose, and the frequency of booster vaccinations.

A broader approach projects a global market worth \$40 billion in 2021. In the long term, investment analysts of *Coherent Market Insights* estimate an expansion of the COVID-19 vaccine market that could reach \$73.2 billion by 2027 (*Business Insider*, 2021).

These market size forecasts will be affected by a number of as yet unknown factors, including the size and duration of the COVID-19 pandemic, the endemic nature of the disease, possible mutations in the virus, the efficacy of a single dose, and the frequency of booster vaccinations.

After a few months of marketing its COVID-19 vaccine, BTN16b2, developed with BioNTech, Pfizer forecasts sales of 15 billion of its vaccine in 2021 (i.e. *Bloomberg*, 2021). Over the half-year of marketing, the company recorded sales of \$154 million of the vaccine (source *Pfizer*).

Due to a later marketing authorization for Moderna's COVID-19 vaccine, revenue figures for Moderna are not yet available but Moderna forecasts more than \$18 billion in sales.

CoVepiT, the vaccine developed by the Company, is particularly suitable for people at risk, the elderly or those suffering from severe illnesses, which represent 25% of the population in Europe and the United States.

The prices announced for a dose of the vaccine vary between approximately \$4 (Oxford-AstraZeneca) and \$37 (Moderna).

### 5.2.3 Autoimmune disease market

The autoimmune disease market is a key market that includes major pharmaceutical industry players.

**Ulcerative colitis:** incidence (patients diagnosed with the disease per year) is between 1.2 and 20 cases per year for every 100,000 people in developed countries and the prevalence of this autoimmune disease is between 7 and 246 cases for every 100,000 people (Danese S et al, Ulcerative Colitis, *New Eng J M* 2011); It affects 3.3 million patients in the United States, Europe and Japan. Approximately 50% of patients suffer from moderate to severe disease and use methotrexate, corticosteroids, anti-TNF $\alpha$ , JAK, etc. Despite the many treatments available, 25 to 30 % of patients remain without satisfactory treatment. (*Drugs Context*. 2019; 8:212572 - doi: 10.7573/dic.212572). 15% of patients do not respond to treatment and require surgery (*Scientific Reports volume 10, Article number: 12,546, 2020*).

In 2019, the global ulcerative colitis market amounted to \$6.3 billion (*EvaluatePharma* 2020). This market is growing and could reach \$7.5 billion in 2025 (*Market Data Forecast*, 2020).

**Sjögren's Syndrome:** it affects around 600,000 patients in the United States, Europe and Japan, half of them in the United States. This is the 3<sup>rd</sup> most prevalent autoimmune disease affecting the salivary and lacrimal glands, lungs, kidneys and the nervous system (e.g. *EvaluatePharma* 2020).

More than 75% of patients suffering from Sjögren's Syndrome are treated. The only registered drug is cevimeline (Exovac $^{\circledR}$ ) and the other main treatments used are generics of Exovac $^{\circledR}$ , lubricants and products for local use and T-lymphocyte modulators (Rituxan $^{\circledR}$ , Benlysta $^{\circledR}$ ) (*Context Drugs*. 2019; 8:212572 - doi: 10.7573/dic.212572).

For example, revenue from leading treatments for autoimmune diseases is as follows (information provided by the websites of pharmaceutical companies):

**Humira $^{\circledR}$**  (adalimumab, AbbVie): \$19.1 billion in 2019 and \$19.8 billion in 2020, in particular, for Crohn's disease and rheumatoid arthritis.

**Remicade $^{\circledR}$**  (infliximab, Merck and Janssen biotech/J&J): \$4.4 billion in 2019 and \$3.7 billion in 2020 in autoimmune diseases.

**Rituxan $^{\circledR}$  Mabthera $^{\circledR}$**  (rituxumab, Roche): \$6.8 billion in 2019; 2020 = \$4.2 billion (in non-Hodgkin's lymphoma, rheumatoid arthritis, transplant rejection), i.e. a sharp decrease mainly due to the emergence of new treatments in the United States during the second half of 2019.

**Enbrel $^{\circledR}$**  (etanercept, Pfizer, Amgen, Takeda): \$6.9 billion in rheumatoid arthritis in 2019 compared to \$4.8 billion in 2018, a decrease of 4%.

**Copaxone $^{\circledR}$**  (copolymers 1, Sanofi-Teva): nearly \$4 billion in 2019 and forecast \$1.3 billion in 2020 (in multiple sclerosis).

**Avonex®** (interferon beta 1a, Biogen): \$1.7 billion in 2019 (in multiple sclerosis). Revenue from the product has been declining for three years. The results for 2020 follow this trend with a total of \$1.5 billion.

**Rebif®** (interferon beta 1a, Merck Serono/ Pfizer): \$2.3 billion in multiple sclerosis. A product whose revenues are declining year on year due to strong competition in the interferon and new therapies market. In 2019, sales of €1.3 billion, in 2020 Rebif® lost 9.4% and ended the year at €1.1 billion.

More often than not, the original patents protecting these biotechnology products, such as Humira®, Enbrel®, Remicade®, Mabthera® and Copaxone®, have expired. Generic products are known as “biosimilar” products and must have documentation as comprehensive as the original product developed by pharmaceutical players such as, for example: Mylan (Glactect®, generic form of Copaxone®), Celltrion Healthcare (Remsima™, biosimilar form of Remicade®; Truxima™, biosimilar form of Rituxan®), Samsung Bioepis (Benepali™, biosimilar form of Enbrel®; Imraldi™, biosimilar form of Humira®).

The key players in the autoimmune disease market are Johnson & Johnson (J&J), AbbVie, Amgen, Genentech/Roche, Astellas, UCB, Eli Lilly, Sanofi, AstraZeneca, Novartis and Biogen.

#### 5.2.4 Renal Transplant Market

The global transplant market was estimated at \$12.8 billion in 2019 and is expected to reach \$25.8 billion in 2027, an annual growth rate of 9.3%.

In 2019, tissue transplants (skin, cornea, bones, heart valves, tendons, etc.) accounted for 60% of this market and organ transplants represented 40%. This segment is expected to grow at a significant rate of 8.6% over the period 2020 - 2027.

According to the World Health Organization, in 2018, organ transplants increased by 7.25% compared to the previous year to reach 138,000, including nearly 56,000 kidney transplants.

The market for immunosuppressants, a lifelong treatment for the transplanted patient, is expected to grow by 4% per year in kidney transplants (*Grandviewresearch.com*, June 2020). As transplant rejection is a major problem for patients who require lifelong immunosuppressive treatment, and despite the progress made in immunosuppressive treatments, the need for medical advances for patients receiving a kidney transplant remains very important (*Grand View Research, 2019*).

#### 5.2.5 Chronic Inflammation Market

Chronic inflammatory diseases are the most significant cause of death worldwide and their incidence is growing, highlighting the patients' need for disruptive innovations to manage such complex diseases. The prevalence of diseases associated with chronic inflammation is expected to increase over the next 30 years, particularly in the United States. In 2014, approximately 60% of Americans suffered from at least one chronic condition, 42% from more than one chronic condition, and 12% of adults suffered from at least five chronic conditions. Globally, three in five people die from chronic inflammatory diseases such as stroke, chronic respiratory diseases, heart disease, cancer, obesity and diabetes\*.

For example:

Diabetes: the number of diabetics worldwide increased from 108 million in 1980 to 422 million in 2014. In the same period, the prevalence among adults over the age of 18 increased from 4.7% to 8.5% (*World Health Organization data, June 2020*).

Cardiovascular diseases: they account for 31% of all deaths worldwide, mainly from coronary heart disease, followed by stroke and heart attacks\*.

Arthritis and joint diseases: these diseases affect around 350 million people worldwide\*.

Chronic obstructive pulmonary disease: in 2014, it was the third-highest cause of death in the United States with 15.7 million Americans diagnosed\*.

(\**Chronic Inflammation, Roma Pahwa; Amandeep Goyal; Pankaj Bansal; Ishwarlal Jialal, updated November 2020*)

The global market for anti-inflammatory drugs amounted to \$93.88 billion in 2019 and is expected to reach \$191.42 billion in 2027, an increase of 9.3% (<https://www.globenewswire.com/news-release/2020/05/28/2040417/0/en/Anti-Inflammatory->

[Drugs-Market-to-Exhibit-9-3-CAGR-by-2027-Owing-to-Rising-Prevalence-of-Inflammatory-Health-Conditions-Fortune-Business-Insights.html\).](#)

### 5.3 Important events in the development of the Company's business

APRIL 2012	Creation of OSE Pharma.
JUNE 2014	Phase 3 pivotal trial protocol in lung cancer accepted by the two regulatory agencies: the FDA in the United States and the EMA in Europe.
JULY 2014	The Company increased its share capital by €3.2 million.
MARCH 2015	IPO of the Company and capital increase of almost €21.1 million.
MAY 2015	First licensing and distribution agreement with Israel entered into with Rafa Laboratories, a pharmaceutical company specializing in oncology and rare lung diseases, with longstanding presence in the country and longstanding expertise in the industry.
FEBRUARY 2016	Start of Phase 3 registration clinical trial (Atalante 1 trial) of Tedopi® in Europe and the United States, in advanced non-small cell lung cancer in second-line treatment.
MAY 2016	Merger of OSE Pharma (Paris) with Effimune (Nantes, France). Change of name to OSE Immunotherapeutics and registered office located in Nantes.
JULY 2016	Exercise of option by Janssen Biotech Inc. (Johnson & Johnson group) as part of the global licensing agreement between Janssen and OSE Immunotherapeutics (signed in October 2013), triggered by the positive Phase 1 results of FR104. According to the terms of this agreement, Janssen was responsible for all clinical development, registration and international marketing of FR104 in autoimmune diseases and transplantation.
DECEMBER 2016	Signature of a two-step worldwide licensing option agreement with Servier, an international independent pharmaceutical company, to develop and market Interleukin-7 receptor antagonist OSE-127/S95011.
JULY 2017	Financing of €9.2 million received from Bpifrance as part of a collaborative project (EFFI-CLIN) to support the development of BI 765063 (OSE-172).
SEPTEMBER 2017	Signature of a collaboration agreement with GERCOR, a cooperative group of digestive oncology experts, to assess Tedopi® in locally advanced or metastatic pancreatic cancer.
DECEMBER 2017	Following its suspension in June 2017, patient enrolment resumed as part of the Atalante 1 trial after approval by the competent authorities, according to a protocol aimed specifically at a group of patients who failed to respond to treatment with PD-1/PD-L1 immune checkpoint inhibitors.
APRIL 2018	Signature of a worldwide licensing and collaboration agreement in immuno-oncology with Boehringer Ingelheim to develop the anti-SIRPa monoclonal antibody, BI 765063 (OSE-172), a new checkpoint inhibitor. OSE Immunotherapeutics could receive up to €1.1 billion if all planned milestones achieved.
JULY 2018	Funding of €435,000 for a translational research project on Tedopi® as part of the European Eurostars program (operated by Bpifrance), called Immunomonitor.
NOVEMBER 2018	Worldwide rights for FR104 taken over from Janssen Biotech by OSE Immunotherapeutics, according to which the Company has exclusive access to all intellectual property, data, files and materials developed by Janssen Biotech as part of the FR104 program. Janssen Biotech's decision to return the FR104 program to OSE Immunotherapeutics was motivated by an internal strategy review and prioritization of its own product portfolio.
	Authorization from the ANSM (French National Agency for Medicines and Health Products Safety) and the CCP (French equivalent of the Institutional Review Board) to start a Phase 2 clinical trial to assess the use of Tedopi® alone or in combination with Opdivo® (nivolumab) versus maintenance standard-

of-care treatment with Folfiri (chemotherapy combining folinic acid, fluorouracil and irinotecan), in advanced or metastatic pancreatic cancer (clinical trial sponsored and conducted by the oncology group GERCOR, with the support of Bristol-Myers Squibb which provided Opdivo®).

Authorization from the Belgian Federal Agency for Medicines and Health Products (FAMHP) and the Belgian Ethics Committee to initiate a Phase 1 clinical trial of OSE-127/S95011, aiming to assess the safety and tolerability of intravenous and subcutaneous administered single- and multiple-doses of OSE-127/S95011.

- FEBRUARY 2019** Exercise by Servier of the first option of the two-step worldwide licensing agreement for the continuation of the clinical development and potential marketing of OSE-127/S95011 in autoimmune diseases. Under the terms of the licensing agreement, exercise of this first option resulted in the payment, by Servier, of a milestone payment of €10 million (excluding tax) to the Company, after validation of a previously defined development stage.
- APRIL 2019** Milestone payment of €880,000 received as part of the EFFI-MAB program financed by Bpifrance.
- JUNE 2019** First patient treated in the Phase 1 clinical trial to evaluate BI 765063, the selective antagonist targeting SIRPa, in patients with advanced solid tumors; milestone payments worth €15 million were made by Boehringer Ingelheim to OSE Immunotherapeutics upon clinical trial authorization and treatment of the first patient.
- JULY 2019** Financing of €800,000 received from the French National Agency of Research (ANR) to validate new targets linked to myeloid cells that could be used to identify innovative immunotherapy targets. The Cancer Research Center of Lyon (CRCL) in France, as part of the Léon Bérard Center, managed the project.
- SEPTEMBER 2019** Milestone payment of €5.4 million received from Bpifrance for developing SIRPa-antagonist monoclonal antibody, BI 765063, as part of the EFFI-CLIN collaborative project.
- NOVEMBER 2019** Licensing agreement with Chong Kun Dang (CKD) Pharmaceuticals Corp. for the development of Tedopi® in Korea. Financial terms of the contract include both upfront and short-term milestone payments of €1.2 million with total milestones payments of €4.3 million, as well as royalties on sales and transfer price in the high twenties. The deal applies specifically to development and licensing of Tedopi® in the Korean market which accounts for approximately 1% of the total global oncology market.
- DECEMBER 2019** Positive results of the Phase 1 clinical trial of OSE-127/S95011 which show a good safety and tolerability profile of the product.
- MARCH 2020** Signature of an amendment to the two-step worldwide licensing option agreement on the exclusive rights of OSE-127/S95011, Interleukin-7 receptor antagonist, signed with Servier in December 2016. This amendment modifies the arrangements for the potential exercise of the licensing option agreement's second step. OSE Immunotherapeutics will thus receive a milestone payment of €5 million from Servier on enrollment of the first patient in Phase 2a clinical study scheduled to start in Sjögren's Syndrome and an additional payment of €15 million on exercise of the option at the end of the two scheduled Phase 2 studies, with priority being given to the study in Sjögren's Syndrome. The initial agreement provided for a total payment of €20 million at the end of Phase 2 in ulcerative colitis.
- APRIL 2020** Announcement of positive result of stage 1 of the Phase 3 clinical trial of Tedopi®, Atalante 1, in non-small cell lung cancer: Primary endpoint of stage 1 achieved with a survival rate at 12 months in patients treated with Tedopi®. In the context of the COVID-19 epidemic, decision taken to voluntarily and definitively discontinue screening and the enrolling new patients in step 2 initially planned in the trial and which will therefore not be conducted. The Company indicates that it is pursuing additional analyses of the Step 1 data and will initiate discussions with the regulatory authorities to determine the best path to take for development of the product, in view of the high therapeutic need in the patient population suffering from advanced lung cancer following failure of treatment by checkpoint inhibitor.

MAY 2020	Announcement of a COVID-19 prophylactic vaccine program that leverages the Company's expertise in the selection and optimization of peptides, and its patented Memopi® technology to explore a T-lymphocyte response with immune memory in COVID-19.
	Signature of a €7 million non-dilutive credit agreement in the form of French Government-Guaranteed loan (PGE) set up in the context of the COVID-19 pandemic, with a group of French banks.
JULY 2020	Funding of €200,000 from Nantes Métropole for the development of a prophylactic vaccine against the pandemic SARS-CoV-2 virus. This grant was awarded as part of the Metropolitan Fund to support health innovations related to the COVID-19 health crisis.
AUGUST 2020	Online publication on BioRxiv of positive data from a preclinical study and an ex vivo study in humans on CoVepiT, a prophylactic vaccine program against COVID-19. These data support CoVepiT's potential as a novel and differentiated vaccine against COVID-19, using technology known to induce memory T lymphocytes against multiple SARS-CoV-2 virus targets. The results show that CoVepiT provides tissue-resident memory sentinel T cell response with long-term protective immunity in barrier tissues such as the respiratory tract and the lung, associated with long-term protective immunity. The clinical trial phase is planned for the end of 2020/beginning of 2021.
SEPTEMBER 2020	Oral presentation at the European Society for Medical Oncology (ESMO) virtual congress of the positive results of step 1 of the Phase 3 Tedopi® trial in patients with non-small cell lung cancer (NSCLC) after failure of an immune checkpoint inhibitor treatment. These results show a clearly improved overall survival time with Tedopi® compared to the standard treatment, a significant increase in survival after progression, the maintenance of a good ECOG score* reflecting the change in the general health of the patient, and the confirmation of a better tolerability profile for Tedopi®. Overall, the benefit/risk ratio is favorable to Tedopi® and better than that of standard treatment in these patients previously treated with checkpoint inhibitors.
OCTOBER 2020	First presentation of data characterizing OSE-230, an innovative monoclonal antibody therapy agonist of ChemR23 that triggers the resolution of chronic inflammation (FOCIS annual meeting).
NOVEMBER 2020	On November 18, 2020, the Company announced the successful completion of its capital increase, launched on November 16, by means of a private placement. It was carried out with cancellation of preferential subscription rights through a private placement with 25 qualified French and international investors, a large majority of which were new shareholders, and by the accelerated construction of an order book, for €18.6 million.
DECEMBER 2020	The French National Medicines Safety Agency (Agence Nationale de Sécurité du Médicament) and the Committee for the Protection of People have given their authorization to start a Phase 1/2 clinical trial evaluating FR104, a CD-18 antagonist monoclonal antibody, in patients who have received a kidney transplant. This study will be conducted as part of a collaboration agreement between OSE Immunotherapeutics and the Center Hospitalier de Nantes, the study sponsor.  The Company obtained funding of €5.2 million under the PSPC-COVID call for projects, operated on behalf of the French government by Bpifrance as part of the Future Investments Program (PIA) and led by the Secrétariat général pour l'investissement (SGPI), to support its CoVepiT development, its second-generation multi-target vaccine against COVID-19, which will begin clinical trials in the 1st quarter of 2021.
	On December 21, the Company announced recruitment of the first patient in the Phase 2 clinical trial evaluating OSE-127/S95011, an IL-7 receptor antagonist, in patients with moderate to severe active ulcerative colitis. This clinical trial is being sponsored by OSE Immunotherapeutics.
FEBRUARY 2021	OSE Immunotherapeutics has signed a loan agreement of up to €25 million with the European Investment Bank (EIB) to expand the clinical development of its leader programs in immunotherapy. The This loan facility of up to €25 million is divided into three tranches including two tranches of €10 million each and a third tranche of €5 million.

MARCH 2021	OSE Immunotherapeutics and the French cooperative group ARCAGY-GINECO announced that the French National Agency for Medicines and Health Products Safety (ANSM) and the French Central Ethic Committee (CPP) approved the initiation of a new Phase 2 clinical trial evaluating Tedopi® in patients with recurrent ovarian cancer (the TEDOVA trial). Tedopi® will be evaluated alone and in combination with Merck's Keytruda® (pembrolizumab), an immune checkpoint inhibitor, as maintenance treatment in ovarian cancer patients after chemotherapy.
APRIL 2021	On April 1 <sup>st</sup> , 2021, OSE Immunotherapeutics announced the authorization from the Belgian Federal Agency for Medicines and Health Products and the Belgian Ethics Committee to initiate a Phase 1 clinical trial to evaluate the safety, reactogenicity and immunogenicity of CoVepiT in healthy adult volunteers.

## 5.4 Strategy and objectives

OSE Immunotherapeutics is an integrated biotechnology company that develops, on its own or in partnership, immunotherapies aimed at controlling the immune system for immuno-oncology and autoimmune diseases. The Company's research and development in immunology is focused on three areas: T-cell vaccination, immuno-oncology (focused on myeloid targets), autoimmunity and inflammation.

The Company's objective is to become a leading international player in the field of immunotherapy. OSE Immunotherapeutics aims to broaden and accelerate the development of its product portfolio at the clinical stage and to explore new therapeutic indications with strong medical need.

It controls the technologies of immunoregulation and immuno-activation of the immune system with complementary international teams and expertise involved in the research and optimization of drug candidates, pharmaceutical development of biotherapies, clinical development and registration. The Company has an innovative technological foundation, expertise in selection and optimization of receptor targeting, enabling significant therapeutic advances.

OSE Immunotherapeutics has a portfolio of five immunotherapy products in clinical trials from Phase 3 to Phase 1. The Company is also developing its technological platforms and selects the most innovative candidates to enter the preclinical and clinical development phases, on its own or as part of a partnership with a pharmaceutical group, for products targeting several indications and a larger market. It is developing immunological activation or regulation (suppression) products to identify and select the most relevant targets to produce agonists or antagonists in immuno-oncology or autoimmune diseases.

To achieve these objectives, the Company plans to increase the number of clinical and preclinical projects to create a richer portfolio and accelerate the transition of its research programs from preclinical to the clinical phase. It plans to advance its development programs either by its own resources or by co-development under new collaboration and licensing agreements with the industrial players involved in the field of activating or regulating immunology. Its products may be developed in therapeutic combinations of high clinical interest, in broad indications in partnership or in niche indications on its own.

### 5.4.1 A dynamic partnership development strategy based on a portfolio of innovative products

Partnerships with international pharmaceutical groups enable OSE Immunotherapeutics to accelerate the clinical development of its products. The Company aims to find the "right" partners, as with Boehringer Ingelheim and Servier, who will include the product candidate in their portfolio as a valuable program and commit the resources required to co-develop the product and ultimately address patients' needs.

Partnerships are also a strong component of the Company's business model, generating non-dilutive revenues to finance R&D programs on innovative therapeutic targets and entities.

Due to the potential of its most advanced programs, the Company signed worldwide strategic partnerships with leading international pharmaceutical companies to conduct the clinical development of key products:

#### **OSE-127/S95011**

After positive phase 1 clinical results (published in December 2019), OSE-127/S95011 is being evaluated in a Phase 2 trial conducted in ulcerative colitis (OSE-sponsored) and another independent Phase 2 trial is planned for Sjogren's Syndrome (Servier-sponsored) with first enrolled patient now expected by the end of Q2 / early Q3 2021.

Two-step optional licensing agreement for OSE-127/S95011 signed with Servier in December 2016: the Company will develop the product until the completion of Phase 2 clinical trials. After that, Servier will continue the development, as part of its licensing option.

This agreement amounts to a total of €272 million, including a payment of €10.25 million on signature (received in early 2017) and a payment of €30 million on exercise of a two-step licensing option, including €10 million at option 1, exercised in February 2019 (following validation of a pre-defined step of development) and a payment in March 2019 (the initial agreement provided for a €20 million milestone payment on exercise of option 2).

In March 2020, OSE Immunotherapeutics and Servier signed an amendment covering the terms of the potential exercise of the licensing option by modifying Step 2 of this option: this amendment provided for a milestone payment of €5 million on the recruitment of the first patient in the Phase 2 clinical trial in Sjögren Syndrome, with first enrolled patient now expected by the end of Q2 / early Q3 2021, sponsored by Servier, and an additional payment of €15 million on exercise of the option at the end of the two scheduled Phase 2 clinical trials, and in priority upon completion of the study in Sjögren's Syndrome sponsored by Servier, the second being led since December 2020 in ulcerative colitis and sponsored by OSE Immunotherapeutics.

#### **BI 765063 (OSE-172)**

Collaboration and exclusive licensing agreement (signed in April 2018) with Boehringer Ingelheim to jointly develop BI 765063 (OSE-172): Boehringer Ingelheim finances the product candidate's development in various types of cancer, its registration and international marketing.

According to the terms of this agreement, OSE Immunotherapeutics will receive from Boehringer Ingelheim a potential amount of more than €1.1 million according to predefined development steps, marketing authorization, and sales, plus royalties on net worldwide sales of the product. This amount includes a €15 million payment on signing the agreement (received in April 2018) and a total amount of €15 million in milestone payments (received in June 2019) after being granted the clinical trial authorization (in March 2019) and on administration of the product to the first patient of the study.

BI 765063 is in Phase 1 clinical trial in patients with advanced solid tumors.

#### **TEDOPI®**

- Tedopi®, for which the first step of Phase 3 in non-small cell lung cancer was validated (Atalante 1 study): the Company's product is at the most advanced stage of clinical development.

The trial was planned in two steps: a first step including approximately 100 patients overall with a planned analysis of data on the percentage of patients achieving 12 months' survival. On April 1, 2020, the Company announced positive results for Step 1 of the study. Analysis of the data showed that the primary endpoint for this milestone was achieved with a 12-month survival rate in patients treated with Tedopi® and a 10% absolute difference in this survival rate compared to chemotherapy.

These positive results confirm the therapeutic benefit of Tedopi® in a patient group for which there is no confirmed treatment to date and which is awaiting new therapeutic options.

The Company is continuing to collect additional clinical data and analyze all the results to identify and confirm a sub-group of patients of interest. Today, the Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from health authorities, the Company will try to obtain a marketing

authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.

At the same time, given that the positive Step 1 results significantly strengthened the value of Tedopi®, the Company is continuing to explore any potential partnering opportunities for the product.

- Tedopi® is in a Phase 2 clinical trial for pancreatic cancer patients called 'TEDOPaM', sponsored by the GERCOR cooperative group in oncology.

Due to the COVID-19 pandemic, accrual of new patients had been temporarily suspended in March 2020. After reviewing data collected until the end of March 2020 and based on the initial protocol (Tedopi® in combination with Opdivo® or alone versus chemotherapy by FOLFIRI) trial's independent committee of scientific experts (IDMC, "Independent Data Monitoring Committee") recommended to stop the evaluation of treatment with Opdivo® in combination with Tedopi® and to integrate the chemotherapy (FOLFIRI) in combination with Tedopi®. GERCOR has consequently modified the treatment design and the new inclusions (subject to the COVID-19 pandemic impact) are expected in Q2 2021 with an amended protocol comparing Tedopi® in combination with FOLFIRI chemotherapy versus FOLFIRI, after treatment with FOLFRINOX. The primary endpoint of the trial remains the one-year survival rate.

- Tedopi® is in a Phase 2 clinical trial as maintenance treatment in ovarian cancer, called 'TDOVA', sponsored by the cooperative group ARCAGY-GINECO.

In March 2021, OSE Immunotherapeutics and ARCAGY-GINECO announced that the French National Agency for Medicines and Health Products Safety (ANSM) and the French Central Ethic Committee (CPP) approved the initiation of a new Phase 2 clinical trial evaluating Tedopi® in patients with recurrent ovarian cancer (the TDOVA trial). This clinical trial will be sponsored and conducted by the French oncology cooperative group ARCAGY-GINECO. Tedopi® will be evaluated alone and in combination with Merck's Keytruda® (pembrolizumab), an immune checkpoint inhibitor, as maintenance treatment in ovarian cancer patients after chemotherapy.

The three arm TDOVA study will evaluate neo-epitope-based vaccine Tedopi® as a maintenance treatment, alone or in combination with anti-PD-1 Keytruda®, versus the best supportive care in platinum-sensitive recurrent ovarian cancer patients with controlled disease after platinum-based chemotherapy.

The Company plans to expand the clinical development of Tedopi® to new cancer indications by evaluating it in combination with a checkpoint inhibitor.

Licensing agreements have also been concluded in two countries to make Tedopi® available to the broadest audience globally and maximizing its potential:

- Licensing agreement (entered into in 2015) with RAFA Laboratories in Israel, which benefits from strong knowledge of and expertise in immunology.
- Licensing agreement (signed in 2019) with Chong Kun Dang (CKD) Pharmaceuticals Corp. for the development of Tedopi® in Korea. As provided for in the agreement, OSE Immunotherapeutics will receive milestone payments amounting to €4.3 million, including €1.2 million on signature and a short-term milestone achievement, and royalties on product sales as well as a margin based on the transfer price, slightly lower than around 30%. The deal applies specifically to development and licensing of Tedopi® in the Korean market which accounts for approximately 1% of the total global oncology market.

The Company could accelerate the development of some of its products in co-development as part of new collaboration and licensing agreements with industrial players involved in the field of activating or regulatory immunology. Its products may be developed in therapeutic combinations of high clinical interest, in broad indications.

#### **5.4.2 Research & Development: active pursuit of new innovative research programs, evolution of the product portfolio to clinical phase**

Research and development is the Company's core business. The Company uses in-house resources as well as partnerships with public research institutes and specialized subcontractors to carry out its preclinical, clinical and regulatory activities. The

Company uses its own research laboratory at its Nantes (France) site where the teams carry out various optimization activities and preclinical studies.

The Company relies on in-house and international expertise in immunotherapy with, in particular, ad hoc models of vaccination based on T cells, the tumor microenvironment (immuno-oncology based on T cells), autoimmune and inflammatory diseases, to accelerate development. It also grows via its network of clinical experts in these immune-related pathologies.

OSE Immunotherapeutics has several scientific and technological platforms, such as neoepitopes and agonist or antagonist monoclonal antibodies, which are used on their own or in combination. The Company intends to actively continue new innovative programs in preclinical research and development in order to develop a balanced R&D portfolio that offers a diversified risk profile, with developed products whose mechanisms of action are independent of one another.

The Company will continue to develop innovative products in preclinical and R&D development through research collaborations with centers of excellence or collaborative programs conducted in consortia financed as part of calls for proposals.

## 5.5 Research & Development, patents and licenses

### 5.5.1 Intellectual property

OSE Immunotherapeutics is assisted in its initiatives and actions to protect its intellectual property rights by specialist intellectual property firms.

#### 5.5.1.1 Memopi® technology and the product, Tedopi® (OSE-2101)

The Company, together with OPI (its wholly-owned subsidiary), owns the worldwide rights to OSE-2101.

A first licensing and distribution agreement for Tedopi® in Israel was signed in May 2015 with Rafa Laboratories, a pharmaceutical company specializing in oncology and rare lung diseases, long established on this market promoting innovation.

On November 7, 2019, the Company announced a licensing agreement with the Korean company Chong Kun Dang (CKD) Pharmaceutical Corporation for the potential registration and commercialization of Tedopi® in Korea, a market that represents approximately 1% of the global oncology market.

OSE-2101 is specifically the subject of a patent family, the original patent family, and the protection is supplemented by other patent families.

#### Original patent family

Claims for patents granted for this family cover a composition comprising the combination of different types of peptides (CTL peptides optimized for greater interaction with the HLA-A2 receptor, CTL peptides optimized for greater interaction with cytotoxic T cells, HTL peptides) for OSE-2101 as well as the therapeutic applications of this composition for the treatment of cancer, in particular, to delay remissions of cancer after surgery, chemotherapy or radiotherapy.

This family is based on an international application, WO 04/094454, filed on April 16, 2004, that claims the priority of an American order filed on April 18, 2003, under number US 60/463,724.

It includes the following patents delivered:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
AU2010214701	Australia	AU2010214701	AU2010214701	02/02/2012	April 2024
CA 2 522 812	Canada	CA2522812	CA2522812	08/21/2012	April 2024

EP04759962.6	Europe (Valid in all European Patent Convention Contracting States)	EP-1 620 456	EP-1 620 456	02/26/2014	April 2024
US14081086	United States	US2010209493	US 8,007,810	8/30/2011	April 2024
	United States	US2014141064	US 9,394,350	07/19/2016	April 2024 + 64 days
	United States	US2017028041	US 9,913,884	03/13/2018	April 2024
JP5156882	Japan	JP2006526628	JP5156882	12/21/2012	April 2024

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### Complementary families

##### T-cell immune therapy and the treatment of brain metastases (HLA-A2 positive patients)

On November 6, 2014, the Company filed an international application for a specific T-cell immune therapy for use in the treatment of brain metastases in HLA-A2 positive patients. This patent application opens the way to new potential indications within the field of brain metastases, a metastatic localization complicating a number of cancers.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2014/073975	International application	WO2016/070928			
AU2014410466	Australia	AU2014410466	AU2014410466	01/02/2020	November 2034
KR10-2017-7015327	South Korea	KR20170098811	KR102043725	11/06/2019	November 2034
US15/524.278	United States	US2017319672	US 10,434,157	10/08/2019	November 2034 + 157 days
IL250576	Israel	IL250576	IL250576	12/27/2019	November 2034
JP2017-518779	Japan	JP2017533898	JP6474893	02/08/2019	November 2034
TW104135282	Taiwan	TW201625287	TW I703982	09/11/2020	October 2035
CA 2,963,184	Canada			Being delivered	November 2034
EP-14796049.6	Europe	EP-3215184	EP-3215184	03/03/2021	November 2034
BR 11 2017 009 358 8	Brazil			Pending	November 2034
CN 201480082351.X	China	CN107073087A	ZL201480082351.X	09/08/2020	November 2034
EA 201790990	Eurasia		EA 201,790,990	01/19/2021	November 2034
MX/a/2017/005807	Mexico			Pending	November 2034
NZ 729514	New Zealand		NZ 729,514	03/24/2020	November 2034

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

##### Immune therapy and an early memory T-cell response

On June 29, 2015, OSE Pharma filed an international patent application with a specific T-cell immune therapy capable of inducing an early memory T-cell response in HLA-A2 positive patients. This patent covers the product's method of administration.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2015/06474	International application	WO2017/000983			
ZA2018/00434	South Africa	ZA201800434	ZA2018/00434	12/19/2018	June 2035
JP 2017-567729	Japan		JP 6654207	01/30/2020	June 2035
EP 15 733431.9	Europe	EP-3 313 431		Pending	June 2035
US 15/578,721	United States	US-2018-0169200		Pending	June 2035
AU2015400687	Australia			Pending	June 2035
BR 11 2017 0 27653 4	Brazil			Pending	June 2035
CA 2,990,299	Canada			Pending	June 2035
EA 201890148	Eurasia			Pending	June 2035
IT 255722	Israel			Pending	June 2035
KR 10-2018-7002801	South Korea			Pending	June 2035
NZ 737717	New Zealand			Pending	June 2035

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### Method of preparing a stable emulsion

On January 24, 2018, OSE Pharma filed an international patent application for an industrial-scale method of preparing a stable emulsion and for the ready-to-use product.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2018/051647	International application	WO 2018/138110			
TW 10710,651	Taiwan	TW 201840331		Pending	January 2038
AR 20180100167	Argentina			Pending	January 2038
EP 18 710760.2	Europe	EP 3 573 600		Pending	January 2038
US 16/477,534	United States	US-2019-0345213		Pending	January 2038
AU 2018213890	Australia			Pending	January 2038
BR 11 2019 014917 1	Brazil			Pending	January 2038
CA 3,047,492	Canada			Pending	January 2038
CN 201880007527.3	China	CN110191703A		Pending	January 2038
IL 267237	Israel			Pending	January 2038
JP 2019-560481	Japan			Pending	January 2038
KR 10-2019-7024340	South Korea			Pending	January 2038
MX/a/2019/008878	Mexico			Pending	January 2038
NZ 745571	New Zealand			Pending	January 2038
ZA 2019/05487	South Africa		ZA 2019/05487	05/27/2020	January 2038
62020006780.4	Hong Kong	40016682A			January 2038

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### Treatment in combination with an immune checkpoint inhibitor

On November 27, 2017, OSE Pharma filed an international patent application for a cancer treatment method involving sequential administrations of Tedopi® and an immune checkpoint inhibitor.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2017/080543	International application	WO2019/101347			
AU 2017440798	Australia			Pending	November 2037
BR 11 2020 010656 9	Brazil			Pending	November 2037
CA 3,081,774	Canada			Pending	November 2037
CN 201780097101.7	China	CN111727051A		Pending	November 2037
EP 17 811880.8	Europe	EP 3 716 999		Pending	November 2037
IL 274748	Israel			Pending	November 2037
JP 2020-528928	Japan			Pending	November 2037
KR 10-2020-7018440	South Korea			Pending	November 2037
MX/a/2020/005454	Mexico			Pending	November 2037
NZ 765655	New Zealand			Pending	November 2037
US 16/767,144	United States	US2020-0384067		Pending	November 2037
ZA 2020/03829	South Africa			Pending	November 2037

### 5.5.1.2. OSE-1101

This family concerns the application/use of the OSE-1101 product in the treatment of cystic fibrosis or its complications, such as inflammatory disorders or infection.

This family is based on international application WO2013/164204, filed on April 19, 2013, that claims priority of a European application filed on April 30, 2012, under number 12 305487.6.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP12 350487.6	EP	EP-2 844 253	EP-2 844 253	03/23/2016	April 2033
Valid in Germany, the United Kingdom, France, Switzerland, Spain, Italy, Portugal, the Netherlands, Belgium, Austria, Finland, Norway, Ireland, Monaco, Luxembourg, Slovakia, Denmark, Croatia, Greece, Poland, Romania, Serbia, Slovenia, Estonia, Sweden.					
US14/397,743	United States	US2015/133487	US 9,301,955	04/05/2016	April 2033
IL235358	Israel	IL235358	IL235358	12/27/2019	April 2033
CA 2,871,815	Canada	CA 2,871,815		Being delivered	April 2033

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

### 5.5.1.3 FR104

The portfolio relating to project FR104 on CD28 antagonist antibodies includes the following patent families.

#### Family 1

This family, in the name of INSERM, concerns the CD28.3 antibody and its derivatives.

This family is based on international application, WO 2002/051871, filed on December 26, 2001, that claims the priority of a French application filed on December 26, 2000, under number FR0017025.

This family includes the following patents:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP01995797.6	Europe	EP1345969	EP1345969	08/11/2010	December 2021
Valid in Austria, Belgium, Switzerland, Germany, Denmark, Spain, Finland, France, the United Kingdom, Greece, Ireland, Italy, Luxembourg, Monaco; the Netherlands, Portugal, Sweden, Turkey.					
US10/450,832	United States	US2008/0038273	US 7723482	01/18/2008	December 2021 + 1,419 days
JP2002552964	Japan	JP2004-516034	JP4066166	05/25/2010	December 2021

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

### Family 2

Family 2 This family, co-owned with INSERM, concerns a specific recombinant monovalent antibody structure, a derivative of the CD28.3 antibody.

This family is based on international application, WO2010/82136, filed on January 13, 2010, that claims the priority of a European application filed on January 14, 2009, under number EP09290029.9.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
CA2749627	Canada	CA2,749,627	CA2,749,627	05/14/2019	January 2030
US13/144,471	United States	US2011/0313135	US 9,587,023	03/07/2017	January 2030 + 949 days
JP2011-545812	Japan	JP2012-514997	JP 5755148	06/05/2015	January 2030
CA3037902	Canada	CA3037902		Pending	January 2030
US15/416513	United States	US2017166643	US 10689444	06/23/2020	January 2030

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known). Patent applications are pending review in Canada and the United States.

### Family 3

This family, co-owned with INSERM, concerns a monovalent ligand of the human CD28 receptor capable of binding to the epitope of the CD28.3 antibody.

This family is based on international application, WO2011/042891, filed on October 8, 2010, that claims the priority of a French application filed on October 9, 2009, under number FR0904866.

This family includes the following patents:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP10785516.5	EP	EP2486059	EP2486059	11/11/2015	October 2030
Valid in Belgium, Switzerland, Germany, Spain, France, the United Kingdom, Ireland, Italy and the Netherlands.					
US13/501015	United States	US2013/058933	US 8785138	07/22/2014	October 2030

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### Family 4

This family, co-owned with INSERM, concerns humanized antibodies derived from the CD28.3 antibody and their use as a drug.

This family is based on international application, WO2011/101791, filed on February 16, 2011, that claims the priority of two European applications filed on February 18, 2010, and July 13, 2010, under number EP10290080.0 and EP 10290389.5, respectively.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP11707918.6	EP	EP2536764	EP2536764	07/04/2018	February 2031
Valid in all European Patent Convention Contracting States EP					
EP18177022.3	EP	EP3428192		Pending	February 2031
CA 2,788,544	Canada	CA 2,788,544	CA 2,788,544	03/05/2019	February 2031
JP2012-553431	Japan	JP2013-519389	JP5992340	08/26/2016	February 2031
US13/577103	United States	US2013/0078236	US 8,785,604	07/22/2014	February 2031
US14/326119	United States	US20150071916	US 9,562,098	02/07/2017	February 2031 + 180 days
US15/386998	United States	US2017/114136	US10364287	07/30/2019	February 2031 + 149 days

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### Family 5

This family, in the name of OSE Immunotherapeutics, concerns a regime for the administration of humanized antibodies derived from the CD28.3 antibody.

This family is based on international application, WO2017/103003, filed on 12/15/2016 that claims the priority of two European patent applications, EP 15200281.2 and EP16306537.8.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP16822423.6	Europe	EP3390450	EP3390450	01/20/2021	December 2036
Validated in: Albania, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Monaco, the Netherlands, Norway, Poland, Portugal, Macedonia, Romania, San Marino, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Liechtenstein, Turkey, United Kingdom.					
EP21150940.1	Europe			Non-initiated review	December 2036
US16/662399	United States	US-2020-0115453-A1		Pending	December 2036
JP2018-532040	Japan	JP2018538309		Pending	December 2036
CN201680080258.4	China	CN108699148		Pending	December 2036
KR10-2018-7020218	South Korea	KR20180087428		Pending	December 2036
HK 19120836.2	Hong Kong	HK1260979		Pending	December 2036

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### 5.5.1.4 OSE-127 or EFFI-7

The portfolio of project Effi-7 covering anti-IL-7R $\alpha$  antagonist antibodies includes two patent families.

##### Family 1

This family bears on anti-IL-7R $\alpha$  antagonist antibodies of the IL7 receptor. It concerns in particular the antibody being developed.

This family is based on an international application WO2015189302 filed on June 10, 2015 that claims the priority of two applications, a provisional American application US 62/010117 filed on June 10, 2014 and a European application EP15305078.6 filed on January 23, 2015.

It includes applications pending review before 34 Patent Offices based on the PCT application, including Europe and the United States. It includes patents granted in the United States, Colombia, Mexico, Russia, Israel and Singapore.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
US15/317355	United States	US2017/0129959	US 10,428,152	10/01/2019	June 2035
NC2016/0005101	Colombia		CO34155	8/13/2018	June 2035
EP15727989.4	Europe	EP3155014		Pending	June 2035
CA 2,950,823	Canada			Pending	June 2035
JP 2017-517406	Japan	2017-522903		Pending	June 2035
KR 10-2017-7000724	South Korea			Pending	June 2035
CN 201580043066.1	China	CN106715471A		Pending	June 2035
IL 249449	Israel		IL 249449	10/01/2020	June 2035
SG11201610036P	Singapore		SG 11201610036P	10/17/2020	June 2035
MX/a/2016/016236	Mexico		376066	11/02/2020	June 2035
RU2016151265	Russia		2734076	10/12/2020	June 2035
National/regional phases entered in: Europe, United States, South Africa, Algeria, Saudi Arabia, ARIPO (African Regional Intellectual Property Organization), Australia, Brazil, Canada, Chile, China, Colombia, Republic of Korea, Costa Rica, Egypt, United Arab Emirates, Eurasia, Hong Kong, India, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, El Salvador, Singapore, Thailand, Tunisia, Ukraine, OAPI (African Intellectual Property Organization), Vietnam.					

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

##### Family 2

This family concerns humanized antibodies directed against CD127, the alpha chain of the IL-7 receptor. It concerns in particular the antibody being developed.

This family is based on an international application WO 2018/104483 filed on December 7, 2017 that claims the priority of a European application filed on December 9, 2016 under number EP16306655.8.

Direct extensions were made in several countries including Argentina, Bolivia, Paraguay, Pakistan, Taiwan, Venezuela, Lebanon and Uruguay.

It includes patents and applications pending review before 34 Patent Offices based on the PCT application, including Europe and the United States. It includes patents granted in Europe, Lebanon, Colombia and Israel.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
National/regional phases entered in: Europe, United States, South Africa, Algeria, Saudi Arabia, ARIPO (African Regional Intellectual Property Organization), Australia, Brazil, Canada, Chile, China, Colombia, Republic of Korea, Costa Rica, Egypt, United Arab Emirates, Eurasia, Hong Kong, India, Israel, Japan, Malaysia, Mexico, New Zealand, Peru, Philippines, Russia, El Salvador, Singapore, Thailand, Ukraine, OAPI (African Intellectual Property Organization), Vietnam.					
11306	Lebanon	11306	11306	03/08/2018	December 2037
US16/467284	United States			Pending	December 2037
EP17835592.1	Europe	EP3551664	EP3551664	02/17/2021	December 2037
CA3042582	Canada			Pending	December 2037
JP 2019-530803	Japan			Pending	December 2037
KR 10-2019-7019889	South Korea			Pending	December 2037
CN 201780076086.8	China	CN 110392695		Pending	December 2037
IL 266837	Israel		IL266837	10/01/2020	December 2037
NC2019/0005909	Colombia		37628	09/15/2020	December 2037

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

### 5.5.1.5 MD-707 and OSE-703 or EFFI-3

#### Family 1

This family concerns antagonist anti-IL-7R $\alpha$  antibodies of the IL7 receptor.

This family is based on international application WO2013056984 filed on October 4, 2012 that claims the priority of a European application filed on October 19, 2011 under number EP11306353.1.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2012/069670	International application	WO2013056984			
US 14/352992	United States	US2014-0308281	US 9,447,182	09/20/2016	October 2032 + 20 days
JP2017106295	Japan	JP2017184753	JP6621778	12/18/2019	October 2032
EP17200006.9	Europe	EP3299392	EP 3299392	11/18/2020	October 2032

Validated in: Germany, Spain, France, United Kingdom, Italy.

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### Family 2

This family designed for immuno-oncology concerns a non-antagonistic anti-IL-7R $\alpha$  antibody of the IL7, presenting a cytotoxic activity.

This family is based on international application WO 2017/149394 filed on February 28, 2017 that claims the priority of a provisional American application filed on February 29, 2016 under number 62/301271.

This family includes the following patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP 17716593.3	Europe	EP3423496	EP3423496	07/03/2019	February 2037
Validated in: Germany, Austria, Belgium, Bosnia and Herzegovina, Bulgaria, Cyprus (Greek part), Croatia, Denmark, Spain, Estonia, Finland, France, Greece, Hungary, Ireland, Iceland, Italy, Latvia, Lithuania, Luxembourg, Macedonia, Malta, Morocco, Moldova, Monaco, Montenegro, Norway, the Netherlands, Poland, Portugal, Romania, United Kingdom, San Marino, Serbia, Slovakia, Slovenia, Sweden, Switzerland, Czech Republic, Turkey.					
US16/080572	United States	US 2020-0308288			February 2037
CN 201780014099.2	China	CN109195987		Pending	February 2037
KR 7028377	South Korea	KR20180118746		Pending	February 2037
JP 2018-545380	Japan	JP2019-515648		Pending	February 2037
IL 261330	Israel			Pending	February 2037
AU 2017225495	Australia	AU2017225495		Pending	February 2037
BR 1120180674796	Brazil	BR112018067479		Pending	February 2037
CA 3014313	Canada	CA3014313		Pending	February 2037
IN 17030581	India	IN201817030581		Pending	February 2037
HK19123912.8	Hong Kong		HK 40000684	09/25/2020	February 2037

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

### Family 3

This family covers reagents, anti-CD127 compounds used for a T cell eff/T reg cellular sorting method.

This family is co-owned with the AP-HP and the Etablissement Français du Sang (French blood agency).

This family is based on an international application WO2019043065 filed on August 29, 2018 that claims the priority of a European application filed on August 29, 2017 under number EP17306109.4.

This family includes the following patents and patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2018/073253	International application	WO2019043065			
EP 1876,082.8	Europe	EP3676292		Pending	August 2018
US 16/643,550	USA	US-2020-0362300-A1		Pending	August 2018

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

### 5.5.1.6 BI 765063 (OSE-172) or EFFI-DEM

The portfolio relating to BI project 765063 relates to antibodies directed against SIRP $\alpha$  and their uses. It includes several patent families.

### Family 1

The first family concerns anti-SIRP $\alpha$  antibodies able to induce the differentiation of MDSC for the treatment of cancer and infectious diseases. This family also concerns more broadly the use of anti-SIRP $\alpha$  antibodies for some therapeutic indications.

This family includes an international application WO2016/063233 filed on October 21, 2015 that claims the priority of a European application filed on October 24, 2014 under number EP14190370.8

This family includes the following patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP 15794641.9	Europe	EP3209691	EP 3,209,691	07/15/2020	October 2035
Validated in Austria, Belgium, Switzerland, Germany, Denmark, Spain, France, United Kingdom, Italy, the Netherlands, Hungary, Poland, Czech Republic, Slovakia, Sweden, Turkey.					
EP 20177260.5	Europe	EP3783027		Pending	October 2035
HK 18102829.3	Hong Kong				October 2035
CA 2964203	Canada	CA 2964203		Pending	October 2035
JP 2017-520986	Japan	JP2017538669		Pending	October 2035
US 15/518803	United States	US 2017/0247464		Pending	October 2035

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

## Family 2

The second patent family concerns the use of anti-SIRP $\alpha$  antibodies capable of inhibiting the polarization of M2-type anti-inflammatory macrophages and/or promoting M1-type pro-inflammatory macrophages for the treatment of cancer.

This family also concerns the use of anti-SIRP $\alpha$  antibodies in combination with check point inhibitor compounds for some therapeutic indications (solid cancers).

This family includes an international application WO 2017/068164 filed on October 21, 2016 that claims the priority of a European application filed on October 21, 2015 under number EP15190918.1

This family includes the following patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP16785163.3	Europe	EP3365370		Pending	October 2036
US15/769.689	United States	US2018312600		Pending	October 2036
JP2018-521040	Japan	JP2018531274		Pending	October 2036

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

## Family 3

The third patent family concerns a humanized anti-SIRP $\alpha$  antibody.

This family includes an international application WO 2017/178653 filed on April 14, 2017 that claims the priority of a provisional American application US 62/322,707 and a European application EP 17305182.2.

This family includes patents and applications under review before 30 Patent Offices on the basis of the PCT application. It includes patents granted in Colombia and Nigeria.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
National/regional phases undertaken in Europe, the United States, China, Japan, Republic of Korea, Canada, Israel, Eurasia, ARIPO, United Arab Emirates, Australia, Brazil, Chile, Colombia, Egypt, Hong Kong, India, Indonesia, Malaysia, Mexico, New Zealand, Nigeria, Peru, Philippines, Thailand, Singapore, Ukraine, Vietnam, South Africa.					
EP 17718881.0	Europe	EP3443010		Pending	April 2037*
US 16/093062	United States	US 2019-0127477		Pending	April 2037*
CN 201780023581.2	China	CN109071664A		Pending	April 2037*
JP 2018-550322	Japan			Pending	April 2037*
KR 10-2018-7032968	South Korea	KR 10-2018-0134397		Pending	April 2037*
CA 3020373	Canada	CA 3020373		Pending	April 2037*
IL 262251	Israel			Pending	April 2037*

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### Family 4

The fourth patent family concerns the use of anti-SIRP $\alpha$  antibodies (including BI 765063) in particular for targeting patients designated V1 (one of the main categories of SIRP); and capable of increasing the "cross-presentation" of antigens to T cells.

This family is based on an international application WO2019/175218 filed on March 13, 2019 that claims the priority of a European application EP 18 305271.1. The theoretical expiration date of this family is March 2039.

This family includes the following patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
AU 2019233577	Australia			Pending	March 2039
BR 11 2020 017709 1	Brazil			Pending	March 2039
CA 3 091 468.	Canada			Pending	March 2039
CN 201980031527.1	China	CN11210564		Pending	March 2039
CL 2305-2020	Chile			Pending	March 2039
EA 202091859	Eurasia			Pending	March 2039
EP 19711862.3	Europe	EP3765512		Pending	March 2039
KR 10-2020-7029293	South Korea	KR20210006338		Pending	March 2039
JP 2020-546939	Japan			Pending	March 2039
MX/a/2020/009121	Mexico			Pending	March 2039
PH 1-2020-551491	Philippines			Pending	March 2039
NZ 767618	New Zealand			Pending	March 2039
US 16/979,627	United States	US2021040206		Pending	March 2039
ZA 2020/05451	South Africa			Pending	March 2039

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### Family 5

A fifth patent family concerns a bifunctional compound including, on the one hand, an anti-SIRP $\alpha$  antibody (including BI 765063), and, on the other hand, coupled with this antibody, an immune agent such as PD-1.

This family is based on an international application WO2019/073080 filed on October 15, 2018 that claims the priority of a European application EP 17,306,396.7. The theoretical expiration date of this family is October 2038.

This family includes the following patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
EP18789355.7	Europe	EP3694881		Pending	October 2038
CN201880079823.4	China	CN111511766		Pending	October 2038
JP2020-546939	Japan	JP2020536573		Pending	October 2038
US16/754,285	United States			Pending	October 2038
HK 6202025276.8	Hong Kong				

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

### 5.5.1.7 BiCKI®, a new platform of bispecific checkpoint inhibitors targeting the PD-1 receptor and other innovative targets

The new platform of bispecific fusion proteins is built around a key anti-PD-1 (OSE-279) backbone component merged with new immunotherapy targets.

A portfolio relating to this platform is being developed. Priority applications and international applications have been filed.

#### 5.5.1.7.1 OSE-279 and variants

These antibodies are PD-1 antagonists (immune checkpoint inhibitor) and are the subject of two patent families.

This family is based on an international application WO 2020/127366 filed on December 17, 2019 that claims the priority of a European application filed on December 21, 2018 under number EP 18 306801.4. The national/regional phases are to be launched in June 2021. The theoretical expiration date of this family is December 2039.

A second family, involving compounds of interest that are variants of the first family, is the subject of a second international application WO2020/127367 filed on December 17, 2019 and which claims the priority of the same European application filed on December 21, 2018 under number EP 18 306801.4. The national/regional phases are to be launched in June 2021. The theoretical expiration date of this family is December 2039.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2019/085776	International application	WO2020/127366			December 2039
RA 20190103789	Argentina				December 2039
TW 108146725	Taiwan	TW 202037608 A			December 2039

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2019/085779	International application	WO2020/127367			December 2039

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### 5.5.1.7.2 BICKI® OSE-279

This family covers the OSE-279 targeting platform for PD-1 (anti-PD-1) onto which is grafted at least one biological ligand such as another immune checkpoint inhibitor.

This family is based on an international application WO 2020/127369 filed on December 17, 2019 that claims the priority of a European application filed on December 21, 2018 under number EP 18 306799.0. The national/regional phases are to be launched in June 2021. The theoretical expiration date of this family is December 2039.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2019/085781	International application	WO2020/127369			December 2039

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### 5.5.1.7.3 BICKI IL7

The portfolio is being built with several families.

A first family relates to bifunctional composite antibodies comprising a first anti-PD1 antibody part, fused to a second interleukin 7 (IL7) part. IL7 is in native form or in mutated form with preferred IL7 mutants.

This family is based on an international application WO 2020/127377 filed on December 17, 2019 that claims the priority of a European application filed on December 21, 2018 under number EP 18 306808.9. The national/regional phases are to be launched in June 2021. The theoretical expiration date of this family is December 2039.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2019/085791	International application	WO2020/127377			December 2039
TW 108147053	Taiwan	TW 20039572 A			December 2039

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### 5.5.1.7.4 BICKI SIRP

This family covers bifunctional compound antibodies comprising a first anti-PD1 antibody part, fused to a second SIRP part, in particular SIRP-alpha and SIRP-alpha variants.

This family is based on an international application WO 2020/127373 filed on December 17, 2019 that claims the priority of a European application filed on December 21, 2018 under number EP306810.5. The national/regional phases are to be launched in June 2021. The theoretical expiration date of this family is December 2039.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2019/085785	International application	WO2020/127373			December 2039

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### 5.5.1.7.5 BICKI IL15Ra

This family covers bifunctional compound antibodies comprising a first anti-PD1 antibody part, fused to a second interleukin 15Ra (IL15Ra) part.

This family is based on an international application WO 2020/165374 filed on February 13, 2020 that claims the priority of a European application filed on February 14, 2019 under number EP 19 305184.4. The national/regional phases are to be launched in August 2021. The theoretical expiration date of this family is April 2040.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2020/053818	International application	WO 2020/165374			February 2040

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

#### 5.5.1.8 New antibodies targeting Chem R23, in particular intended for treatment of anti-inflammatory diseases.

These antibodies target the mechanism of inflammation resolution, with action on the CMKLR1 (ChemR23) receptor of myeloid cells.

A first patent family covers anti-ChemR23 antibodies.

This family is based on an international application WO2019/193029 filed on April 3, 2019 that claims the priority of a European application filed on April 3, 2018 under number EP 18 305 395.8. The theoretical expiration date of this family is April 2039.

This family includes the following patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
AU 2019247068	Australia	AU2019247068		Pending	April 2039
CN20198037 001.4	China	CN112218894 (A)		Pending	April 2039
CA 3102607	Canada	CA 3102607		Pending	April 2039
EP 19715092.3	Europe	EP3774899		Pending	April 2039
IL 277701	Israel			Pending	April 2039
IN 202017043525	India			Pending	April 2039
KR 10-2020-7031788	South Korea			Pending	April 2039
JP 2020-554298	Japan			Pending	April 2039
BR11 2020 020118 9	Brazil			Pending	April 2039
US 17/045,130	United States			Pending	April 2039

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

A second family of patents, not yet published, covers improved anti-ChemR23 antibodies.

#### 5.5.1.9 New antibodies targeting SIRP gamma.

Family 1: A first family concerns the use of antibodies directed against SIRP gamma for treatment of various diseases.

This family is based on an international application WO2018149938 filed on February 15, 2018 that claims the priority of a European application filed on February 17, 2017 under number EP 17305184.8. The theoretical expiration date of this family is April 2038.

This family includes the following patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
AU 2018221774	Australia			Pending	February 2038
BR 11 2019 016 356 5	Brazil			Pending	February 2038
CA 3051318	Canada			Pending	February 2038
CN 201880012199.6	China	CN 110300764		Pending	February 2038
EP 18707306.9	Europe	EP 3583128		Pending	February 2038
HK 62020002193.4	Hong Kong	HK 40012839		Pending	February 2038
IL 268731	Israel			Pending	February 2038
IN 201917030178	India	IN 201917030178		Pending	February 2038
JP 2019-544888	Japan	JP2020510643		Pending	February 2038
KR 10-2019-7027076	South Korea			Pending	February 2038
US 16/485.697	United States	US2019382483		Pending	February 2038

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

**Family 2:** a second family concerns the use of antibodies directed against SIRP gamma (and in particular the epitope of SIRP gamma; interaction with CD47), for the treatment of various diseases.

This family is based on an international application WO2020/039049 filed on August 22, 2019 that claims the priority of a European application filed on August 22, 2018 under number EP18 306 131.6. The theoretical expiration date of this family is April 2039.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2019/072527	International application	WO 2020/039049			August 2039
National/regional phases undertaken in: Europe, United States, Canada, Japan					

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

### 5.5.1.10 New antibodies targeting CLEC-1

These products target C-type lectin, designated CLEC-1 for treatment of various diseases.

A first family, co-held with the INSERM and the University of Nantes, covers the use of antibodies directed against CLEC-1 for the treatment of various diseases.

This family is based on an international application WO2018/073440 filed on October 20, 2017 that claims the priority of two European applications filed under numbers EP16306381.1 and EP17305988.2.

This family includes the following patent applications:

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
AU 2017345286	Australia	AU2017345286		Pending	October 2037
BR1120190079246	Brazil			Pending	October 2037
CA3039348	Canada	CA3039348		Pending	October 2037
CN 201780065072.6	China	CN 110291102		Pending	October 2037
EP 17797066.2	Europe	EP3529262		Pending	October 2037
HK 19130492.2	Hong Kong	HK40007035		Pending	October 2037
IL 266111	Israel			Pending	October 2037
IN 201917,014,926	India			Pending	October 2037
JP 2019-521034	Japan	JP2020503252		Pending	October 2037
KR 10-2019-7014209	South Korea	KR20190068605		Pending	October 2037
US 16/343,757	United States	US2019309075		Pending	October 2037

(\*) The expiration date may be extended in some countries up to five years (via supplementary protection certificates) if marketing authorizations have been obtained in the countries considered, or as part of certain procedures specific to these countries (such as "patent term extension/adjustment" in the U.S. – the additional duration is indicated when granted and known).

### 5.5.1.11 Biomarkers of anti-TNF alpha treatment

This family concerns biomarkers used to evaluate the response to therapeutic treatment with anti-TNF alpha agents.

This family is held as co-property with the Nantes CHU (University Hospital).

This family is based on an international application WO2019025624 filed on August 3, 2018 that claims the priority of a European application filed on August 3, 2017 under number EP17306039.3.

Filing no.	Country	Publication no.	Patent no.	Delivered on	Theoretical expiration date*
PCT/EP2018/071206	International application	WO2019025624			August 2038
EP 18746241.1	Europe	EP3662081		Pending	August 2038
US 16/636,162	United States	US-2020-0181706		Pending	August 2038

### 5.5.1.12 Comments

The strategy followed by OSE Immunotherapeutics concerning patents is to ensure the existence and protect the intellectual property rights that are the foundation of its drug research programs, and, as necessary, to take legal recourse against any harm to its intellectual property rights.

## 5.5.1 Brands and domain names

At the date of this Universal Registration Document, the Company has protected the trademarks "OSE PHARMA", "OSE IMMUNOTHERAPEUTICS", "MEMOPI", "TEDOPI" as well as its corporate name by registering them in France, then they were registered in countries where it was considered useful, including in the European Union (European Union brand), the United States, China or South Korea.

The names "OSE-172" and "OSE-127" (formerly named "Effi-DEM", "Effidem" and "Effi-7") were chosen by OSE Immunotherapeutics to designate its technologies. In all countries, including the European Union and the United States, and initial approval of the commercial name of a pharmaceutical product by the supervisory authorities is mandatory, and these designations may therefore be modified.

The trademark "ATALANTE" designating the phase 3 clinical trial of Tedopi® was filed in January 2016 and registered in May 2016 in France.

The trademark "OSE IMMUNOTHERAPEUTICS" was filed in February 2016 and registered in June 2016 in France.

The Chinese trademark OSE No. 22180371 was registered on April 7, 2019.

The trademarks "BiCKI", "B-Cool", "B-TIC" and "BiCKAN" were filed in May 2018 in France and the European Union and filed in September 2018 in the United States. The BiCKI, B-TIC and BiCKAN brands were registered in October 2018 in France and in the European Union.

The trademark "B-COOL" was contested in France and the European Union. In France, this trademark was registered in February 2019 only for certain services. In the European Union, this trademark was registered in December 2019 for certain products and services. In the United States, we have requested a change in the filing basis in order to produce proof of use later. Our request is under review.

In the United States, the BiCKI brand was registered on September 10, 2019. The B-TIC and BICKAN brands were registered on June 23, 2020. The Company reserved various domain names, including the following: osepharma.com, osepharma.fr, effimune.com, ose-immuno.com, oseimmunotherapy.com, oseimmunotherapy.fr, oseimmuno.com, oseimmuno.fr, ose-immuno.com and ose-immuno.fr.

## 5.6 Competitive position

### 5.6.1 Non-small cell lung cancer treatments

Despite the new treatments, five-year survival rates are around 6% for patients with a metastatic cancer (American Cancer Society, 2019).

For non-small cell lung cancer, a classification known as "TMN" is used which takes into consideration the appearance of the lung tumor, any presence of tumor cells in the Nodes and any Metastasis. Depending on the result of this classification, non-small cell lung cancers are referred to as "stage 0, Ia, Ib, IIa, IIb, IIIa, IIIb or IV", in increasing order of severity.

Small cell lung cancers are classed as being "localized" Ia to IIIa and "diffuse" IIIb or "metastatic" IV.

Current treatments vary depending on the stage and the various treatment lines:

The treatment of NSCLC-type lung cancers varies according to their type and stage of development. Histological types are most often adenocarcinomas (40.8%), squamous cell carcinomas (21.4%), large-cell carcinomas (3%) and other forms of carcinomas (20.4%) (Howlader N et al., 2013):

- . Stage I: surgery consisting of removing the part of the lung that is affected or the entire lung. If surgery is not possible, radiotherapy is given
- . Stage Ib: surgery possibly followed by chemotherapy. If surgery is not possible, radiotherapy is given
- . Stage IIa and IIb: surgery followed by chemotherapy. If surgery is not possible, radiotherapy is given
- . Stage IIIa: chemotherapy, possibly combined with surgery or radiotherapy
- . Stage IIIb: chemotherapy combined with radiotherapy, surgery is highly unlikely
- . Stage IV: chemotherapy which may be combined with other types of treatment ("targeted therapy" when a gene is expressed, for example EGFR, with a particular mutation, tyrosine kinase inhibitors act on the gene mutations observed)

Two-thirds of non-small cell bronchial cancers are diagnosed at the metastatic stage.

Three types of existing treatments are mainly used to treat bronchial cancers: surgery, radiotherapy and medical treatments (chemotherapy and targeted therapies). Immunotherapy is becoming a clinical reality with checkpoint inhibitors proving to be more effective than chemotherapy in some cancer subtypes and considered a revolutionary therapeutic breakthrough for the first time at ASCO 2015.

Generally speaking, lung cancer chemotherapy consists of intravenous infusion sessions (cures) every one to four weeks depending on the drugs used. The treatment lasts between three and four months, sometimes longer. The choice of drugs used depends on the tumor's characteristics. Chemotherapy is, therefore, the mainstay treatment for the majority of patients. Other factors to be considered when selecting treatments are general health, age and medical history. The main products are cisplatin, carboplatin, paclitaxel (Taxol®), albumin bound paclitaxel (nab-paclitaxel, Abraxane®), docetaxel (Taxotere®), gemcitabine (Gemzar®), vinorelbine (Navelbine®), irinotecan (Camptosar®), etoposide (VP-16®), vinblastine and pemetrexed (Alimta®).

Chemotherapy-related treatments include anti-angiogenic-type therapies that act on the blood vessels. Vargatef® (nintedanib, Boehringer Ingelheim) combined with chemotherapy (docetaxel) is an anti-angiogenic therapy, i.e., blocking angiokinase receptors such as the VEGF, FGF or PDGF receptors, expressed on the vessels nourishing the tumor. This product was registered at the end of November 2014 in Europe in adenocarcinoma-type NSCLC cancer after first-line therapy (EPAR - EMA). Likewise, ramucirumab, another anti-angiogenic (Cyramza®, acting on a VEGF R2 receptor, from Eli Lilly) was registered in December 2014 in lung cancer (NSCLC) after first-line therapy failed. Median survival time was improved in the group combining ramucirumab with docetaxel versus docetaxel (10.5 months vs 9.1 months); hemorrhagic-type side-effects have been described.

An important deciding factor is the search for a particular molecular anomaly for non-squamous cell carcinomas: finding out if there is a molecular anomaly on the tumor cell enables patients presenting with this anomaly to receive targeted therapy. Currently, the existence of an EGFR gene mutation (approximately 10 to 15% of the population) impacts the treatment from the first-line therapy with the option to treat with EGFR tyrosine kinase inhibitors like erlotinib (Tarceva®), gefitinib (Iressa®), afatinib (Gilotrif®), osimertinib (Tagrisso®) or dacomitinib (Vizimpro®). They inhibit an enzyme, vital to many cell membrane receptors. In addition, there is necitumumab (Portrazza®) which targets EGFR in squamous cell cancers. They are prescribed in lung cancers where the EGFR gene is mutated (EGFR+); their adverse effects include diarrhea and skin disorders.

Another targeted therapy is indicated in the event of the molecular rearrangement of the ALK gene (approximately 4% of the population) which enables treatment with a product acting on ALK from second-line therapy onwards. As a result, crizotinib (Xalkori® Pfizer), ceritinib (Zykadia® Novartis), alectinib (Alecensa®), brigatinib (Alunbrig®) and lorlatinib (Lorbrena®) were registered. In addition, Zykadia® was approved for patients with an ALK gene mutation after treatment with Xalkori® has failed, in the United States and Europe, in May 2015. In practice, this targeted therapeutic approach only affects the minority of patients with identified mutations, often those with little exposure to smoking, and the treatment frequently fails.

At the diffuse or metastatic stage, platinum-based first line therapies are administered: this is called platinum-based combination chemotherapy. Those who respond or who have a stable disease may receive a first-line maintenance therapy such as, for example, pemetrexed for particular non-squamous cell histological-type cancers and docetaxel for other patients.

Keytruda® was the first checkpoint inhibitor registered as a first-line therapy after its superiority over chemotherapy was established for patients strongly expressing the PD-L1 marker (with approximately 25% of NSCLC patients at the invasive or metastatic stage expressing the PD-L1 marker at > 50% at tumor level). It was also registered as a first-line therapy in combination with chemotherapy for all patient types, irrespective of their PD-L1 marker level. In 2020, it was registered in combination with Opdivo® as a first-line therapy in metastatic NSCLC with PD-L1 expression ≥ 1%.

The Yervoy® + Opdivo® combination was registered in 2020 as a first-line therapy for NSCLC whose PD-L1 expression is ≥ 1%.

Tecentriq® has now been registered as a first-line therapy, in combination with Avastin® and chemotherapy. In 2020, it obtained registration as a first-line therapy for metastatic NSCLC in patients with high PD-L1 expression (TC ≥ 50% or CI ≥ 10%), without tumor aberration of the AGFR or ALK gene.

A second-line therapy will be offered in the event of intolerance or progression of the disease (if no EGFR or ALK-type mutation or molecular anomaly can be accessed by a targeted therapy).

## 5.6.2 Existing second-line therapies for advanced lung cancer and choice of comparator for phase 3

Treatments registered as second-line therapies (after a first-line treatment fails) are checkpoint inhibitors of the pembrolizumab and nivolumab type, docetaxel and pemetrexed, two chemotherapies (erlotinib, a targeted therapy for patients with a particular mutation). The median survival rate is between five and eight months for chemotherapy and the one-year survival rate is 33% (Hanna N 2004; Shepherd FA 2005; Ciuleanu T 2012; Garassino TM 2013). Docetaxel and pemetrexed are considered to be benchmark second-line therapies and are used as third-line treatments if checkpoint inhibitors have failed. They were the comparators used in the phase 3 trial of Tedopi®.

Four checkpoint inhibitor-type treatments producing a non-specific activation of cytotoxic T lymphocytes by releasing the brakes of immunity are now registered as second-line therapies: nivolumab (Opdivo® BMS) registered in squamous cell cancers and non-squamous cell cancers in progression as a second-line therapy, pembrolizumab (Keytruda® Merck) registered as a second-line therapy in patients expressing the PD-1 ligand known as PD-L1 (approximately 20% of patients

expressing the PD-L1 marker) whatever the histology, atezolizumab (Tecentriq®) registered in squamous cell and non-squamous cell cancers in patients expressing PD-L1 and durvalumab (Imfinzi®) registered as a second-line therapy in inoperable tumors in patients whose cancer has progressed after chemotherapy and radiotherapy, targeting the PD-1/PD-L1 signaling pathway. The survival rate for these new checkpoint inhibitor therapies acting on the PD-1/PD-L1 axis is three to four months longer than with chemotherapy and this survival rate is observed as a median between nine and thirteen months for the four checkpoint inhibitor therapies.

More recently, checkpoint inhibitors were compared with chemotherapy. Opdivo® (nivolumab, registered in 2015 as a second-line therapy for squamous cell NSCLC cancers), obtained a median survival rate of nine months (versus a median rate of six months for docetaxel in this sub-group of patients with a particular histology). In 2019, an analysis, presented to the AACR (American Association for Cancer Research) conference, on pooled data from four trials showed that 14% of patients treated with Opdivo® were still alive after four years. Data from two Phase 3 clinical trials showed an overall survival rate of 14% in patients treated with Opdivo® versus 5% in patients treated with docetaxel (abstract CT195: Long-term survival outcomes with Nivolumab (NIVO) in pts with previously treated advanced non-small cell lung cancer (NSCLC): Impact of early disease control and response; Julie Brahmer et al., DOI : 10.1158/1538-7445.AM2019-CT195 Published July 2019).

The other inhibitory checkpoints recorded since 2015 also published a median survival rate of around 9 to 13 months in patients with squamous or non-squamous cell cancer as a second line therapy (Nivolumab: Brahmer J. et al. NEJM 2015; Paz-Ares L. et al., J Clin Oncol 33, 2015 ; atezolizumab : Spira A et al., J Clin Oncol 33, 2015 - abs 801.0; Keytruda®, pembrolizumab: Garon et al. NEJM 2016 in PD-L1 positive patients in second line NSCLC). Tecentriq® (atezolizumab), within the context of the annual European Society of Medical Oncology conference (ESMO 2016) showed that median survival of patients under atezolizumab was 13.8 months, i.e., 4.2 months longer than patients receiving chemotherapy with docetaxel (overall survival rate of 13.8 months versus 9.6 months) irrespective of their PD-L1 marker expression rates.

(At Rittmeyer et al., the Lancet 2016; Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomized controlled trial).

Third-line treatments are offered but are essentially palliative.

In short, there is still a great need for active and well-tolerated treatments for advanced-stage NSCLC cancers, in particular, after checkpoint inhibitors have failed.

## COMPETITION AND IMMUNO-ONCOLOGY PRODUCTS

In the field of antigen-specific immunotherapy targeting tumor antigens, therapy targeting a single tumor antigen through a mainly humoral response did not prove efficacy in phase 3. This relates to a MAGE-A3 long peptide (developed by GSK). Previously, in phase 2, the humoral (antibody) response observed for this recombinant peptide (called Antigen-Specific Cancer Immunotherapeutic: ASCI) had a majority and did not correlate with the clinical outcome sought in terms of the recurrence of the cancer (Vansteenkiste J et al., 2013). This MAGE-A3 long peptide was administered immediately after a tumor resection (surgery) in early stage cancer (in patients with a high level of MAGE-A3 proteins). The product did not prove to have any preventive effect on relapse or recurrence of this cancer (phase 3 trial-MAGRIT).

Since 2014, there has been a great deal of renewed interest in the field of immunotherapy with a number of products proving to have compelling results in lung and other cancers:

These include belagenpumatumucel-L (Lucanix® developed by the biotechnology company NovaRx) which is a product made from modified tumor cells prompting a cytotoxic T-cell response. The main survival rate measurement criterion in a phase 3 trial was not, however, met in 532 stage III and IV NSCLC patients. In a predefined group of 305 patients (enrolled in the trial within 12 weeks of first-line chemotherapy) a survival rate of 20.7 months was observed versus 13.4 months in the control group ( $p = 0.08$ ) (G Giaccone, ESMO 2013).

Tecemotide (developed by the biotech company Oncothyreon in conjunction with Merck KGaA) is a 25-amino acid peptide from a single tumor antigen called MUC-1 in a liposomal formulation to stimulate a T-cell response against MUC. In stage III NSCLC patients, there proved to be no survival benefit in the overall population (25.6 months versus 22.3 months). In a predefined group (65% or 806 patients) receiving combined chemotherapy and radiotherapy at the same time, the median survival rate was greatly improved with 30.8 months versus 20.6 months for the control group ( $p=0.016$ ) (Butts CA et al. ASCO 2013). Merck KGaA stopped developing the product in September 2014.

The first immune activation product, Provenge®, to have entered the market in this field is a cell therapy product to combat prostate cancer which was licensed in the United States in 2010 (Provenge® or sipuleucel-T, developed by the US company Dendreon, since acquired by the pharmaceutical company Valeant).

The first cancer immunotherapy products registered were checkpoint inhibitors acting on T cells (Opdivo® BMS, Keytruda® Merck, Tecentriq® Roche, Yervoy® BMS, Bavencio® Merck Serono/Pfizer, Imfinzi® AstraZeneca), and a therapeutic vaccine, Provenge®.

Checkpoint inhibitors, producing non-specific cytotoxic T lymphocytes by effectively releasing the brakes of immunity, demonstrated clinical activity in lung cancer.

**Opdivo®** (nivolumab, monoclonal antibody, anti-PD-1 checkpoint inhibitor from BMS)/First marketing authorization: December 2014 (metastatic melanoma). Since then, Opdivo® has been registered in non-small cell lung cancer (NSCLC), small cell lung cancer, pleural mesothelioma, renal cancer, Hodgkin's lymphoma, head and neck Cancer, urothelial carcinoma, metastatic MSH-H or dMMR colorectal cancer, hepatocellular carcinoma and oesophageal squamous cell carcinoma.

**Keytruda®** (pembrolizumab, monoclonal antibody, anti-PD-1 checkpoint inhibitor from Merck MSD)/First marketing authorization: in 2011 in metastatic melanoma. Since then, Keytruda® has also been registered in non-small cell lung cancer (NSCLC) and small cell lung cancer, head and neck cancer, Hodgkin's lymphoma, large B-cell lymphoma, bladder cancer, advanced colorectal cancer with Microsatellite Instability-High (MSI-H) or Mismatch Repair— Deficient (dMMR), stomach cancer, oesophageal cancer, cervical cancer, hepatocellular carcinoma, Merkel cell carcinoma, kidney cancer, endometrial cancer, advanced renal cancer, squamous cell carcinoma and triple negative breast cancer.

After registration in 2015 as a 2nd-line therapy for patients suffering from metastatic non-small cell lung cancer (NSCLC) with a PD-1 biomarker expression, in October 2016, Keytruda® was registered in 1st-line therapy in NSCLC for patients expressing the PD-1 marker (PD-L1 expression over 50% at tumor level). In May 2017, Keytruda® obtained its conditional registration in 1st-line therapy (in combination with pemetrexed and carboplatin) in NSCLC, whatever the PD-L1 expression. In August 2018, Keytruda® was registered in 1st-line therapy (in combination with pemetrexed and platinum-based chemotherapy) in metastatic non-epithelial NSCLC without tumor-genomic aberration of the EGFR or ALK gene. In October of the same year, it was registered in 1st-line therapy (in combination with carboplatin and paclitaxel) in NSCLC, whatever the PD-L1 expression. In April 2019, the product was registered as a first-line monotherapy for stage III NSCLC (PD-L1 factor expressed at > 1% at the tumor level) and in 2020, it was registered in combination with Opdivo® as a first-line therapy in metastatic NSCLC with PD-L1 expression ≥ 1%.

**Tecentriq®** (atezolizumab, anti-PD-L1 checkpoint inhibitor from Roche)/First marketing authorization: in May 2016 in urothelial bladder cancer, with a companion test to identify PD-L1 positive patients (Ventana PD-L1-SO 142 trial). Then in October 2016, Tecentriq® was registered in the treatment of lung cancer as a second-line therapy for patients suffering from metastatic non-small cell lung cancer (NSCLC) whose disease has progressed during, or after, platinum-based chemotherapy and during an appropriate targeted treatment in the presence of a tumor with EGFR or ALK gene mutation. In December 2018, Tecentriq® obtained its registration in first-line therapy for non-epithelial metastatic NSCLC in combination with Avastin® and chemotherapy. In March 2019, the product was registered in metastatic triple negative breast cancer and in 1st-line therapy of small cell lung cancer. In 2020, it obtained registration as a first-line therapy line for metastatic non-small cell lung cancer in patients with high PD-L1 expression (TC ≥ 50% or CI ≥ 10%), without tumor aberration of the AGFR or ALK gene.

**Yervoy®** (ipilimumab, monoclonal antibody targeting CTLA-4, from BMS)

First marketing authorization in 2011 in melanoma. In 2018, the product was registered in combination with nivolumab (Opdivo®) in metastatic colorectal cancer and in first-line treatment of renal cancer. In 2020, in combination with Nivolumab, Yervoy® was registered in hepatocellular carcinoma (after failure with sorafenib), in metastatic non-small cell lung cancer as a first-line therapy whose PD-L1 expression ≥ 1% and as the first immunotherapy treatment in untreated, unresectable malignant pleural mesothelioma.

**Bavencio®** (avelumab, monoclonal antibody targeting anti-PD-L1, from Merck Darmstadt or EMD Serono in collaboration with Pfizer-Javelin program): this antibody is an IgG1, a cytotoxic antibody. Two registrations were obtained in 2017: in Merkel cell carcinoma (an aggressive skin tumor) and in bladder cancer or urothelial carcinoma. It is also registered in advanced renal cancer, in combination with Inlyta® (axitinib), and as a first-line maintenance therapy in locally advanced metastatic urothelial cancer.

**Imfinzi®** (durvalumab, humanized monoclonal antibody targeting the PD-L1 ligand, checkpoint inhibitor MEDI 4736d)

First marketing authorization in 2017 in bladder cancer or urothelial carcinoma. Then, in 2018, registration in inoperable non-small cell lung cancer (NSCLC) in patients who have not progressed after chemo or radiotherapy. In 2020 it received registration for non-small cell lung cancer at an extended stage.

Drug	Target	Indication	Registration
Opdivo® (nivolumab, BMS) Monoclonal antibody	PD-1	Advanced melanoma	2014
		Metastatic squamous cell and non-squamous cell non-small cell lung cancer (NSCLC) (with particular histology representing around 25% of NSCLCs).	2015
		Metastatic renal cancer after anti-angiogenic treatment failure	2015
		Recurrence of Hodgkin's lymphoma after a bone marrow transplant	2016
		Relapsing or metastatic head or neck cancer	2016
		Metastatic or locally advanced bladder cancer	2017
		Metastatic colorectal cancer (MSI-H or dMMR) in progression after treatment with fluoropyrimidine, oxaliplatin and irinotecan	2017
		Hepatocellular carcinoma (liver cancer) following treatment with sorafenib	2017
		Non-small cell lung cancer  In combination with ipilimumab (Yervoy®): Metastatic colorectal cancer and renal cancer first-line therapy	2018
		In combination with ipilimumab (Yervoy®): Advanced esophageal squamous cell carcinoma and metastatic non-small cell lung cancer first-line therapy for which PD-L1 expression is ≥ 1%	2020
		In combination with Cabometyx® (carbozantinib): advanced renal cancer first-line therapy	2021
Keytruda® (pembrolizumab, Merck & Co.Inc.) Monoclonal antibody	PD-1	Advanced or inoperable melanoma	2014
		Advanced non-small cell lung cancer (NSCLC)	2015
		Relapsing or metastatic squamous cell head and neck cancer	2016
		Non-small cell lung cancer (NSCLC) in first-line therapy in patients expressing a high level of the PD-1 marker (PD-1 expression over 50% at tumor level)	2017
		Hodgkin lymphoma	2017
		Metastatic non-small cell lung cancer (NSCLC) in first-line therapy, in combination with pemetrexed and carboplatin, whatever the PD-L1 expression — conditional registration	2017
		Metastatic or locally advanced bladder cancer (urothelial carcinoma)	2017
		Metastatic or relapsing gastro esophageal junction cancer/stomach cancer	2017

		Metastatic, non-epithelial non-small cell lung cancer (NSCLC)	2018
		Metastatic non-small cell lung cancer (NSCLC) in first-line therapy, in combination with pemetrexed and carboplatin, whatever the PD-L1 expression	2018
		Relapsing or metastatic cervical cancer	2018
		Diffuse large B-cell lymphoma	2018
		Hepatocellular carcinoma (liver cancer) after failed treatment with sorafenib	2018
		Merkel cell carcinoma (an aggressive skin tumor)	2018
		Advanced renal cancer in combination with axitinib, in first-line therapy	2018
		Non-small cell lung cancer (NSCLC) in Stage III monotherapy (PD-L1 proportion expressed at over 1% at the tumor level)	2019
		Metastatic or locally advanced epithelial esophageal cancer	2019
		Endometrial cancer, in combination with lenvatinib	2019
		Non-muscle-invasive, high-risk bladder cancer that does not respond to BCG	2020
		Squamous cutaneous carcinoma (cSCC) not eligible for surgery or radiotherapy, relapsed or metastatic	2020
		MSI-H or dMMR colorectal cancer, unresectable or metastatic, as first-line therapy	2020
		Relapsed Classic Hodgkin's lymphoma (cHL)	2020
		Metastatic triple negative breast cancer in combination with chemotherapy (PD-L1 expressing tumor)	2020
Tecentriq® (atezolizumab, Roche) Monoclonal antibody	PD-L1	Bladder cancer (urothelial carcinoma)	2016
		Metastatic non-small cell lung cancer (NSCLC) following progression during, or after, platinum-based chemotherapy and during an appropriate targeted treatment in the event of a tumor with EGFR or ALK gene mutation	2017
		Metastatic, non-epithelial non-small cell lung cancer (NSCLC), in combination with Avastin® and chemotherapy	2018
		Metastatic triple negative breast cancer	2019
		Small cell lung cancer, in first-line therapy	2019
		First-line therapy for metastatic non-small cell lung cancer in patients with high PD-L1 expression (TC ≥ 50% or CI ≥ 10%), without tumor aberration of the AGFR or ALK gene.	2020
		Hepatocellular carcinoma in combination with Avastin	2020
		Advanced melanoma, in combination with Cotellic and Zelboraf	2020
Imfinzi® (durvalumab, MedImmune-AstraZeneca)	PD-L1	Metastatic bladder cancer	2017

		Unresectable non-small cell lung cancer (in patients whose cancer has not progressed after chemo and radiotherapy)	2018
		Extended-stage small cell lung cancer (in the US)	2020
Bavencio® (avelumab, Merck Serono)	PD-L1	Merkel cell carcinoma (an aggressive skin tumor) Bladder cancer (urothelial carcinoma)	2017
		Advanced kidney cancer, in combination with Inlyta® (axitinib)	2019
		Locally advanced metastatic urothelial cancer as first-line maintenance treatment line	2020
Yervoy® (ipilimumab, BMS)  Monoclonal antibody	CTLA-4	Advanced stage melanoma	2011
		Metastatic colorectal cancer and renal cancer first-line therapy (in combination with nivolumab)	2018
		Hepatocellular carcinoma in combination with Nivolumab after treatment with sorafenib	2020
		Metastatic non-small cell lung cancer first-line treatment whose PD-L1 expression is ≥ 1% in combination with Nivolumab	2020
		First immunotherapy treatment in untreated, unresectable malignant pleural mesothelioma in combination with Nivolumab	2020

Products that can help the immune system to develop a specific T response with an immunological memory may have a long-term effect on tumors. Tumor heterogeneity, the possible loss of expression of a tumor antigen and the variability of the human T-cell repertoire suggest greater efficacy based on a large induction of cytotoxic T specificities, which can be obtained with a cytotoxic T immunotherapy targeting several tumor antigens. Despite the heterogeneity of lung cancer vaccine trials, a meta-analysis conducted in 2016 concluded that there was a positive effect on survival and progression-free time (Dammeijer F. et al.; JCO 2016 Efficacy of Tumor Vaccines and Cellular Immunotherapies in Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis).

Tedopi®, in Phase 3 clinical trial in NSCLC, is positioned in specific cytotoxic T-cell immunotherapy, after progression of the tumor under PD-1 or PD-L1 checkpoint inhibitor, in patients at inoperable invasive stage IIIB or at metastatic stage IV.

Step 1 of Tedopi® Phase 3 study in NSCLC showed positive results and the primary endpoint was met: a 12-month survival rate in patients treated by Tedopi® and a 10% absolute difference in this survival rate in comparison with chemotherapy.

These results confirm the value and therapeutic interest of Tedopi® in a population of patients suffering from advanced lung cancer after failure of a checkpoint inhibitor treatment for which there is no confirmed treatment to date and which is awaiting new therapeutic options. The Company is continuing to collect additional clinical data and analyze all the results to identify and confirm a sub-group of patients of interest. Today, the Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from health authorities, the Company will try to obtain a marketing authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.

#### **THERAPEUTIC COMBINATIONS WITH CHECKPOINT INHIBITORS ARE CURRENTLY THE SUBJECT OF WIDE-RANGING STUDIES.**

##### **Immuno-oncology products under development according to their mechanisms of action**

###### **Immune defences against cancer**

When the immune system recognizes tumor cells as foreign bodies, it triggers an immune response involving a series of cells (lymphocytes and antigen-presenting dendritic cells) and specialized proteins (antibodies, cytokines). The coordinated action of these different elements should end in the destruction of the tumor cells, and this is what happens in cancer immuno-surveillance.

This response is characterized by two levels of defence: the first level is non-specific; it is innate immunity; the second level is called specific or adaptive immunity. This defence system can be overridden. In fact, some tumor cells present few characteristics that betray their true nature; they are neither recognized, nor attacked by the immune system. They present tumor antigens, but these are also present on other healthy organs and the immune reaction will not be triggered against these "self"-antigens. They will not be recognized as being alien. Other tumor cells may also use strategies to escape detection, for example, by multiplying very rapidly and overwhelming the immune system's reaction capacity. Oncogenes (tumor genes) are expressed at the surface of the tumor by tumor antigens (macromolecules or proteins). They themselves can directly inhibit the normal functioning of the immune system by deregulating it, thereby blocking immuno-surveillance.

### **NON-SPECIFIC IMMUNOTHERAPY: NON-SPECIFIC T-CELL ACTION CHECKPOINT INHIBITORS**

Immune checkpoints regulate the breadth of the T-lymphocyte response and are key to avoiding auto-immunity. However, they also limit the robustness and duration of the anti-tumor immune responses. The molecules that play a role in regulating these checkpoints are currently in clinical development in many cancers. They include molecules regulating T-cell activity: CTLA-4, PD-1/ PD-L1, TIM 3 and LAG-3. These molecules can be blocked by monoclonal antibodies (MAb) which are capable of releasing the brakes on these molecules from T lymphocytes, not only preventing them from attacking tumors, but also from attacking other self-cells. Since 2011, this non-specific approach has led to a number of checkpoint inhibitors being marketed (see "Competition and immuno-oncology products" table).

### **THERAPEUTIC COMBINATIONS WITH CHECKPOINT INHIBITORS**

The research has moved into a completely new phase with the search for better combinations for each patient that are more efficient and less toxic. The combination of a specific T-cell therapy and a non-specific therapy is logical and holds great therapeutic promise. These combinations are very interesting. (Pardoll D, Nature Reviews Drug Discovery, 12, 489-492, 2013).

Other treatments targeting cells in the tumor micro-environment or new, second-generation checkpoint inhibitors are expected in this field as a result of interesting tumor responses observed in 20% of patients on average in patients at the metastatic stage. Time without progression and survival rate are observed, but still over a limited period, when these products are used on their own. Auto-immune reactions are observed for around 10% of patients treated. Primary or secondary resistance was described for these products used alone. All these reasons encouraged researchers and clinicians to explore new therapeutic combinations.

Keytruda® (Merck & Co) a checkpoint inhibitor acting on PD-1, registered in melanoma, advanced lung cancer (second- and first-line therapy in combination with pemetrexed and carboplatin), metastatic lung cancer (in first-line therapy in combination with pemetrexed and carboplatin, whatever the PD-L1 expression), as first-line treatment in metastatic non-small cell lung cancer whose PD-1 expression is ≥ 1% (in combination with Opdivo®), bladder cancer (urothelial carcinoma), squamous cell head and neck cancer, and gastroesophageal junction/stomach cancer, Hodgkin's Lymphoma, large B cell lymphoma, uterine cancer, hepatocellular carcinoma, Merkel cell carcinoma, renal cancer, endometrial cancer, advanced renal cancer, squamous skin carcinoma and triple negative breast cancer.

It is associated in clinical development, for example, with many other therapies such as:

Ramucirumab, an Anti-VEGF-2 monoclonal antibody (MAb) studied in multiple tumors (Eli Lilly); Epacadostat IDO1 inhibitor, in solid tumors of the NSCLC type (Incyte) with negative results in 2018; MK-4166, Anti-GITR MAb in solid tumors (Merck); Ipilimumab, Anti-CTLA4 Mab in many cancers (BMS).

Opdivo® (Bristol-Myers Squibb), a checkpoint inhibitor acting on PD-1 recorded in melanoma, lung cancer (squamous cell cancer), metastatic kidney cancer, recurrent or metastatic head and neck cancer, relapsed Hodgkin's Lymphoma to a bone marrow transplant, metastatic bladder cancer, metastatic colorectal cancer and hepatocellular carcinoma, small cell lung cancer, squamous oesophageal carcinoma. It is associated in clinical development, for example, with many other therapies such as:

ALT-803 IL-15 superagonist/ IL-15R $\alpha$ -Fc, fusion protein in NSCLC lung cancer (Altimmune); Urelumab Anti-CD137 MAb in solid tumors; Ipilimumab Anti-CTLA-4 MAb in many cancers (Bristol-Myers Squibb; Lirilumab Anti-KIR MAb in multiple myeloma, lymphoma and solid tumors (Bristol-Myers Squibb/ Innate); Epacadostat IDO1 inhibitor in multiple tumors (Incyte).

#### **THERE ARE ALSO NUMEROUS CLINICAL COMBINATIONS OF CHECKPOINTS WITH THERAPEUTIC VACCINES**

**Keytruda®** — Merck & Co (PD-1 MAb) was studied in combination, notably:

with ADXS-PSA, a therapeutic vaccine against cancer targeting a prostate tumor antigen (PSA), in resistant prostate cancer (Adaxis); (*phase 1/2 results in 2020: overall median survival rate of 16.4 months with ADXS-PSA versus 11 months with standard treatment*); with G100, a therapeutic vaccine in non-Hodgkin's lymphoma (Immune Design); with BCG in bladder cancer (Merck); with a viral vaccine expressing p53, MVA, a vaccine virus expressing this target for solid tumors (NIH).

**Opdivo®** — Bristol-Myers Squibb (PD-1 MAb) was studied in combination, notably:

with Viagenpumatumcel, a cell-based therapeutic vaccine (Heat Biologics) in non-small cell lung cancer; with ISA101, a therapeutic vaccine against the HPV virus in solid tumors (ISA Pharmaceuticals); with GVAX, a therapeutic vaccine against pancreatic cancer (Pancreatic cancer Sidney Kimmel Cancer Center).

#### **SPECIFIC IMMUNOTHERAPY: COOPERATION BETWEEN CELLS IS NECESSARY**

The response may be humoral (antibodies) or cellular (cytotoxic T).

The adaptive immunity acquired is specific and endowed with memory. This specific characteristic is the result of an activation process, during which certain lymphocytes learn to recognize tumor antigens via their epitopes.

T lymphocytes ensure a specific cellular response. Cooperation between lymphocytes is necessary to trigger an immune response. A distinction is made between T8 lymphocytes (identified by a T-CD8 marker), activated into cytotoxic lymphocytes which will directly attack tumor cells, and T4 cells (T-CD4 marker); auxiliary T lymphocytes mainly function to stimulate/regulate the immune response. Initially naive (i.e., not informed), these cells are educated by antigen-presenting cells which teach them to specifically recognize tumor antigens.

Cancer immunotherapy aims, therefore, to trigger or stimulate the body's own immune system to fight the disease. This type of immunotherapy combines B-cell antigen stimulation or T-cell antigen stimulation approaches. They involve a single antigen or a group of particular antigens, designed to activate the patient's immune system so that it recognizes and kills cells carrying the same antigen. The immunocompetence of a lymphocyte is dependent on the synthesis of a membrane receptor specifically capable of recognizing an epitope: the BCR receptor for B cells (this receptor is a membrane-bound immunoglobulin molecule), with the TCR receptor acting as an epitope recognition site for T cells. Unlike the B-lymphocyte receptor, the T-lymphocyte receptor only recognizes protein antigens which have been divided into epitopes. Proteins must be divided into peptides or epitopes which are then combined with MHC or major histocompatibility complex molecules. Cytotoxic cells recognize the antigen presented by an MHC class I molecule. The antigens presented are endogenous antigens produced by the cell.

Recognition is the first activation signal. A second co-stimulation signal permits the expression of the lymphocyte's cytotoxic power.

The therapeutic action of a specific immunotherapy is not direct. The product does not kill the tumor cell directly but activates the patient's immune system to recognize and kill the target cell. Adjuvants combine to generate an inflammatory reaction at the injection point and activate antigen-presenting cells leading to recognition of targeted antigens. Then, co-stimulation signals on the surface of antigen-presenting cells will be necessary to activate T lymphocytes.

#### **IMMUNOTHERAPY TARGETING INNATE IMMUNITY IN CANCER**

Anti-KIR antibodies (Lirilumab, IPH2102/BMS-986015, Innate pharma) block the interaction of NK-cell inhibitor receptors, thus activating these "Natural Killer" cells that are part of innate immunity. Anti-KIR lirilumab was tested in a phase 2 trial with checkpoint inhibitors from BMS, namely Yervoy® and Opdivo®. These two molecules are antibodies directed against checkpoints (activation brakes). They activate cytotoxic T cells in a non-specific way by releasing the brakes of their activation.

## ANTIGEN-SPECIFIC CANCER IMMUNOTHERAPIES

ASCI — antigen specific cancer immunotherapies

These antigen immunotherapies most often target a single tumor antigen such as, for example, MUC 1 or MAGE-3 or TERT.

They use a natural or recombinant macromolecule. They induce a cytotoxic T-cell response or a humoral B-cell response, producing antibodies against the tumor antigen.

They require the tumor antigen to have a detection threshold with definable detection limits.

## TARGETED THERAPIES

This therapeutic approach is very different from immunotherapy since these targeted therapies directly target tumor cells expressing a specific mutation.

Registered products are as follows:

Tyrosine Kinases inhibitors, TKIs, targeting a mutation on the cancerous cell like EGFR (EGFR+) accounting for around 10% of NSCLC patients. The products are erlotinib (Tarceva®) and gefitinib (Iressa®). More recently (2018), afatinib (Giotrif®, Gilotrif®) was registered in Europe and in the United States for EGFR+ patients as first-line therapy.

In addition, ALK protein mutations corresponding to 3% to 5% of NSCLC patients have been targeted with crizotinib (Xalkori®). These EGFR or ALK mutations are mutually exclusive. Ceritinib (LDH 378 Zykadia® Novartis) acts on patients who became resistant to crizotinib and was registered in 2014 for patients with ALK mutations (Shaw, AT et al. Ceritinib in ALK-rearranged non-small-cell lung cancer; NEJM; March 27, 2014) and it was also registered in Europe in May 2015 for the same indication (patients who escaped Ceritinib and presented an ALK mutation). These targeted therapies frequently encounter resistance or new mutations after a few months of treatment (six to seven months) resulting in the failure of the treatment.

The range of therapeutic combinations is also logical in light of the failures and acquired resistances and is being considerably expanded to include combinations of targeted therapies and immunotherapies, with clinicians seeking optimal therapeutic combinations.

Conclusion: Immunotherapy is currently center stage at US and European international oncology conferences and T-cell checkpoint inhibitors are now registered in several different cancers. Checkpoint inhibitor outcomes demonstrated a high level of effectiveness compared with chemotherapy in patients with advanced non-small cell lung cancer. Immunotherapies which are already indicated in lung cancer and melanoma seem to be just as effective in other types of cancer with cross-cutting action in different types of cancers. These treatments are not effective for all patients. The clinicians in question need to better identify patients likely to respond and better understand future combinations and the reasons for the failure of, or primary resistance to, these treatments.

## 5.6.3 Autoimmunity and Inflammation

### 5.6.3.1 Targeted pathologies and treatments for autoimmune diseases

#### AUTOIMMUNE DISEASES

Autoimmune diseases are diseases in which the lesions observed are due to the activation of an immune response against part of the body.

Tolerance is a state of non-immune response to an antigen, specific to that antigen. It is an active phenomenon, caused by a prior contact with the antigen. Normally, an organism is tolerant of its own parts: it is self-tolerant or auto-tolerant. This latter involves T lymphocytes and, to a lesser degree, B lymphocytes.

Autoimmune diseases can be schematically divided into organ- or tissue-specific autoimmune diseases (such as autoimmune thyroiditis, myasthenia, pemphigus, etc.) and non-organ-specific autoimmune diseases also called systemic diseases (ASSIM D. Bernard, Marseille, autoimmune pathologies). Autoimmune diseases are of multifactorial origin (genetic, endocrinological and environmental factors).

Sexual hormones have an important role in the appearance of autoimmune diseases. This has been demonstrated in animal and human experimental models. The number of women affected is significantly greater. Genetic factors associated with autoimmune diseases initially concerned certain markers of major histocompatibility complex (MHC). For example, the DR1 and DR4 alleles are risk factors for rheumatoid arthritis, but in view of the number of genes involved, these are polygenic diseases.

The frequency of autoimmune diseases, even if some are very rare, makes this group of diseases a public health problem, the same as cardiovascular or cancerous diseases since these are chronic pathologies affecting young people with long treatment. Better understanding of their physiopathology allows considerable therapeutic progress of the most serious of them.

**Table 1—Main Autoimmune Diseases**

<b>Non-organ-specific autoimmune diseases</b>	
-	Systemic lupus erythematosus
<b>Organ-specific autoimmune diseases</b>	
<b>Endocrine glands</b>	
-	Thyroiditis: Hashimoto's disease and Basedow's disease
-	Addison's disease
-	Insulin-dependent diabetes
-	Polyendocrinopathies
<b>Gastrointestinal tract</b>	
-	Biermer's disease
-	Celiac disease
<b>Kidney</b>	
-	Goodpasture syndrome
<b>Muscles and Nerves</b>	
-	Myasthenia
-	Polyneuropathies
-	Guillain-Barré syndrome
-	Multiple sclerosis
<b>Eyes</b>	
-	Uveitis
-	Sympathetic ophthalmia
<b>Skin</b>	
-	Pemphigus, bullous pemphigoid, alopecia, vitiligo
<b>Liver</b>	

- 
- Autoimmune hepatitis
  - Primary biliary cirrhosis
- 

*According to D. Bernard, Marseille, autoimmune pathologies*

## EPIDEMIOLOGY

The epidemiology of autoimmune diseases shows great variations in frequency: autoimmune thyroid diseases are extremely frequent.

The prevalence of autoimmune diseases is greater among women, who are affected five to ten times more often than men.

Rheumatoid arthritis, Gougerot-Sjögren's syndrome and autoimmune diabetes (type 1, insulin dependent) are frequent systemic diseases. Their respective prevalence is from 1,000 to 4,000 patients affected per 100,000 inhabitants, 100 to 500 cases per 100,000 inhabitants and 200 to 300 per 100,000 inhabitants. The prevalence of celiac disease would be from 100 to 200 per 100,000 inhabitants. Systemic lupus erythematosus, scleroderma and dermatopolymyositis are much rarer diseases with respective prevalence of 15 to 50 per 100,000 inhabitants, 20 per 100,000 inhabitants and 5 to 10 cases per 100,000 inhabitants. In total, better diagnostic effectiveness, an increase in the life span of populations and a reduction of mortality for the most severe autoimmune diseases through better therapy give this group of pathologies an overall prevalence of 5% to 10%.

## CLINICAL EXAMPLES OF AUTOIMMUNE DISEASES

### Rheumatoid arthritis

Rheumatoid arthritis is a chronic inflammatory rheumatism, i.e., a disease of the joints manifested by persistent inflammation. The disease progresses by inflammatory flareups of variable duration and intensity and progressively spreads to new joints. It causes swelling and pain, in particular in the hands, wrists and knees. In the beginning, it is evidenced by nocturnal pain, especially in the second part of the night, and by morning stiffness. Fever and fatigue are also frequent symptoms. Then, in 20% to 30% of cases, the inflammation causes the progressive deterioration of the cartilage and bones of the joints affected and leads to their deformation. When untreated and in the most serious cases, the disease can be handicapping after about 10 years and prevents the patient from daily movements and professional activity.

Extra-articular manifestations can sometimes occur, such as rheumatoid nodules, a kind of "bump" often located at the elbows or next to the finger joints, or dryness of the eye and mouth (referred to as Gougerot-Sjögren's dry syndrome). In the most serious cases, the disease also affects other organs such as the eyes, heart, lungs, nerves or blood vessels.

### Chronic inflammatory bowel disease (CIBD)

Chronic inflammatory bowel disease (or CIBD) includes Crohn's disease and ulcerative colitis (UC). These are both characterized by inflammation of the wall of a portion of the digestive tract. In Crohn's disease, it may be located in the entire digestive system, from the mouth to the anus (most often in the intestine) whereas with ulcerative colitis is located in the rectum and the colon. These diseases progress by inflammatory flareups of extremely variable duration and frequency depending on the patient, alternating with remission phases. CIBD is most often diagnosed in young people aged between 20 and 30 but can occur at any age; 15% of cases are among children. Their frequency varies considerably from one country to another, but the most significant rates are found in the industrial countries and in particular in northwestern Europe and the United States. In France, approximately five new cases of Crohn's disease and as many cases of ulcerative colitis are diagnosed each year per 100,000 inhabitants.

During the flareups, the CIBDs are usually characterized by abdominal pain, frequent, sometimes bloody, diarrhea, or even attacks in the anal region (cracks, abscesses). The symptoms are often accompanied by fatigue, anorexia and fever, even non-intestinal manifestations, in the joints, skin, eyes and liver.

In approximately 20% of patients, the crises are severe. Their intensity may require hospitalization, suspension of food intake and infusion therapy for several days. Moreover, the progress of the disease may lead to narrowing of the affected intestinal segment and possibly occlusion or abscesses that could result in a fistula, which is a perforation and an abnormal path from the diseased intestine to another organ. These complications require surgical intervention. CIBDs are associated with increased risk of colorectal cancer, in particular when the lesions are present in the colon.

## Celiac disease

This is a frequent disease with prevalence in Europe that can affect 1 out of 200 inhabitants (France, 120,000 to 600,000 individuals). It is especially observed in children between 6 and 12 months of age (following the introduction of gluten in the baby's usual food). It may, however, be diagnosed at any age. Hypersensitivity to an antigen contained in food gluten develops over time. Gluten is present in cereals (wheat, proteins rich in lysine and glutamine = gliadins), rye (proteins = secalins), oats and barley (proteins = hordeins).

In the digestive mucosa, gliadin forms a complex with an enzyme that deaminates certain glutamine residues and that increases the immunogenicity of the complex. Macrophages of the digestive mucosa then present the enzyme/gliadin complex to the CD4+ T lymphocytes. The T lymphocytes are activated and stimulate the production of anti-gliadin antibodies and anti-enzyme autoantibodies. The antibodies are found in the mucus membranes and in the serum. Cellular immunity is strongly involved and there is a major expansion in the mucus membranes of the intraepithelial T lymphocytes able to secrete cytokines, in particular interferon-gamma. Cellular activation (macrophages, lymphocytes, plasmocytes) and local synthesis of cytokines are responsible for the histological lesions observed. Interleukin 15, involved in the regulation of many cells, is a strongly over-expressed interleukin in this pathology (Abadie V et al., 2014).

There is also a genetic likelihood of celiac disease and most patients are carriers of a special HLA phenotype (DQ2).

The classical form is chronic diarrhea of variable intensity associated with malabsorption, loss of weight and frequent abdominal pain and/or abdominal meteorism. This form generally corresponds to an extensive disorder of the small intestine.

Clinical presentation with discrete digestive systems is possible (arthritis, neurological disorder, elevated hepatic transaminases, dermatitis herpetiformis, iron- or folate-deficient anemia).

Signs of variable intensity malabsorption are frequent: hypocholesterolemia, hypocalcemia, hypokalemia and hypoalbuminemia.

Among the autoantibodies, it is important to identify anti-gliadin antibodies (G or A isotype), anti-smooth muscle antibodies and anti-tissue transglutaminase antibodies. The histological lesion analyzed in the biopsy shows intestinal villous atrophy and interepithelial lymphoplasmocytic infiltrate. Three criteria are recognized as a diagnosis of celiac disease: the presence of a characteristic histological lesion, malabsorption syndrome and clinical and histological improvement (regression of intestinal villous atrophy in approximately one year) under gluten-free diet, the recommended treatment.

Celiac disease can be complicated by non-Hodgkin's malignant lymphoma (most often located in the digestive system) and epithelial cancers (small intestine, pharynx and oesophagus), especially in the case of a poorly maintained diet.

Other autoimmune pathologies may also be indications of interest depending on the targets involved.

Vasculitis with ANCA (antineutrophil cytoplasmic autoantibodies) is a subgroup of systemic inflammatory and necrotizing vasculitis that affects small diameter vessels (arteries, arterioles and capillaries). These primarily affect the kidney and the lungs. Three somewhat rare affections are concerned: Wegener's disease, microscopic polyangiitis (or micro-PAN) and Churg-Strauss syndrome.

## CURRENT TREATMENTS OF AUTOIMMUNE DISEASES

Treatment of autoimmune diseases has several objectives: to prevent disease flareups, to fight the progression of visceral attacks, to sustain employability and cure the disease while preventing the undesirable effects of treatments.

Immunological treatment of autoimmune diseases is based on three points: to eliminate pathogenic autoantibodies (plasmapheresis method), to modulate activation of lymphocytes and synthesis of cytokines (immunosuppressants such as corticosteroids, cyclosporin A, the molecules interfering with purine metabolism such as azathioprine (Imurel®) or mycophenolate mofetil (Cellcept®) and, in a more targeted fashion, to modify the immune response to make it non-pathogenic (principle of immunomodulation, for example by inhibiting the cytotoxic action of TNF $\alpha$  by anti-TNF $\alpha$  antibodies by blocking B lymphocytes by anti-CD20s).

**The most commonly used therapies are the following:**

### CORTICOSTEROIDS

They have anti-inflammatory and immunosuppressive properties in strong doses, acting on the T lymphocytes, antibody production and the gene transcription of many cytokines. These are prednisone (Cortancyl®), prednisolone (Solupred®) or

methylprednisolone (Solumedrol®) for intravenous administration. The corticosteroids exert their effect through intracytoplasmic receptors (glucocorticoid receptors). They inhibit synthesis of many proteins and transcription factors involved in the production of many cytokines.

### IMMUNOSUPPRESSANTS

Cyclosporin A (Neoral®) CNI or calcineurin inhibitor. This substance, known as an antifungal, has shown excellent immunosuppressive properties. It works selectively and reversibly with respect to activated T lymphocytes, in particular CD4+ T lymphocytes. Cyclosporin A binds to intracytoplasmic receptors (cyclophilins, from the family of immunophilins) — the cyclosporin A/cyclophilin complex inhibits the activity of calcineurin that is a phosphatase that activates a transcription factor called NFATc. This results in the blocking of the gene transcription of interleukin 2 genes and other cytokine genes.

This molecule is very often used in preventing allogeneic graft rejection. It may be used in inflammatory myositis in cases of failure of corticosteroids, immunoglobins and methotrexate.

Azathioprine (Imurel®), mycophenolate mofetil (Cellcept®) and methotrexate (Methotrexate®):

These are immunosuppressive drugs with cytotoxic action acting as inhibitors of purine metabolism.

They also inhibit proliferation of T and B cells by blocking the DNA synthesis of the dividing molecules, formation of antibodies and glycosylation of adhesion molecules. These molecules are also toxic on hematopoietic cells.

Azathioprine (Imurel®) is inactive in vivo but deteriorates into active metabolites. Imurel® is indicated as a disease-modifying treatment for systemic lupus, or in some cases of Gougerot-Sjögren's syndrome or in some systemic vasculitides. It may be prescribed as a bridge of cyclophosphamide, as maintenance treatment. Its effectiveness is often delayed (approximately four weeks).

Mycophenolic acid (active metabolite of mycophenolate, mofetil-Cellcept®) has a more powerful immunosuppressant effect than azathioprine in preventing transplant rejection. It is used in systemic lupus (lupus nephritis).

Methotrexate is a tetrahydrofolate reductase inhibitor that blocks thymidylate synthesis, de novo purine synthesis and cell division. Methotrexate is indicated as a disease-modifying treatment for rheumatoid arthritis and inflammatory myositis. It becomes effective in one to two months. The decrease of certain bloodlines (dose-dependent cytopenia observed under methotrexate) is prevented by the administration of folic acid.

Cyclophosphamide (Endoxan®) is an alkylating agent forming covalent bonds with DNA leading to the death of dividing cells. It acts mainly on B lymphocytes (suppression of antibody production) and CD8+ T lymphocytes. It is indicated for treatment of some serious forms of systemic lupus and some systemic vasculitides. It quickly becomes effective by the second week.

Leflunomide (Arava®) is an immunosuppressant that inhibits de novo synthesis of pyrimidines by inhibiting dihydro-orotate dehydrogenase. It is indicated as a disease-modifying treatment for rheumatoid arthritis.

Rituximab (MabThera®) is an anti-CD20 monoclonal antibody, a membrane molecule of B lymphocyte. Its binding leads to destruction and rapid and prolonged decrease of B lymphocytes as well as their production of immunoglobulin. Rituximab is used in autoimmune hemolytic anemias, autoimmune thrombocytopenic purpura, serious refractory lupus, cryoglobulinemia and in some vasculitides. It is indicated in resistant rheumatoid arthritis with methotrexate.

### IMMUNOMODULATORS:

#### Intravenous immunoglobulins

Following the demonstration of their efficacy in the treatment of autoimmune thrombocytopenic purpura, their beneficial effect extends to other autoimmune diseases. They are used in the management of myasthenia, polymyositis, dermatopolymyositis, lupus and anemia or autoimmune thrombocytopenia. This treatment works in multiple ways and is not always well understood.

#### Anti-TNF $\alpha$

Adalimumab (Humira®) acts by inhibiting a protein that is over-produced during Crohn's disease, TNF $\alpha$ . TNF $\alpha$  is produced by the cells of the organism and promotes inflammation, taking part in the fight against certain infections. Adalimumab is a monoclonal antibody, i.e., a very targeted molecule, produced using biotechnology to specifically neutralize TNF $\alpha$ . It is used for the synthesis of isolated cells of human origin and this antibody is 100% humanized. Several other molecules are available on the market:

Infliximab (Remicade®) is also a monoclonal antibody that neutralizes the activity of TNF $\alpha$ .

Etanercept (Enbrel®) is a chimeric molecule made of an antibody fragment called human IgG Fc associated with the soluble TNF $\alpha$  receptor. Certolizumab pegol (Cimzia®) is a monovalent fragment of a monoclonal antibody, modified by pegylation.

These molecules block the effect of TNF $\alpha$  by neutralizing the soluble TNF alpha and/or by preventing it from binding to a receptor. Anti-TNF $\alpha$  drugs are used for rheumatoid arthritis, severe cases of Crohn's disease, ankylosing spondylitis, juvenile idiopathic arthritis or psoriatic arthritis.

Prescription of anti-TNF $\alpha$  drugs must be systematically paired with immunosuppressant treatment in order to prevent the appearance of anti-TNF $\alpha$  antibodies.

The therapeutic schema of this autoimmune disease includes purely symptomatic anti-inflammatory, immunosuppressant treatment and/or substitutive treatment.

The limits of these treatments are linked to intolerances of these chronic treatments and to frequent escape. The use of long-term anti-TNF $\alpha$ -type biotherapies showed that approximately 20% of patients do not respond to these treatments and that they do not function after one year, in one out of two patients.

Associated risks:

Long course immunosuppressant treatment of the autoimmune disease itself increases the risk of developing cancer or a cancerous haematological disease. Thus, for celiac disease (Franks A. L. et al., 2012) associations with different cancers (haematological cancers such as non-Hodgkin's lymphoma or other organ tumors) appear over time in the development of that autoimmune enteropathy with a chronic inflammatory response and T-cell activation. These associations of autoimmune diseases with chronic inflammation and different cancers are also observed with a more elevated risk over time, for other pathologies such as Crohn's disease, lupus and rheumatoid arthritis.

### 5.6.3.2 CoVepiT, vaccine against COVID-19

The principle of vaccination is always the same: it involves presenting a pathogen (virus, but also a parasite or bacterium) to our immune system so that it learns to recognize it and to produce specific antibodies that will be ready to neutralize it when we meet it in real life. It is above all very specific proteins found on the surface of the virus that trigger the immune response: these are the antigens, the key that allows the virus to penetrate the cell that it will then use to reproduce itself. For coronaviruses, the best recognized antigen is the "S" protein (for Spike).

Several techniques are used to develop a vaccine, ranging from proven techniques such as the use of the whole virus rendered harmless to more recent techniques such as DNA/RNA vaccines. CoVepiT belongs to another category, it is a vaccine based on the selection and optimization of epitopes to generate an immune response from sentinel memory T lymphocytes against SARS-CoV-2. All these avenues are currently being used in the search for a vaccine against Covid-19 and have already given rise to registrations.

#### LIVE INACTIVATED OR ATTENUATED VACCINES

The first technique, used since the existence of vaccination, consists in presenting the whole virus to the immune system, which involves culturing it in very large quantities. This is the path followed by Chinese laboratories (Sinopharm, Sinovac) to develop an anti-Covid vaccine. To ensure that the vaccine will be safe for the body, the virus can either be presented in an inactivated (killed) form, after having previously heated it or passed it through formalin, using the Pasteur technique, or presenting it in attenuated form. In this second case, the virus is still alive but not dangerous.

#### MESSENGER RNA

In the case of vaccines from Pfizer and its German partner BioNTech (Comirnaty®, also named BNT162b2), as well as Moderna, (mRNA-1273) strands of genetic instructions called "Messenger RNA" are injected into the body. The messenger RNA of the vaccine is manufactured in the laboratory. It has been programmed to manufacture specific coronavirus proteins or "antigens". It is a much more targeted method. This molecule is called a "messenger" because it directly tells our cells what to make. The molecule tells our immune system to recognize and neutralize the coronavirus if it enters our body. The antibodies that will be produced will "stand guard" for a long time.

This RNA cannot integrate into our genome and modify our DNA. This technique has been known since the early '90s. It seems the messenger RNA technology is more efficient but is nevertheless fragile, and the vaccine must be stored at very low temperatures.

#### DNA/RNA VACCINES

Given that the role of the Spike protein, the spike-shaped protein of the coronavirus, is crucial in triggering the neutralizing immune response of Covid-19, the aim is to have it produced directly by the human body, by introducing into our cells the genetic sequence that codes for the production of this viral protein. This avoids injecting whole Covid-19 particles into the body or using adjuvants. But DNA or RNA is broken down by our enzymes as soon as they enter the body. To ensure that the Spike protein code reaches our cells intact, it needs a vehicle capable of transporting it: the virus itself.

Scientists have two options. Either make a virus in the form of a totally artificial envelope composed of molecules that mimic lipids and proteins, which will have all the attributes of a virus without being one. This is the option taken by the laboratory Pfizer/BioNTech, or by the biotechnology company Moderna Therapeutics. Or use a real virus, but harmless to humans.

#### VACCINES WITH NON-REPLICATING VIRAL VECTORS

The vaccine developed by AstraZeneca (COVID-19 VACCINE ASTRAZENECA), Johnson & Johnson (COVID-19 vaccine Janssen) and the Russian vaccine from the research institute Gamaleya (Sputnik V) are based on a viral vector. This technique helped to put an end to the Ebola epidemic in West Africa at the end of 2014. This involves using a non-replicating chimpanzee viral vector, based on an attenuated version of a common cold virus (adenovirus) which contains the genetic material of the spike protein characteristic of SARS-CoV-2. This spike protein is the key that allows SARS-CoV-2 to enter our cells. After vaccination, this spike protein is produced, priming the immunized subject, allowing it to defend itself against the SARS-CoV-2 virus if it is subsequently infected. This vaccine takes longer to produce but is easier to store. These vaccines are therefore more resistant than the Pfizer-BioNTech and Moderna viruses since they are based on DNA and not mRNA, they can be stored for several months at a temperature between -8 °C and -2 °C.

### 5.6.3.3 OSE-127/S95011, designed for autoimmune diseases, including ulcerative colitis (UC) and Sjögren's Syndrome

Ulcerative colitis (UC), an inflammatory bowel disease, is a long-term inflammatory disease whose cause is unknown. It is characterized by persistent ulcers of the colon and the rectum. Digestive and non-digestive complications can also develop over time, including inflammation of the megacolon, eyes or joints and colon cancer. Due to its prevalence in Western countries (60-280/100,000), its human, social and economic impact and its uncertain origin, UC is a disease with high unmet therapeutic need.

#### TREATMENT OF UC

To date, there is no cure for patients with UC. The main objective of medical treatment is to induce and maintain remission of the disease and prevent, in the long term, disability, colectomy and colorectal cancer. Patient care relies mainly on diet (still controversial) and on the administration of anti-inflammatories and/or immunomodulators, standard treatments for alleviating symptoms. In patients who do not respond to these treatments, biological drugs are used as second-line treatment (Harbord M. et al., J. Crohn's Colitis, 2017). Steroid-free endoscopic and clinical remission is currently the ultimate objective expected from maintenance treatment for UC (EMA 216, Guideline on the development of new medicinal products for the treatment of ulcerative colitis).

For patients with severe UC or during flareups, hospitalization may be necessary. When the disease cannot be controlled by drugs, surgery (including colectomy) is then the final option for patients with severe and unresponsive UC (approximately one third of patients), with potentially significant morbidity and often major consequences on the patient's quality of life.

#### COMPETITION AND PRODUCTS IN UC

The world market for UC is dominated by immunomodulator drugs (such as thiopurines, aminosalicylates and steroids) and by biological drugs (mainly anti-TNF monoclonal antibodies: Remicade® [infliximab], Humira® [adalimumab], Simponi® [golimumab] and more recently, an anti- $\alpha$ 4 $\beta$ 7 antibody, Entyvio® [vedolizumab]). The clinical data on anti-TNF treatments

collected during the last 10 years has shown that primary resistance develops in approximately 30% of the native UC patients, whereas secondary resistance develops in more than 50% of primary responders in less than five years. Anti-TNF treatment is therefore unable to control the disease in approximately two thirds of all patients not presenting full remission (Sandborn W.J. et al., N. Engl. J. Med., 2016) and most of them resort to surgical intervention as a last recourse. There is thus still an unmet therapeutic need to induce and maintain control of the disease in primary patients unresponsive to standard treatments and maintain long-term remission and prevent consequences.

#### PRODUCTS BEING DEVELOPED IN THE DIRECT AREA OF OSE-127/S95011

**OSE-127/S95011:** a humanized monoclonal antibody (IgG4), directed against the IL7 receptor alpha (CD127). The main characteristic of this antibody is that it recognizes an identified and patented epitope of the receptor giving it the specific property of not inducing internalization of the receptor while blocking the binding of the IL7 to its receptor. This allows it to block the proliferation of effector T cells without impacting the regulatory T cells. This non-internalization characteristic of the receptor is a very differentiating point compared with other competitors, in particular with respect to the two other products available in the domain of the IL7 described below.

**GSK2618960** is a monoclonal antibody (IgG1) targeting the IL7 receptor alpha and internalizing the receptor. Phase 1 clinical trials have been developed by the company GSK. A trial was carried out among healthy volunteers (NCT02293161) and the results, in December 2018, demonstrated good product tolerance and blockage of IL-7 receptor signaling, consistent with the objectives that had been set. Moreover, it was demonstrated that even without discernible impact on a subgroup of peripheral T cells in healthy subjects, GSK2618960 effectively modulates the auto-inflammatory activity of the pathogenic T cells in the diseased tissue (Joanne Ellis et al., Br. J. Clin. Pharmacol., 2019 Feb).

The trial on multiple sclerosis (NCT01808482) was interrupted in June 2013 (after fraud was discovered concerning the data linked to a research team located in Shanghai).

**PF-06342674** is a monoclonal antibody (IgG1) targeting the IL7 receptor alpha and internalizing the PF-06342674 receptor. Pfizer conducted two Phase 1b trials with this product: one trial on diabetes (trial NCT02038764 terminated in September 2016) and a trial on multiple sclerosis (NCT02045732 terminated in April 2015). Following strategic company decisions, the company withdrew PF-06342674 from its product portfolio in July 2018.

In 2017, a Phase 2 trial (NCT03239600) conducted on primary Sjögren's syndrome was stopped.

Several candidate drugs are in clinical development in UC to evaluate different ways of working including blocking of integrin or interleukin 12 and/or 23, modulation of sphingosine-1-phosphate receptors, inhibition of Janus kinases or antisense oligonucleotides. None of these therapeutically target the IL-7R (Sandborn W.J. et al., N. Engl. J. Med., 2016).

Oral **ABX464** (Abivax) is a highly differentiated therapeutic candidate with anti-inflammatory properties, with an innovative way of working based on the positive regulation of a unique microRNA (miRNA-124). In December 2020, the Company announced the preparation of phase 3 studies in the treatment of moderate to severe ulcerative colitis. During 2021, Abivax will have the results of the phase 2b induction study in ulcerative colitis and will launch the pivotal phase 3 in UC as well as the pivotal phase 2b/3 in Crohn's disease.

#### SJÖGREN'S SYNDROME

Sjögren's syndrome occurs when a person's immune system attacks and destroys secretion-producing glands, in particular salivary and lacrimal glands. The lungs, intestines and other organs are less often affected by Sjögren's syndrome.

Sjögren's syndrome presents in two forms:

- . primary Sjögren's syndrome (pSS): the disease itself, not associated with any other disease;
- . secondary Sjögren's syndrome (sSS): a disease that develops in the presence of another autoimmune disease such as rheumatoid arthritis, systemic lupus erythematosus or vasculitis.

Sjögren's syndrome is a rare disease affecting somewhat fewer than 1 out of 10,000 adults. Women are ten times more affected than men.

Primary Sjögren's syndrome is characterized by lymphocytic infiltrates and progressive destruction of exocrine glands (saliva and tear glands) leading to xerostomy (dry mouth) and xerophthalmia (dryness and atrophy of the conjunctiva) associated with fatigue and pain. The inflammatory process may, however, affect any organ.

pSS is considered as a multifactor disease in which environmental factors trigger inflammation in genetically predisposed individuals. The pathological process implies both innate and adaptive immune systems. The precise physiopathological mechanisms of the disease are not completely understood. A complex interaction of types of immune cells, such as T cells, B cells, dendritic cells, monocytes/macrophages and NK cells and their effector molecules, would be the origin of the disease, eventually leading to hyperactivity of B cells, the production and formation of autoantibodies of germinal center type structures in the salivary glands.

#### COMPETITION AND PRODUCTS

To date no systemic treatment has proved effective in altering the progress of pSS whose therapeutic need has not been met. Treatment of pSS relies mainly on symptomatic agents, in particular tear and saliva substitutes, saliva stimulating agents such as pilocarpine or cevimeline and analgesics. Severe symptoms affecting the organs are treated according to recommendations for treating systemic lupus erythematosus and other conjunctive tissue disorders. These treatments include corticosteroids, hydroxychloroquine, immunosuppressants such as methotrexate, mycophenolate sodium, azathioprine and cyclosporin.

Many therapeutic trials are currently in progress to evaluate the efficacy and the tolerance of new biotherapies in the treatment of Sjögren's syndrome.

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#### 5.6.3.4 FR104, designed for autoimmune diseases and transplantation

FR104: is a monovalent antagonist antibody in Fab format, directed against the co-stimulatory molecule CD28, for an effect that inhibits the responses of effector T cells and induces regulatory T cells (via CTLA-4) resulting in suppressive T activity. for potential clinical applications in autoimmune pathologies and transplantation.

#### AUTOIMMUNE DISEASES: PRODUCTS UNDER DEVELOPMENT IN THE DIRECT FIELD OF FR104

**Lulizumab pegol** (BMS-931699) targets T cells and CD28. This product was evaluated by the company BMS as part of a Phase 2 study (NCT02265744 trial) evaluating the safety and efficacy of lulizumab versus placebo in the treatment of an autoimmune disease, systemic lupus erythematosus. The abstract presented to the 2018 ACR/ARHP conference (“An Anti-CD28 Domain Antibody, Lulizumab, in Systemic Lupus Erythematosus: Results of a Phase II Study”, Joan T. Merrill et al.) did not show any significant difference between lulizumab and the placebo in terms of primary and secondary criteria but a profile of favorable tolerance.

**TGN1412** (CD28 superagonist developed by TeGenero that became TAB08 theralizumab developed by TheraMAB) also targets CD28 but works differently. It is a humanized monoclonal antibody that binds to the CD28 receptor of the T cells of the immune system, but it has a “superagonist” activity with T-cell activation independent from the TCR and the massive release of pro-inflammatory cytokines. The Phase 1 clinical trials of TGN1412 were suspended in March 2006 after inducing severe inflammatory reactions in the first study in humans in London. The drug was taken over and renamed TAB08 theralizumab by the Russian biotechnology company TheraMAB which conducted phase 1 trials with a much weaker dose (0.1%) than those used in the London study and continued its development. (From TGN1412 to TAB08: the return of CD28 superagonist therapy to clinical development for the treatment of rheumatoid arthritis; Tyrsin D et al.; Clin Exp Rheumatol. 2016 Jul-Aug; 34 (4 Suppl 98): 45-8. Epub 2016 Jul 20) with a phase 2 completed but whose results have not been published.

**ALPN-101** is a first-in-class double inhibitor of the CD28 and ICOS costimulatory pathways expressed by cells. It is developed by AbbVie under a partnership agreement with Alpine Immune Sciences: after positive phase 1 results in terms of safety, tolerance, pharmacokinetics and pharmacodynamics, the product is ready to enter phase 2 in systemic lupus erythematosus.

## KIDNEY TRANSPLANTS: COMPETITION AND PRODUCTS IN KIDNEY TRANSPLANTS

Kidney transplant is the treatment of choice for end-stage renal disease and improves the quality of life and quantity of life of patients compared to dialysis thanks to the use of more effective immunosuppressive treatments. Knowledge of the mechanisms of lymphocytic activation and rejection phenomena has made it possible to define the use of these treatments and their combinations.

The principle of immunosuppression in kidney transplants is a strong initial treatment, effective in the prevention of acute rejection, followed by effective maintenance immunosuppression to contain the immunological part of allograft nephropathy. Nevertheless, in the long term, these immunosuppression strategies have not yet shown significant long-term benefits, whether in the prevention of chronic allogeneic kidney disease or the occurrence of cardiovascular and/or oncological complications.

The therapeutic arsenal currently available comprises molecules mainly used at the time of transplantation and in the days following it. Used as an induction treatment, they cause a state of non-response to the transplant by depleting or blocking T lymphocyte proliferation, a key element of the allo-immune response. Other molecules, whose objective is to prevent acute rejection by blocking cellular signals between the lymphocytes and the antigen-presenting cells, will be used in the long term as maintenance treatment.

### INDUCTION TREATMENTS

These are **antilymphocytic immunoglobulins** (ATG-Fresenius®, thymoglobulin) and **interleukin -2 receptor antibodies** (Anti-CD-25 Ab) (basiliximab, daclizumab).

### TREATMENTS FOR INITIAL IMMUNOSUPPRESSION AND MAINTENANCE

**Steroidal anti-inflammatory drugs** have been used from the start for their immunomodulation potential. However, due to the many side effects, their use is currently limited.

**Calcineurin inhibitors**, which appeared in the '80s (cyclosporine/Neoral®, Sandimmune®; tacrolimus/Prograf®, Advagraf®), with comparable efficacy in preventing acute rejection, are chosen based on their metabolic side effects (hypercholesterolemia and hypertension). blood pressure for cyclosporine and diabetes for tacrolimus).

**Cell multiplication inhibitors (IMPDH)**: azathioprine (Imurel®), mycophenolate mofetil/CellCept®, unlike anticalcineurins, are devoid of nephrotoxicity and do not induce metabolic disorders (but still have side effects, particularly haematological and digestive effects).

**Mamalian target of rapamycin (mTOR) inhibitors**: sirolimus (Rapamune ®) and everolimus (Certican ®) are most often used as a maintenance immunosuppressive treatment, replacing anticalcineurins. Their main side effects are hyperlipidemia, thrombocytopenia and arthralgia.

**Immunosuppressants blocking the second signal**: belatacept is used to prevent calcineurin inhibitors. In addition, it has been shown to improve long-term survival after transplantation.

### KIDNEY TRANSPLANTS: PRODUCTS UNDER DEVELOPMENT IN THE DIRECT FIELD OF FR104

**Lulizumab pegol** (BMS-931699) targets T cells and CD28. This product is currently undergoing a phase 1/2 clinical trial in patients who have received a kidney transplant. It assesses the safety of a combination of four products: lulizumab pegol, tocilizumab, belatacept and everolimus. Post-transplant follow-up is at least one year.

Other immunosuppressive therapies, acting at different levels of the immune response, are being evaluated.

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### 5.6.3.5 Resolution of inflammation

Persistent inflammation is a hallmark of all chronic inflammatory and autoimmune diseases. If it is not controlled or resolved, it can lead to worsening tissue damage and cause tissue fibrosis, possibly associated with the loss of organ function. Most anti-inflammatory agents act using a mechanism that blocks pro-inflammation pathways. In contrast, OSE Immunotherapeutics is developing OSE-230 as a first-in-class therapeutic agent with the potential to resolve chronic inflammation by driving affected tissues to complete the inflammation program and restore tissue integrity.

Chronic inflammatory diseases are the most significant cause of death worldwide and their incidence is growing, highlighting the patients' need for disruptive innovations to manage such complex diseases. (*Chronic Inflammation; Roma Pahwa, Amandeep Goyal, Pankaj Bansal, Ishwarlal Jialal ; In: StatPearls. Treasure Island (FL): StatPearls Publishing; January 2020 ; 2020 Aug 10*).

Metformin is commonly used in the treatment of type II diabetic patients with dyslipidemia and low-grade inflammation. The anti-inflammatory activity of metformin is evident by reductions in circulating TNF-alpha, IL-1beta, CRP, and fibrinogen in these patients.

Statins are anti-inflammatory as they reduce multiple circulating and cellular biomediators of inflammation. This pleiotropic effect appears to contribute in part to the reduction in cardiovascular events.

Non-steroidal anti-inflammatory drugs (NSAIDs) like naproxen, ibuprofen, and aspirin acts by inhibiting an enzyme cyclooxygenase (COX) that contributes to inflammation and are mostly used to alleviate the pain caused by inflammation in patients with arthritis.

Corticosteroids also prevent several mechanisms involved in inflammation. Glucocorticoids are prescribed for several inflammatory conditions including inflammatory arthritis, systemic lupus, sarcoidosis, and asthma.

Herbal supplements like ginger, turmeric, cannabis, hyssop, and Harpagophytum procumbens are shown to have anti-inflammatory properties, however, one should always consult with a doctor before their use and caution should be taken for using some herbs like hyssop and cannabis.

## 5.7 Investments

The following financial information is derived from the Company's consolidated financial statements for fiscal year ended December 31, 2020, set out in paragraph 18.1 of this Universal Registration Document.

### 5.7.1 Key investments made by the Company

The Company invested in laboratory equipment in fiscal years 2018 and 2019, as well as the development of its laboratories for €945,000. They were financed out of equity as well as through subsidies received by the Company.

At the start of 2020, the Company also acquired a cytometer for nearly €300,000, financed by a lease from a long-standing banking partner, as well as some office equipment and fit out works for additional premises located at avenue de Suffren in Paris and the existing premises in Nantes (France).

### **5.7.2 Future key investments**

Since the Company made significant investments in the last two fiscal years, it does not intend to reinvest heavily in additional non-current assets in the short term.

### **5.7.3 Information on joint ventures or companies in which the Company holds a capital share likely to have a significant impact on the valuation of its assets and liabilities, its financial position or results**

The information on the Company's subsidiaries is set out in paragraph 6.2 below.

### **5.7.4 Environmental impacts of investments made by the Company**

Since industrial production and distribution are not included in research and development activities, the Company only invested in laboratory equipment as part of its property, plant and equipment assets. In this respect, the Company uses little raw materials and its activities neither release significant emissions in the environment nor greenhouse gases.

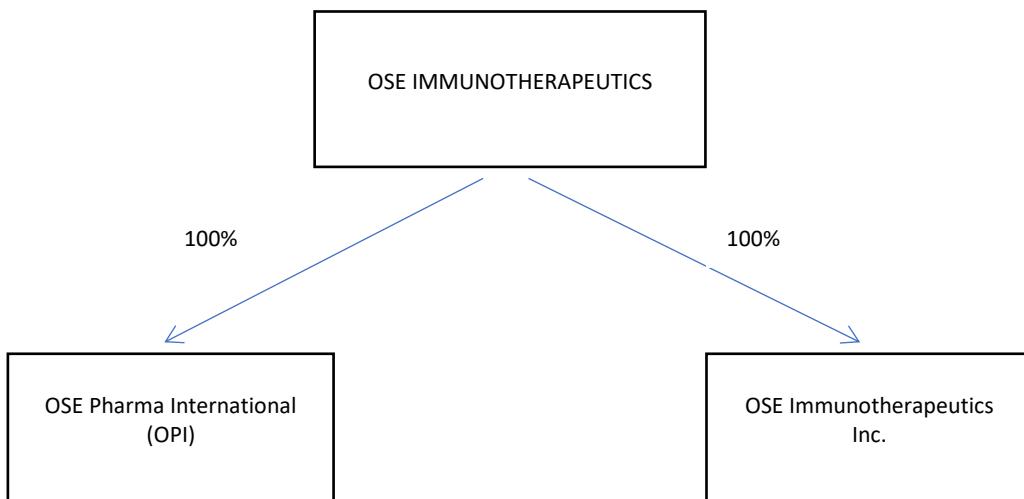
Furthermore, all the waste resulting from the tests conducted by employees are treated in accordance with existing regulations.

## 6 Organizational structure

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### 6.1 Overview of the Company

At the date of this Universal Registration Document, the legal organizational chart of the Group is as follows:



### 6.2 Subsidiaries and investments

#### OPI

Since March 25, 2014, the Company holds all of the capital and voting rights of the Company OSE Pharma International, a public limited company whose registered office is located in Switzerland (called OPI SA).

OPI has share capital of 100,000 Swiss francs and was created in February 2012. Its corporate purpose is the acquisition, holding, operation, development and marketing of intellectual property rights in biotechnology; research and development of products and treatments resulting from such rights, the conduct of studies and clinical trials and the granting of licenses; the identification and the building of relationships involving partners and scientific, financial, manufacturing and governmental investors; investment in companies active in the same sector (in compliance with the Swiss Federal Law on Acquisition of Real Estate by Persons Resident Abroad — LFAIE).

Its main assets are world rights relating to the composition of peptides. It has no employees.

The existing agreements between OSE Immunotherapeutics and OPI are the European agreement for the OSE-2101 project signed in July 2012 and the agreement for the purchase of OPI by its shareholders on March 25, 2014.

The European license agreement is maintained since the intellectual property is owned by OPI. The Company expects, as part of its intragroup relations, to extend this licensing agreement to the other territories outside of Europe. The interest in maintaining the licensing agreement is to ensure the industrial property is financed through the OPI subsidiary and to finance, through these payments, the commitments made by OPI with respect to the pharmaceutical group Takeda. In fact, the Company made a commitment to pay an additional amount to Takeda when it registered its product in the United States and Europe, then royalties on future sales, limited to a single digit (see Section 20).

#### OSE IMMUNOTHERAPEUTICS INC.

On March 28, 2017, the Board of Directors authorized the creation of a subsidiary in the United States wholly owned by the company, in order to serve as a point of support for international scientific collaboration. Having an American presence is

also justified given the current and future developments of Tedopi® in the United States (recruitment, partnership, licensing, etc.).

This subsidiary, named OSE Immunotherapeutics Inc., was founded in the state of Delaware, and is managed by Alexis Peyroles as CEO.

## 7 Review of the financial position and results

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Chapter 7 presents the Company's results and financial position for fiscal years ended December 31, 2019, and 2020. The Company's financial statements are prepared in accordance with existing IFRS accounting standards.

Readers are invited to read this chapter in conjunction with the Universal Registration Document as a whole. In particular they should read the description of the Company's activities presented in Chapter 5 of this Universal Registration Document.

The following presentation and analysis should be read in conjunction with the Universal Registration Document as a whole, especially the Company's consolidated financial statements for fiscal years ended December 31, 2020, and 2019 set out in paragraph 18.1 of this Universal Registration Document.

### 7.1 Financial position

ASSETS IN K€	Note	December 31, 2020	December 31, 2019
Intangible assets	1.1	52,600	52,600
Tangible assets	1.2	947	1,009
Right-of-use assets	1.3	2,848	1,692
Financial assets	1.4	581	287
Differed tax assets	10.1	165	283
<b>TOTAL NON-CURRENT ASSETS</b>		<b>57,141</b>	<b>55,871</b>
Trade receivables	2.2	1,074	747
Other current assets	2.3	9,390	6,474
Cash and cash equivalents	2.1	29,368	25,842
<b>TOTAL CURRENT ASSETS</b>		<b>39,832</b>	<b>33,062</b>
<b>TOTAL ASSETS</b>		<b>96,973</b>	<b>88,933</b>

EQUITY & LIABILITIES IN K€	Note	December 31, 2020	December 31, 2019
<b>SHAREHOLDERS' EQUITY</b>			
Stated capital	4.1	3,597	3,001
Share premium	4.1	65,449	48,397
Treasury stock	4.4	(93)	(148)
Reserves and retained earnings		8,966	11,838
Consolidated result		(16,555)	(4,652)
<b>TOTAL SHAREHOLDERS' EQUITY</b>		<b>61,364</b>	<b>58,536</b>
<b>NON-CURRENT DEBTS</b>			
Non-current financial liabilities	5	16,552	9,211
Non-current lease liabilities	5	2,318	1,413
Non-current deferred tax liabilities	10.1	2,080	5,066
Non-current provisions	7	531	377
<b>TOTAL NON-CURRENT DEBTS</b>		<b>21,481</b>	<b>16,067</b>
<b>CURRENT DEBTS</b>			
Current financial liabilities	5	50	548
Current lease liabilities	5	594	309
Trade payables	6.1	10,286	6,918
Corporate income tax liabilities	6.2	2	20

Social and tax payables	6.2	2,108	1,723
Other debts and accruals	6.3	1,088	4,812
<b>TOTAL CURRENT DEBTS</b>		<b>14,128</b>	<b>14,330</b>
<b>TOTAL LIABILITIES</b>		<b>96,973</b>	<b>88,933</b>

## 7.2 Operating profit

### 7.2.1 Key factors affecting operating revenues

On April 3, 2018, the Company entered into a worldwide collaboration and exclusive licensing agreement with Boehringer Ingelheim International GmbH, an independent international pharmaceutical laboratory, to develop OSE-172. According to the terms of the agreement, OSE Immunotherapeutics granted Boehringer Ingelheim International GmbH the license for the worldwide exclusive rights for the development, registration and marketing of its OSE-172 product candidate. In return, OSE Immunotherapeutics will receive cash flows for a total amount up to €1.1 billion (exclusive of royalties), including an upfront payment of €15 million on signature of the agreement (the total amount was paid in 2018), a €15 million payment at the start of a Phase 1 trial (milestone reached in 2019), milestone payments throughout the various clinical development stages and milestone payments related to sales targets.

In view of the accounting rules used for revenue recognition, the Company was able to recognize €3.7 million in revenue for the 2020 fiscal year.

In December 2016, the Company signed a worldwide licensing option agreement with Servier, an international independent pharmaceutical company, to develop and market OSE-127/S95011, an interleukin-7 receptor antagonist. According to the terms of the agreement, OSE Immunotherapeutics granted Servier a licensing option on the worldwide exclusive rights for the development and marketing of the product candidate. The agreement covers an amount up to €272 million, including a €10.25 million payment on signature of this option and a payment of €30 million on exercise of a two-step licensing option. Since the first step was achieved with the start of Phase 1, the Company received €10 million in 2019. In March 2020, OSE Immunotherapeutics and Servier signed an amendment covering the terms of the potential exercise of the licensing option by modifying Step-2 of this option. Thus, OSE Immunotherapeutics will receive from Servier a milestone payment of €5 million on the recruitment of the first patient in the Phase 2 clinical trial in Sjögren's Syndrome, expected to start in the 3<sup>rd</sup> quarter of 2021, and an additional payment of €15 million on exercise of the option at the end of the two scheduled Phase 2 clinical trials, and in priority upon completion of the study in Sjögren's Syndrome sponsored by Servier, the second being sponsored by OSE Immunotherapeutics (the agreement providing for a total payment of €20 million at the end of a Phase 2 clinical trial).

Subsequent payments will be linked to clinical development milestones, registration in multiple indications, then sales-related milestones with double-digit royalties.

In view of the accounting rules used for revenue recognition, the Company was able to recognize €6.2 million in revenue for the 2020 fiscal year.

Furthermore, in 2019, the Company continued the Phase 3 clinical trial, known as "Atalante 1" in Europe, the United States and Israel. This trial assesses Tedopi®, its leading product in non-small cell lung cancer in HLA-A2 positive patients post checkpoint inhibitor treatment failure. The Company signed a licensing agreement with Chong Kun Dang (CKD) Pharmaceutical Corporation for the potential registration and marketing of Tedopi® in Korea.

According to the terms of the agreement, the Company will receive milestone payments amounting to €4.3 million, including €1.2 million on signature and achievement of a short-term milestone, and royalties on product sales as well as a margin based on the transfer price, of just under 30%. The short-term milestone was reached in 2020 and CKD therefore paid the Company a milestone payment of €500,000.

The development of OSE-127/S95011 and BI 765063 (OSE-172) products continued at the clinical stage, in particular with the production of GMP-compliant batches and completion of Phase 1 clinical trials, and the launch of Phase 2 clinical trials for OSE 127/S95011.

## 7.2.2 Explanation of material changes in revenue or net income in the COMPARATIVE annual financial statements

### 7.2.2.1 Comparative figures from the consolidated statements of operations at December 31, 2020, and 2019

Annual financial statements (in €K)	2020	2019
	12 months	12 months
<b>Operating income</b>	<b>10,432</b>	<b>25,952</b>
of which Revenue	10,418	25,952
of which Other operating income	13	0
<i>R&amp;D expenses</i>	-22,355	-21,655
<i>Overhead expenses</i>	-4,783	-3,898
<i>Expenses related to share-based payments</i>	-2,283	-1,868
<i>Other operating expenses</i>	0	-2
<b>Operating profit/loss</b>	<b>-18,989</b>	<b>-1,472</b>
Financial income	31	221
Other financial expenses	-288	-213
<b>Profit/(Loss) before tax</b>	<b>-19,246</b>	<b>-1,464</b>
Income tax	2,692	-3,188
<b>Net result</b>	<b>-16,555</b>	<b>-4,652</b>

#### Operating income

Revenue stood at €10,418,000 and comprised:

- €3,502,000 for re-invoicing of expenses as provided in the agreement signed with Boehringer Ingelheim (BI) and €189,000 of co-development fees related to the staggering of milestone payments received and deferred to include development services to be provided by OSE.
- €3,355,000 corresponding to the recognition in revenue of a portion of the amount of the option received in 2019 following the signature of the amendment signed with Servier in March 2020 and €2,872,000 related to the sale of bottles of OSE-127 including the rebilling of a part of intellectual property costs.
- 500,000 for meeting the first milestone in the contract with CKD signed in 2019.

The Company's revenue is directly correlated with the signing of licensing agreements and achieving key milestones.

As a result, the partnership agreements signed with Servier and Boehringer Ingelheim mainly accounted for 2020 revenue.

## 8 Capital resources

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### 8.1 Information on the Issuer's capital

Since 2012, the Company has been financed by capital increases, loans and repayable advances. The following table summarizes all various sources of financing.

<b>Financing sources – in €K</b>	
2012 capital increase (1)	527
2013 capital increase	0
2014 capital increase (2)	3,148
2015 capital increase (3)	19,304
2016 capital increase (4)	852
2017 capital increase (5)	17
2018 capital increase (6)	23
2019 capital increase (7)	0
2020 capital increase (8)	17,427
<b>Subtotal capital raised*</b>	<b>41,298</b>
P2RI loan	1,500
French Government-Guaranteed loan (PGE)	6,960
<b>Subtotal loans</b>	<b>8,460</b>
OSEO repayable advances	330
Bpifrance repayable advance	100
Bpifrance EFFI-CLIN repayable advance	6,044
Bpifrance EFFiMab repayable advance	3,148
<b>Subtotal repayable advances</b>	<b>9,622</b>
<b>Total financing sources</b>	<b>59,380</b>

\* These amounts have been restated for capital increase costs.

- (1) In 2012, the Company's sole shareholder decided to carry out two capital increases, the first by capitalization of reserves of €255,000, the second by means of a cash injection of €500,000. These capital increases have been carried out to finance the Company's activities and the entry of new shareholders into the Company.
- (2) Two capital increases were carried out in July 2014, the first one with a nominal value of €71,189.40 (and €2,776,386.60 of share premium) by issuing 316,572 Class B shares and 39,375 ordinary shares, the second one with a nominal value of €7,500 (and €292,500 of share premium) by issuing 31,250 Class B shares and 6,250 ordinary shares issued on conversion of the remaining Class B shares.

With the capital raised in 2014, the Company was able to start manufacturing products based on its Memopi® technology, for a Phase 3 clinical trial in advanced non-small cell lung cancer (NSCLC) in the United States and Europe.

- (3) In 2015, the Company's IPO resulted in a capital increase with a nominal value of €391,000 (and an issue premium of €20,723,000) by issuing, through a public offering, 1,955,000 ordinary shares, the subscription of which completed in cash or by offsetting against liquid and payable debts, and by converting all Class B shares for a like number of ordinary shares. This transaction provided the Company the resources needed to complete the Phase 3 clinical study for its Tedopi® product, conducted in Europe and the United States for a registration of the drug in the treatment of non-small cell lung cancer on 500 patients. The IPO also enabled the Company to develop Tedopi® in a new exploratory Phase 2 under a partnership, in new therapeutic combinations or for other types of cancer, such as breast, colon and ovarian cancer.

The Company also received requests for the exercise in June 2015 of 31,250 of the 2014-2 share subscription warrants, giving right to the same number of shares, by a cash subscription, and in September 2015 of 36,744 of the 2014-4 share subscription warrants, by offset of debt. Exercise of these share subscription warrants resulted in a capital increase with a nominal value of €13,598.80 (and an issue premium of €530,353.20). Readers are invited to refer to Sections 19.1.4 and 19.1.7 of this Universal Registration Document for more information on these warrant exercises.

- (4) In May 2016, the Company received a request to exercise 88,256 of the 2014-4 share subscription warrants, by offset of debt resulting in a share capital increase with a nominal value of €17,651.20 (and an issue premium of €697,222.40). In June 2016, the Company received a request to exercise 3,300 Effimune 2010 share subscription warrants in cash, which, as a result of the merger, resulted in the issuance of 6,369 shares, and a share capital increase was carried out with a nominal value of €1,273.80 (and an issue premium of €17,866.20). In December 2016, the Company received several requests for the exercise of a total of 20,320 Effimune 2010 share subscription warrants, as result of the merger, giving right to the issue of 39,217 shares, and a share capital increase was carried out with a nominal value of €7,843.40 (and an issue premium of €110,012.60). Readers are invited to refer to Sections 19.1.4 and 19.1.7 of this Universal Registration Document for more information on these warrant exercises.
  
- (5) In March 2017, the Company received a request for the exercise of 85,000 of the 2012 share subscription warrants, giving right to the same number of shares, and a share capital increase was carried out with a nominal value of €17,000. Readers are invited to refer to Sections 19.1.4 and 19.1.7 of this Universal Registration Document for more information on these warrant exercises.
  
- (6) In 2018, the Company received a request to exercise 23,000 of the 2012 share subscription warrants, giving right to 115,000 shares, and a share capital increase was carried out with a nominal value of €23,000. Readers are invited to refer to Sections 19.1.4 and 19.1.7 of this Universal Registration Document for more information on these warrant exercises.
  
- (7) In 2019, no funds were received to carry out a capital increase (the only capital increases recorded during the fiscal year concerned the exercise of free shares).
  
- (8) In 2020, the Company completed a capital increase with cancellation of preferential subscription rights through a private placement with 25 qualified French and international investors, a large majority of them new shareholders, and by the accelerated construction of an order book, for €18.6 million.

The data included in the table below are from the consolidated financial statements for fiscal years ended December 31, 2020, and 2019 under IFRS standards.

In €K	December 31, 2020	December 31, 2019
<b>Consolidated equity</b>	<b>61,364</b>	<b>58,536</b>
<i>Loans and financial liabilities</i>	16,601	9,759
<i>Cash and cash equivalents</i>	29,368	25,842
<b>In debt (Net cash) – Net position</b>	<b>-12,767</b>	<b>-16,083</b>

Cash stands at €29,368,000 and an amount of €19,008,000 is held in term deposit accounts.

## 8.2 Cash flows

### 8.2.1 Statement of cash flows

In K€	Note	2020	2019
<b>CONSOLIDATED RESULT</b>		(16,555)	(4,652)
+/- Depreciation, amortization & provision expenses	1.2	273	231
+/- Provision for pensions and retirement	7	151	92
+ Amortization on "right-of-use"	1.3	457	251
+/- Shares based payments (1)	8.4	1,787	1,511
<b>CASH FLOW BEFORE TAX</b>		(13,888)	(2,568)
+ Financial charges	5	273	30
- Income tax expenses	10.3	(2,692)	3,188
<b>CASH FLOW FROM OPERATIONS BEFORE NET BORROWING COST AND TAXES (A)</b>		(16,306)	650
- Tax paid		(50)	(70)
+/- Working capital variation (2)		(2,920)	8,555
<b>CASH FLOW FROM OPERATING ACTIVITIES (D)</b>		(19,277)	9,135
- Tangible assets increase	1.2	(210)	(336)
+/- Financial assets variation	2.1	0	2,861
+/- Mutual funds units accounted in current financial assets		0	34
+/- Loans and advances variation	1.4	(294)	(184)
<b>CASH FLOW FROM INVESTING ACTIVITIES (E)</b>		(504)	2,375
+ Capital increase	4.1	18,630	0
+/- Capital increase costs	4.1	(1,203)	0
+ Loan subscription	5	6,960	5,628
- Loan repayment	5	(325)	(455)
- Lease debt repayment (3)	5	(482)	(251)
- Financial charges	5	(273)	(164)
<b>CASH FLOW FROM FINANCING ACTIVITIES (F)</b>		23,306	4,759
+/- Currency translation transactions (G)		0	0
<b>CASH VARIATION H = (D + E + F + G)</b>		3,526	16,269
<b>CASH OPENING BALANCE (I)</b>	21	25,842	9,573
<b>CASH CLOSING BALANCE (J)</b>	21	29,368	25,842

(1) €1,787,000 in valuation costs for free shares and founders' warrants allocated as of December 31, 2020.

(2) The change in working capital requirement was primarily due to the following:

- increase in trade receivables amounting to €277,000
- increase in other current assets amounting to €2,916,000
- increase in trade payables amounting to €3,368,000
- increase in tax and employee-related payables amounting to €385,000
- decrease in other payables amounting to €3,724,000

(3) This line relates to the application of IFRS 16 and corresponds to the repayment of lease liabilities amounting to €482,000.

(4) Of which €1,000 of CCB

## 8.3 Financing requirements and structure

### 8.3.1 Financing requirements

The Company updated its projections of working capital requirements as a result of the COVID-19 crisis.

Despite a strong cash position that will help the Company through the current crisis, it needs to anticipate any delay in product development that could delay expected cash inflows.

As a result, the Company is assessing various options for potentially strengthening its financing structure in the coming months. The reader is invited to refer to section 3.5.1 of this Universal Registration Document.

In €k	12/31/2019	Increase	Decrease	Other transactions*	12/31/2020	Interest at 12/31/2020
BPI EFFIMAB advance	3,148	-	-	142	3,290	
BPI EFFICLIN Advance	6,044	-	-	258	6,302	
P2RI Loan	0	-	-		0	
BPI EFFIDEM Advance	19	-	-	(19)		
Loan guaranteed by the French State	-	6,960	-	-	6,960	
<b>Non-current financial liabilities</b>	<b>9,211</b>	<b>6,960</b>	<b>-</b>	<b>380</b>	<b>16,552</b>	
<hr/>						
Nantes Lot 1 Lease	332			(104)	228	
Nantes Lot 2 Lease	149			(35)	114	
Paris Suffren Lease 1	932			(139)	793	
Paris Suffren Lease 2	-	1,172		(157)	1,015	
Leasing Cytometre	-	209		(41)	168	
<b>Non-current lease liabilities</b>	<b>1,413</b>	<b>1,381</b>		<b>(476)</b>	<b>2,318</b>	
<hr/>						
BPI EFFIMAB Advance	92			(92)		(50)
BPI EFFICLIN Advance	95			(95)		(163)
P2RI Loan	321		(305)	(16)	0	9
BPI EFFIDEM Advance	39		(20)	19	38	0
Loan guaranteed by the French State		11			11	(11)
Bank overdrafts	3	1	(3)		1	
<b>Current financial liabilities</b>	<b>549</b>	<b>12</b>	<b>(327)</b>	<b>(184)</b>	<b>50</b>	<b>(214)</b>
<hr/>						
Nantes Lot 1 Lease	112		(99)	104	117	(8)
Nantes Lot 2 Lease	37		(32)	35	40	(3)
Paris Suffren 1 Lease	160		(122)	139	176	(20)
Paris Suffren 2 Lease		160	(135)	157	182	(25)
Leasing Cytometre		72	(36)	41	78	(3)
<b>Current lease liabilities</b>	<b>309</b>	<b>232</b>	<b>(423)</b>	<b>476</b>	<b>594</b>	<b>(59)</b>
<hr/>						
<b>Total financial liabilities</b>	<b>11,482</b>	<b>8,585</b>	<b>(751)</b>	<b>196</b>	<b>19,513</b>	<b>(273)</b>

\* This column includes the recurring and non-recurring breakdown as well as IFRS 9, IAS 20 and IFRS 16 restatements for the year.

### **8.3.1.1 Non-current financial liabilities**

Non-current financial liabilities are:

#### **A P2RI (REGIONAL INDUSTRIAL REDEPLOYMENT) LOAN OF €1,500,000 AND A DERIVATIVE INSTRUMENT TRANSFERRED AT THE TIME OF THE MERGER.**

In September 2013, the Company received loans from BNP Paribas, CIC, Crédit Mutuel and from Région des Pays de la Loire, each for €375,000, i.e. a total loan of €1.5 million. The purpose of this loan is to finance development and innovative projects.

This loan was recognized at amortized cost, calculated using the effective interest rate.

The loan from the banking pool amounts to €1,125 million. It has a term of seven years, including a three-year grace period for capital repayment. The interest rate is equal to the three-month Euribor rate plus a fixed margin of 300 basis points. This loan has been repaid quarterly since October 5, 2016. Interest is payable quarterly.

This loan was fully repaid as of December 31, 2020.

The Company received the full amount of the loan from Région des Pays de la Loire, amounting to €375,000, in December 2013. The term of the loan is seven years, including a three-year grace period for repayment. The annual percentage rate stands at 4.06% payable annually.

This loan was fully repaid as of December 31, 2020.

#### **REPAYABLE ADVANCE OF €100,000 FROM BPIFRANCE TRANSFERRED AT THE TIME OF THE MERGER**

In September 2014, the Group also obtained an interest-free repayable advance from Bpifrance for a maximum of €100,000, as part of the OSE 172 (Formerly EFFI-DEM) project: Feasibility of immunomodulatory monoclonal antibodies in the treatment of cancer.

Bpifrance payments were staggered between the signing of the contract and the end of the project, i.e.:

An initial payment of €80,000 once the contract was signed (received on December 23, 2014).

A second payment of €20,000 received on December 2, 2015, settling the balance of payments to be received from this advance.

As a result of the success of this project, repayment of this support will commence as follows:

- €20,000 on September 30, 2018,
- €40,000 on September 30, 2019,
- €40,000 on September 30, 2020, which was subject to a six-month repayment delay in the context of the COVID-19 pandemic.

The fair value of this advance was determined on the basis of a market interest rate. The difference between the advance amount at historical cost and that of the advance discounted at market rate is recognized less R&D expenses, as costs are incurred for the relevant research programs.

At December 31, 2020, the remaining balance stood at €40,000.

#### **BPIFRANCE REPAYABLE ADVANCE FOR EFFIMAB PROJECT OF €2,328,000 AND €820,000**

On June 19, 2017, the Company received from Bpifrance the first payment of €2,328,000 as part of a repayable advance for the EFFIMab project.

This interest-bearing advance (interest rate of 1.66% under the contract) was initially for an amount up to €3,609,000 paid on achievement of three key milestones within a completion period of 72 months.

If all milestones are achieved, a notional repayment in annual installments was to be put in place from June 30, 2021, based on a notional amount of €3,609,000 at the applicable contractual discount rate of 1.66%, i.e. a fixed amount of €4,100,000, including interest of €490,595. Repayments, amounting to €4,100,000, were spread between June 30, 2021, and June 30, 2025.

Following the signature of Amendment no. 2 on December 28, 2018, this interest-bearing advance now stands at an amount of up to €3,991,000 to be paid on achievement of four key milestones within a completion period of 115 months.

If all milestones are achieved, the notional repayment in annual installments from December 31, 2024, based on a receivable notional amount of €3,991,000, now stands at a fixed amount of €4,590,000.

Repayments will be spread between December 31, 2024, and December 31, 2028.

The Company received a portion of the advance on achievement of the third key milestone, i.e. €2,328,000 in accordance with the amendment to the initial contract.

The Company received the second payment of the repayable advance, i.e. €820,000, on achievement of the fourth key milestone on April 10, 2019.

Following the signature of Amendment no. 3 in October 2020, this interest-bearing advance now stands at an amount of up to €5,264,000 to be paid on achievement of four key milestones within a completion period of 122 months.

If all milestones are achieved, the theoretical repayment is now a fixed amount of €6,198,000, which will be paid in annual installments from September 30, 2025, and which has been calculated on the basis of the theoretical €5,264,000 receivable.

Repayments will be spread between September 30, 2025, and September 30, 2030.

#### **BPIFRANCE REPAYABLE ADVANCE OF €1,236,000 AND €4,808,000**

On December 18, 2017, the Company received from Bpifrance a first payment of €1,236,000 as part of a repayable advance for the EFFI-CLIN project. This interest-bearing advance (discount rate of 0.90% according to the contract) is for up to €8,106,000 paid on achievement of four key milestones within a completion period of 60 months.

If all milestones are achieved, a notional repayment in annual installments from June 30, 2024, based on the notional amount of €8,106,000 at the applicable contractual discount rate of 0.90%, will be a fixed amount of €9,850,000, including interest of €1,744,000.

Repayments, amounting to €9.85 million, will be spread between June 30, 2024, and March 31, 2028.

The Company received a portion of the advance, i.e. €1,236,000 at the start of the study.

On September 18, 2019, the Company received the second payment of the repayable advance, i.e. €4,808,000 on achievement of the first key milestone.

If the Company's program is successful, the first payment will be repaid between June 30, 2024, and March 31, 2028.

#### **FRENCH GOVERNMENT-GUARANTEED LOAN**

To address the financial consequences of the COVID-19 pandemic, on May 5, 2020, a French Government-Guaranteed loan of €6,960,000 was granted, split between three banks (CIC, CM and BNP).

These loans meet the conditions of the Rectifying Finance Law for 2020, n°2020-289, of March 23, 2020, and the specifications defined in the decree dated March 23, 2020, providing the French Government guarantee to credit and financial institutions under that law.

This funding is one-year cash loan immediately made available to the borrower for the full amount on the date that the funds are transferred into their current account. Capital will be repaid and interest and ancillary costs paid in a single installment

on the annual repayment date, with the option for the borrower to apply to spread the outstanding amount due on the repayment date over a further four years. Management has already decided to exercise the option and repay this loan at the end of 5 years. This loan is therefore presented as non-current in the consolidated financial statements. This is a French Government-Guaranteed loan under article 6 of the aforementioned law. This French Government-Guaranteed loan constitutes a form of public aid and has been recognized at fair value on the date it was obtained and at amortized cost with an overall effective rate of 0.25% (corresponding to the guarantee commission and in the context of the extension of the loan after the 1st year, the interest rate will be determined by amendment). The fair value of the loan has been assumed to be equal to the amount of cash received net of transaction costs.

The funds received and conditions are as follows:

- Crédit Mutuel = €2,300,000 received May 6, 2020, repayable on May 6, 2025
- BNP = €2,300,000 received on May 6, 2020, repayable on May 6, 2025
- CIC = €2,360,000 received on May 18, 2020, repayable on May 18, 2025

#### **8.3.1.2 Lease liabilities and leases**

OSE Immunotherapeutics reviewed its operating leases to assess the potential impact of first-time adoption of IFRS 16 which resulted in a future lease payment liability and a right-of-use asset being recognized in the statement of financial position for operating leases.

A right-of-use asset was recognized in an amount identical to the liability for future lease payments adjusted, where applicable, for advance payments or amounts set aside for future lease payments.

OSE Immunotherapeutics identified two new leases (covered by the standard) during 2020 with the following characteristics:

- A lease for real estate in France. The incremental borrowing rate used was 2%.
- A sale-leaseback agreement under property, plant and equipment ("Cytometry" research equipment) initially acquired on May 28, 2020, and sold on June 24, 2020. This is considered a sale under IFRS 15 and a right of use was measured applying an interest rate implicit in the lease of 2.11%.

The net value of the leases mentioned below amounted to €2,848,000 at December 31, 2020.

### **8.4 Restrictions on the use of capital resources that have materially affected, or could materially affect, directly or indirectly, the issuer's operations**

N/A.

### **8.5 Expected financing sources**

The Company is primarily aiming for partnering and licensing agreements for some of its products and further public funding for its programs.

With €29.4 million in cash and cash equivalents at December 31, 2020 (excluding €5.1 million in 2020 research tax credits), the Company believes it has the financing resources necessary to continue its clinical and preclinical programs at least for the twelve months following its published financial statements for the fiscal year ended December 31, 2020.

The Company also has the funds necessary to finance investments planned in 2021 for an amount of approximately €922,000.

## 9 Regulatory environment

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The description of the risks linked to the Company's regulatory environment is available in the paragraphs 3.1 "preclinical and clinical development of drug candidates") and 3.3 "drug marketing".

### 9.1 Introduction

The research and development work, preclinical studies, clinical studies, facilities, as well as the manufacturing and marketing of our drug candidates are and will be subject to complex legislative and regulatory requirements defined by various public authorities in France, Europe, the United States and other countries of the world.

The European Medicines Agency (EMEA), the US Food and Drug Administration (FDA), the French National Agency for the Safety of Medicines and Health Products (ANSM) and the equivalent regulatory agencies in the other countries impose significant restrictions concerning development (including clinical trials), manufacturing and sales of products such as those developed by the Company. Failure to comply with these regulations can lead to the imposition of fines, the seizure or withdrawal of the products from the market or even the partial or total suspension of their production by the regulatory authorities. They may also withdraw marketing authorizations granted previously or refuse applications for authorizations that the Company has filed or even pursue legal remedies. Regulatory constraints are important for assessing whether a main asset can eventually become a drug and evaluating the time and the investments necessary for such development.

Although there are differences from one country to another, the development of therapeutic products for human usage must comply with certain common regulatory prerequisites in all developed countries.

To obtain marketing authorization for a product, proof of its efficacy and safety, as well as detailed information on its composition and its process of manufacturing, must generally be provided. Laboratory tests, pharmaceutical development, preclinical studies and clinical trials are conducted in this framework.

The development of new drugs, from basic research to product marketing includes five stages:

- Research
- Preclinical studies, pharmaceutical development, manufacturing
- Clinical trials in humans
- Marketing authorization (MA)
- Sales

Regulatory authorities require follow-up after marketing authorization is granted in order to continue monitoring the effects and the safety of the authorized products (pharmacovigilance). After obtaining marketing authorization, authorities may also ask for additional trials to evaluate tolerance and efficacy on special populations of patients or impose conditions that could limit the commercial development of some products.

### 9.2 Preclinical studies

Preclinical studies include laboratory evaluation of the purity and stability of the main pharmaceutical asset and the formulated product, as well as studies to evaluate tolerance (toxicological studies), in vitro and in vivo studies of the behavior of the drug candidate before being able to launch clinical trials in humans. The conduct of preclinical studies is subject to legislative and regulatory requirements, as well as Good Laboratory Practice (GLP). All results of preclinical trials are provided to the regulatory authorities jointly when applying to start medical trials.

### 9.3 Conduct and regulation of clinical trials

- **PHASE 1:** the product is administered in order to determine its initial tolerance profile, identify the side effects and evaluate the tolerance to the doses administered, as well as its distribution in the organism and impact on metabolism.

Developers sometimes name their trials Phase 1a or Phase 1b. Phase 1b trials generally aim to confirm dosage, pharmacokinetics and tolerance in a greater number of patients than Phase 1a. In oncology, accelerated development is sometimes pursued, based on Phase 1 trials including cohort extensions leading to marketing authorization for the drug. This is for example the case of molecules developed for rare diseases.

- **PHASE 2:** the product is studied in a limited population of patients in order to obtain signs of preliminary efficacy and determine the level of optimal administration as well as any side effects and risks linked to tolerance.
- **PHASE 3:** Phase 3 trials are carried out on a large number of patients carrying the targeted disease to compare the study treatment to a reference treatment in order to produce the data demonstrating its relative efficacy and tolerance.
- **PHASE 4:** trials, sometimes referred to as Phase 4 trials, may also be conducted following the initial marketing authorization. These trials aim to obtain more information on the treatment of patients in the targeted therapeutic indication. In some cases, the competent regulatory agency may require a Phase 4 clinical trial as a condition of approval.

Clinical trials may be carried out in Europe, the United States or the rest of the world when authorized by the regulatory authorities and the independent ethics committee of each country in question. In fact, regulatory authorities may oppose clinical trial protocols proposed by the companies that seek to test the products, suspend them or require major modifications.

The purpose of the clinical trials is to administer the drug candidate to human subjects under the supervision of qualified investigators, in compliance with good clinical practices defined by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). These latter require that all research subjects give their informed consent in writing in order to participate in any clinical trial. Clinical trials are conducted according to protocols that describe in detail, among others, the objectives of the trials, the parameters used to control the safety of use and the criteria for evaluating efficacy.

In addition, EU Regulation 2016/679 of the European Parliament and of the Council of April 27, 2016, on the protection of physical persons with respect to the processing of personal data and the free circulation of data (GDPR), that became effective on May 25, 2018, significantly increases the rights of citizens, giving them more control over their personal data. French national law was brought into compliance with the GDPR through the updating of French Law no. 78-17 of January 6, 1978, on computer processing, data files and freedom (Law no. 2018-493 of June 20, 2018, and re-drafting Order no. 2018-1125 of December 12, 2018).

In compliance with the data protection law, personal data collected as part of clinical trials is subject to a declaration with the French data protection authority (CNIL). Patients have a right to access and correct this data. Finally, patients must be regularly informed of the conduct of clinical trials and the overall results of the research.

The conduct of clinical trials must therefore comply with complex regulations throughout the different phases of the process that rely on the principle of the informed consent of the patient to whom the product(s) will be administered. The information relating to the objective, the methodology and the duration of the research, as well as the expected benefits, the constraints and the foreseeable risks due to the administration of the products provided are summarized in a written document provided to the patients prior to their participation in the research.

### **9.3.1 Clinical trial authorization in the European Union**

In the European Union, the texts governing clinical trials are currently based on Directive n ° 2001/20 / EC of April 4, 2001, relating to the application of good clinical practices in the conduct of clinical trials of drugs for human use, while waiting for the application of Regulation (EU) n ° 536/2014 of the European Parliament and of the Council of April 16, 2014 repealing Directive 2001/20 / EC. Each Member State had to transpose this directive into its national law.

In France, this is Law no. 2004-806 of August 9, 2004, relating to public health policy and Decree no. 2006-477 of April 26, 2006, amending the title of the Public Health Code dedicated to biomedical research, supplemented by several Ministerial Decrees of May 24, 2006. An interventional clinical trial bearing on a drug must first receive a favorable opinion from a French Institutional Review Board (IRB) and authorization from the ANSM.

**Opinion of the Central Ethics Committee:** the three types of research (i) interventional research which includes an intervention on the person not justified by his usual care; (ii) intervention research which involves only minimal risks and constraints; (iii) non-interventional research) can only be implemented after a favorable opinion from the competent CPP.

Pursuant to article L.1123-7 of the public health code, the competent CPP - now selected randomly under article L.1123-6 of the public health code - must in particular give its opinion on the conditions of validity of the research , in particular as regards the protection of participants, the information communicated to them and the procedure followed to obtain their informed consent, as well as the relevance of the research, the satisfactory character of the evaluation of the expected benefits and risks, the adequacy between the objectives pursued and the means implemented, the qualifications of the investigator (s), the amounts and terms of compensation for participants and the terms of recruitment of participants.

**Authorization from the French National Agency for Medicines and Health Products Safety (ANSM):** after submission of the complete trial authorization application file, containing an administrative file, a research file including in particular the protocol and the investigator brochure and, where applicable, a technical file relating to the product, the acts performed and methods used, as well as the opinion of the ethics committee, the ANSM can inform the sponsor that it is opposed to the implementation of the research or ask it for any additional information to decide on its request. The latter can then modify the content of his research project and submit his modified or completed request to ANSM; procedure which, however, cannot be followed more than once. If the sponsor does not modify the content of his request or does not produce the requested elements within the allotted time, he is deemed to have waived his request.

Generally speaking, the Agency evaluates the efficacy and the quality of the products used during the research, with the goal to guarantee the safety of the persons involved in biomedical research. The French Institutional Review Board (IRB) gives its opinion on the validity conditions of the research, in particular on the protection of the participants, their information and the methods of collecting their informed consent, as well as the general relevance of the project, whether the evaluation of benefits and risks is satisfactory, and the adequacy of the resources implemented for the objectives pursued. Since the application of the Jardé Law no. 2012-300 of March 5, 2012, relating to research involving humans, amended by Order no. 2016-800 of June 16, 2016, and by the publication of Decree no. 2016-1537 of November 16, 2016, the previous regional authority of the IRBs is now national. The time for approval of applications for authorization from the authorities cannot exceed 60 days starting from the receipt of the full dossier.

In accordance with article L. 1123-11 of the public health code, in the event of a risk to public health or of a lack of response from the sponsor or if the ANSM considers that the conditions under which the research is conducted no longer correspond to those indicated in the authorization request or do not comply with the provisions of the CSP, it may, at any time, request that modifications be made to the methods of carrying out the research, to any document relating to the research, as well as suspend or ban this search.

The ANSM decision of November 24, 2006 sets the rules of good clinical practice ("GCP") in the conduct of clinical trials on medicinal products for human use, provided for in Article L. 1121-3 of the public health code. The purpose of the public health code is to ensure the reliability of data from clinical trials and the protection of trial participants. GCPs should be applied in all clinical trials, including pharmacokinetic, bioavailability and bioequivalence studies conducted in healthy volunteers

Current European regulations on clinical trials of drugs for human use is governed by EU Regulation no. 536/2014 of April 16, 2014. The major points of this regulation are the following:

- Applications for single authorization must be filed through the portal associated with the European Union database, including a common portion evaluated jointly by all participating members of the European Union and a national portion covering the ethical and operational aspects of the trial evaluated by each member of the European Union independently. A single decision covering all aspects of the application is delivered by each of the Member States concerned;
- Increased transparency regarding clinical trials authorized in the EU: the European Union database is a source of public information, notwithstanding the protection of personal data, the protection of confidential commercial data and the protection of confidential communication between Member States and the supervision of trials between Member States. For drugs in development, the public information includes the authorization of the clinical trial, general information on the trial and the summary of the final results.

Depending on the processing of personal data carried out during clinical trials and the nature of these trials, it may be necessary to carry out formalities with the National Commission for Informatics and Freedoms ("CNIL"). The sponsor of the clinical trial may be required to make a commitment to comply with one of the CNIL's reference methodologies through a simplified notification procedure or to submit an authorization request if necessary. Patients then have in all cases the right

to access and rectify their personal data as well as the right to oppose their collection / withdraw their consent in accordance with Law No. 78-17 of 6 January 1978, as amended and the General Data Protection Regulation (GDPR). The European Commission published on April 10, 2019 questions / answers on the interaction between Regulation (EU) No 536/2014 of the European Parliament and of the Council of April 16, 2014 on clinical trials of medicinal products for human use (the "Regulation on clinical trials") and the GDPR, carried out after consultation of the European Data Protection Council. They relate to the general obligations put in place by the Regulation on clinical trials in relation to those of the GDPR, the responsibility for determining the legal basis for the processing of personal data in the context of a clinical trial, the legal basis for the processing of personal data of subjects of a clinical trial in the context of these trials (primary use), the difference between informed consent (Regulation on clinical trials) and consent within the meaning of the GDPR, or the meaning of the GDPR requirements regarding the information to be provided to clinical trial subjects.

### **9.3.2 Authorization of clinical trials in the United States**

In the United States, a clinical trial can only begin after it obtains authorization from the Food & Drug Administration (FDA) and from an ethics committee, the Institutional Review Board (IRB). An Investigational New Drug (IND) application must be filed with the FDA and must be approved before a clinical trial can be started in humans. This application includes the early scientific data of the product being studied, the manufacturing data, the preclinical and clinical data (including the clinical trial protocol). Unless the FDA objects, the application for an IND is approved 30 days after receipt. The FDA may, at any time, request that a clinical trial that is planned or in progress be interrupted. This temporary interruption is maintained as long as the FDA has not obtained the information that it requires. Moreover, each ethics committee (IRB) having authority over an investigating site, can delay, even temporarily or permanently interrupt, a clinical trial if it believes that the safety of patients is not ensured or in the case of noncompliance with regulatory requirements.

### **9.3.3 Publication of information on clinical trials**

In the United States, sponsors of clinical drug trials regulated by the FDA must register and publish a certain amount of information related to the clinical trial and its results, available publicly on the website [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

In Europe, the information on the clinical trial as well as the results at the end of study are made public for Phase 2 to 4 trials, as well as for any pediatric study on the website [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu).

## **9.4 Regulation of marketing authorizations**

In order to be marketed, all drugs must obtain a marketing authorization (MA) delivered by the competent European or national authorities (the ANSM in France, the EMA in Europe, the FDA in the US, etc.) and after filing an application for an MA or NDA (New Drug Application). This application will be evaluated according to scientific criteria of quality, safety and efficacy.

The MA application is drafted in the standardized CTD (Common Technical Document) format, used in Europe, the United States and Japan. This application includes detailed and precise information on the product, in particular its composition, the way it works, the associated quality elements, its toxicity, efficacy and safety. It also describes the manufacturing process of the active substance, the finished product manufacturing process and the preclinical and clinical studies.

In Europe, applications for marketing authorization (MA) can be made via two types of procedures: Community procedures used when the drug is innovative or intended for several member states of the European Community and the national procedure for drugs that are not marketed in more than one Member State. According to the Community procedure used, the EMA or the company chooses, respectively, the reporting State or the referring State.

A drug may be withdrawn from the market, either directly by the company or at the request of health authorities, when a serious problem arises, in particular concerning safety or noncompliance with manufacturing rules.

### **9.4.1 Community procedures**

Access to the Community market has been, since January 1, 1998, subject either to the centralized procedure (defined in Regulation no. 2309/93/EEC amended by Regulation no. 726/2004/EEC), or to the mutual recognition procedure (specified

in Directive 2001/83/EC amended by Directive 2004/27/EC) and, since October 2005, to the decentralized procedure (specified in Directive 2004/27/EC).

- **THE CENTRALIZED PROCEDURE** (mandatory for products from biotechnology, new products developed in the field of cancer and drugs with orphan drug status): a single registration application file must be submitted to the EMA. The Committee for Medicinal Products for Human Use (CHMP) of the EMA (composed of one member appointed by each Member State of the European Union and country of the European Economic Area, and of five scientific experts) issues its recommendation with respect to the approval of the drug with the European Commission. The European Commission then makes the final decision to deliver the marketing authorization (MA), valid throughout the European Union. The drug can then be marketed in all member states of the European Union.
- If granted, the MA is valid for five years, without prejudice to paragraphs 4, 5 and 7 of Article 14 of the Regulation (Article 14). The MA may be renewed after five years, based on a reassessment of the benefit / risk ratio carried out by the competent authority. Once renewed, the MA is in principle valid for an unlimited period, unless the Commission decides otherwise in relation to pharmacovigilance (Article 14).
- Pursuant to article 10 bis of Regulation 726/2004, after having issued the MA, the EMA can thus require its holder to carry out (i) post-authorization safety studies if there are concerns regarding the safety risks posed by an authorized medicinal product and / or (ii) post-authorization efficacy studies when the understanding of the disease or clinical methodologies indicate that previous efficacy evaluations may need to be significantly revised (Article 10 bis)
- **MUTUAL RECOGNITION PROCEDURE AND THE DECENTRALIZED PROCEDURE:** these enable harmonized national marketing authorizations to be more easily obtained in several Member States. These two procedures are founded on the recognition, by the competent national authorities, of the first evaluation made by the regulatory authorities of one of the Member States (Reference Member State).
 

The decentralized procedure is provided for by Directive 2001/83 / EC of the European Parliament and of the Council of 6 November 2001, as amended. It can be used when the applicant wishes to authorize a medicine in more than one Member State, provided that this medicine is not already authorized in a Member State. Under this procedure, the applicant submits an application based on an identical dossier to the competent authorities of each of the Member States, one of which is selected by the applicant to act as Reference Member State ("RMS"). The competent authorities of the RMS prepare a draft assessment report for the medicinal product, a draft summary of product characteristics ("SPC") and a draft labeling and package leaflet, which are sent to the other Member States, referred to as the Member States concerned ("MS") for approval and to the applicant.

- The mutual recognition procedure is for its part provided for by Directive 2001/83 / EC of the European Parliament and of the Council of 6 November 2001, as amended. It can be used when the applicant wishes to authorize a medicinal product in more than one Member State and this medicinal product has already received a Marketing Authorization at the time of the request in a Member State.
- **NATIONAL PROCEDURE:** The MA, issued at national level by the competent authorities of the EEA Member States, covers only its respective territory. It can be requested when the medicinal product concerned is not within the scope of the centralized procedure
  - Registration of an international drug (in more than one country of the European Union) must use one or the other of these procedures.
  - Products developed by the Company in immuno-oncology or in transplantation, all derived from biotechnology, are therefore subject to the centralized procedure for their application for marketing authorization.

#### **9.4.2 Registration procedures outside the EU**

Companies that wish to market their products outside of the European Union must again file applications to register the drugs with the national authorities of the countries concerned, for example with the FDA in the United States, the Kosheisho (Pharmaceutical and Medical Device Agency, PMDA) for Japan.

In the United States, the application for drug approval must be submitted to the FDA that has regulatory powers over all pharmaceutical and biological products intended to be marketed in American territory.

Applications for marketing authorization must be submitted to the FDA, depending on whether it is a request for the approval of a new drug (NDA, New Drug Application) or a request for a biological product license (BLA, Biological License Application). The application must provide all information enabling the FDA to determine whether the drug is safe and effective for the targeted indication, whether the benefits are greater than its risks, whether the summary of the product characteristics is adequate and whether its manufacturing process and the controls intended to ensure quality enable the identity, dosage, quality and purity to be guaranteed.

#### **9.4.3 Exceptions to the usual registration procedures**

Exceptions to the traditional procedure for granting a marketing authorization (MA) as described above exist to enable quicker marketing of drugs.

**In Europe**, the following exists:

- **CONDITIONAL MA:** this is valid for one year instead of five. It is only granted when the drug meets unmet medical needs and if the benefits for public health are greater than the risk linked to an uncertainty due to an incomplete evaluation of the drug. The delivery of a conditional marketing authorization is subject to the finalization of clinical trials and/or the completion of new trials, in order to confirm the benefit/risk of the drug.
- **ACCELERATED ASSESSMENT:** the evaluation procedure is accelerated (150 days instead of 210 days) when a drug presents a major interest from a public health standpoint or represents a therapeutic innovation. The PRIME project (priority drugs), an EMA initiative launched in 2015, allows the early identification (from Phase 2/3) of drugs eligible for the accelerated procedure and enhanced assistance by scientific advice and dialogues throughout development.
- **MA FOR EXCEPTIONAL CIRCUMSTANCES:** a MA may be authorized on an exceptional basis, and may be reevaluated each year, when the drug's evaluation file cannot initially be submitted completely, for example, when a therapeutic indication applies to too few patients, or the collection of necessary data would be unethical.
- **TEMPORARY AUTHORIZATION FOR USE (TAU):** A Member State may use a drug that does not yet have marketing authorization in the country, in order to treat serious or rare diseases that do not have adequate treatment. In France, a Temporary Authorization for Use may be given by the ANSM for a particular patient (nominative TAU) or for a group of patients (cohort TAU).

**In the United States**, procedures allow more rapid development and market access for drugs for serious pathologies for which there is not yet any appropriate treatment or if there is a high medical need (cancer, AIDS, Alzheimer's disease, etc.):

- **"ACCELERATED APPROVAL":** this procedure is intended to allow marketing of promising products to treat serious pathologies on the basis of initial evidence prior to the formal demonstration of patient benefits. The FDA may in fact rely on an effect, an alternative result or any other result that has reasonable chances of being predictive of a clinical benefit and not on a well-defined clinical criterion. As such, a substitute result or marker (surrogate endpoint) is a result obtained in the laboratory or a physical sign that does not constitute, in itself, a direct measure of how the patients feel, their organ functions or their survival, but enables a therapeutic benefit to be expected. The MA granted may be considered as a provisional approval with written commitment to complete the clinical studies that demonstrate true benefit for the patient. This procedure corresponds to the "Conditional MA" procedure in Europe.
- **"PRIORITY REVIEW":** this procedure is used for drugs treating serious diseases that present a major therapeutic advance or provide treatment for a disease for which there is no suitable therapy. This procedure means that the time for evaluation of the application by the FDA is reduced from ten months to six months. This procedure corresponds to the "Accelerated Assessment" in Europe.
- **"FAST TRACK DESIGNATION":** a program of interactions with the FDA to facilitate the development and accelerate the review of new drugs that are used in the treatment of serious or potentially fatal diseases that are likely to respond

to an unmet therapeutic need. The advantage of this process is that the company may benefit from more frequent meetings with the FDA in order to discuss the product development plan and ensure the appropriate data are collected for the MA. Fast Track designation does not necessarily lead to the Priority Review procedure nor to Accelerated Approval.

- **"BREAKTHROUGH THERAPY DESIGNATION":** this procedure, put in place in 2012, aims to accelerate the development and review of drugs for treating serious diseases or potentially fatal diseases, and for which the preliminary clinical proof demonstrates substantial improvement from the drug with respect to treatments available on a clinically significant criterion. A drug that is designated "Breakthrough Therapy" may receive the following:
  - . all the special characteristics of the Fast Track designation;
  - . starting at the Phase 1 clinical trial, intensive support in a development program for effective drugs;
  - . an organizational commitment involving senior managers.

If additional research or experiments demonstrate that a product presents risks while being marketed, the FDA can require it to be withdrawn immediately. In addition, the FDA can withdraw a marketing authorization for other reasons, in particular if studies after authorization are not conducted with the necessary diligence.

#### 9.4.4 Orphan drugs

There is a specific procedure for the authorization for orphan drugs.

Orphan drugs are drugs used for the diagnosis, prevention and treatment of fatal or very serious and rare diseases. To be qualified as rare or orphan within the European Union, a disease must affect fewer than 1 person out of 2,000, and in the United States the disease must affect fewer than 200,000 persons.

These drugs are called "orphan" because the pharmaceutical industry has little interest in the usual market conditions to develop and market products intended only for a limited number of patients (so-called orphan diseases). For the pharmaceutical companies, the cost of marketing a product recommended for a rare disease might not be covered by the expected sales in this market.

In Europe, legislation was adopted to promote treatments for rare diseases. By virtue of Regulation no. 847/2000/EC of December 16, 1999, as amended by Regulation no. 847/2000/EC of April 27, 2000, a drug is considered an orphan drug if its developer demonstrates, in an application filed with the EMA, that it is used for the treatment of a so-called orphan disease in the European Union, or when it is used for the treatment of a disabling or serious and chronic disease for which there is yet no treatment or satisfactory treatment, and that in the absence of incentive measures, the costs incurred in the development cannot be covered by the profits from sales.

In the United States, the 1983 American law on orphan drugs (Orphan Drug Act) combines several laws encouraging the development of treatments for rare diseases. The Orphan Drug Act also provides for the chance to obtain subsidies from the American Government to cover clinical trials, tax credits for covering research expenses, possible waiver of filing costs when applying for registration with the FDA and seven years of exclusivity of the active ingredient for the given indication in the case of a marketing authorization.

If the orphan drug status is obtained, the product then receives an exclusive marketing period of ten years, during which no similar product can be marketed for the same indication, as well as a waiver of regulatory fees and other advantages.

### 9.5 French Sunshine Act — Transparency of interests

Decrees no. 2013-414 of May 21, 2013 "on the transparency of benefits granted by companies manufacturing or marketing health and cosmetic products intended for human use" and no. 2016-1939 of December 28, 2016, on the public declaration of interests and transparency of benefits, specify the conditions of public "transparency" concerning relations (benefits procured or agreements made) between the companies that introduce or sell health and cosmetic products and some healthcare providers. As soon as the Company markets drugs, it must then make public:

- the information relating to agreements existing with healthcare professionals and other similar persons (except for agreements governed by Articles L.441-3 and L.441-7 of the French Commercial Code);
- all compensation, benefits in kind or cash given in an amount greater than or equal to €10;

- The information is centralized on a single website ([www.transparence.sante.gouv.fr](http://www.transparence.sante.gouv.fr)) under the responsibility of the French Ministry of Health.

These requirements took effect on July 1, 2017. Similar resources exist in other countries, especially the United States (US Sunshine Act).

The Public Health Code also contains “anti-gift” provisions which provide for a general ban on companies that manufacture or market health products from making payments and benefits to health professionals, with limited exceptions, and strictly defines the conditions under which these payments or benefits can legally be granted. The provisions arising from Law No. 2011-2012 were amended by Ordinance No. 2017-49 of January 19, 2017, which notably extended their application to a wider range of legal and physical persons, clarified the scope of operations excluded from the ban and those authorized under certain conditions, and provided for a new authorization process. The decree of August 7, 2020 set the amounts for which the service, depending on the service provided, is considered negligible and does not require any declarative action. A second decree of August 7, 2020 defined the amounts beyond which the agreement is subject to an authorization regime, the amounts less than or equal to these amounts requiring a simple declaration. The decree also provides the reporting schedule to the competent authority.

## 10 Information on trends

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### 10.1 Main trends since the end of the last fiscal year

With five of its product candidates in clinical development, including two with leading pharmaceutical partners, and the progress of new preclinical programs towards the clinical phase, the Company is entering the next stages of its growth, financially supported, in particular, by partnerships with international pharmaceutical groups and grants from Bpifrance:

#### **TEDOPI® (COMBINATION OF NEOEPITOPES):**

- Phase 3 clinical trial in non-small cell lung cancer in Europe, the United States and Israel. The trial was conducted in HLA-A2 positive patients in second- or third-line therapies post checkpoint inhibitor treatment failure.
  - The trial was planned in two steps: a first step including approximately 100 patients overall with a planned analysis of data on the percentage of patients achieving 12 months' survival.
  - At the end of this first step, and depending on the results obtained, the Company had to decide on the best development strategy for Tedopi® in lung cancer after failure of checkpoint inhibitor therapy.
  - On April 1, 2020, the Company announced positive results for Step-1 of the study. Analysis of the data showed that the primary endpoint for this milestone was achieved with a 12-month survival rate in patients treated with Tedopi® and a 10% absolute difference in this survival rate compared to chemotherapy.
  - These results confirm the value and therapeutic benefit of Tedopi® in a patient population for which there is no validated treatment to date, and which is awaiting new therapeutic options. The Company will initiate discussions with the regulatory authorities to analyze these positive clinical results and determine the best options to pursue the development of Tedopi® and maximize the positive benefit/risk ratio data obtained. At the same time, given that the positive Step-1 results significantly strengthened the value of Tedopi®, the Company is continuing to explore any potential partnering opportunities for the product.
  - Due to the global COVID-19 epidemic, the Company, in conjunction with the Independent Data Monitoring Committee (IDMC) and the Trial Steering Committee, analyzed the potential impact of this epidemic on the Atalante 1 trial. The clinical trials data could be strongly impacted by the worldwide COVID-19 pandemic and by the increased risk for patients with advanced lung cancer, as COVID-19 can cause serious pulmonary complications in this immunocompromised patient population. Moreover, for patient safety, several scientific and medical societies currently recommend the voluntary suspension of new patient recruiting in clinical trials in oncology.
  - Consequently, following the recommendation from both IDMC and Atalante 1 Steering Committee, OSE Immunotherapeutics voluntarily decided to terminate patient screening and accrual in the Step 2 initially planned and now canceled.
  - To date, the Company intends to discuss with the regulatory health authorities (FDA and EMA) to analyze the positive clinical results of the Atalante 1 study, and to determine the best options to continue the development of Tedopi® and to maximize the data obtained in terms of risk / benefit ratio. Based on these future discussions, and according to the feedback from health authorities, the Company will try to obtain a marketing authorization in a subgroup of identified patients, unless health agencies consider that one or more additional studies are necessary.
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- The Phase 2 clinical trial, TEDOPaM: Tedopi® is being evaluated in the Phase 2 clinical trial, TEDOPaM, sponsored by the GERCOR cooperative oncology group in HLA-A2 positive patients with locally advanced pancreatic cancer.

Due to the COVID-19 pandemic, the screening and enrollment of new patients in TEDOPaM had been temporarily suspended in March 2020. After a review of the data collected before the end of March 2020 according to the initial protocol (Tedopi® alone or in combination with Opdivo® versus chemotherapy with FOLFIRI), the Independent Data Monitoring Committee (IDMC) of the trial recommended stopping the assessment the treatment arm of Tedopi® in

combination with Opdivo® and introducing a treatment arm of Tedopi® + chemotherapy (FOLFIRI). GERCOR has modified the treatment regimen accordingly and the first new enrollments are expected during the second quarter of 2021 (based on the COVID-19 impact) with an amended protocol comparing Tedopi® in combination with Folfiri versus Folfiri as maintenance therapy after induction therapy with Folfirinox. The main endpoint of the trial remains the one-year survival rate.

*\*\* FOLFIRINOX: a chemotherapy regimen combining folinic acid, fluorouracil, irinotecan and oxaliplatin*

*\* FOLFIRI: a chemotherapy regimen combining folinic acid, fluorouracil and irinotecan*

- Phase 2 clinical trial, TEDOVA: in March 2021, the National Medicines Safety Agency (ANSM) and the Committee for the Protection of People (CPP) gave their approval to start a new Phase 2 clinical trial assessing Tedopi® in patients with ovarian cancer relapse (TEDOVA trial), sponsored by ARCAGY-GINECO. Tedopi® will be evaluated as a single agent and in combination with Keytruda® (pembrolizumab), a Merck checkpoint inhibitor, as maintenance therapy after chemotherapy in patients with ovarian cancer.

The TEDOVA trial will include three treatment arms and will evaluate Tedopi® as a monotherapy maintenance treatment or in combination with the anti-PD-1 Keytruda® versus the reference treatment in patients with ovarian cancer in a situation of platinum-sensitive relapse, and whose disease is controlled following chemotherapy with platinum. This study should include 180 patients.

#### **COVEPI (COMBINATION OF EPITOPES)**

- Positive preclinical and *ex vivo* results in humans for this prophylactic COVID-19 vaccine, multi-target and long-term protection:
  - Data support the potential as a novel and differentiated COVID-19 vaccine designed against multiple SARS-CoV-2 targets with technology known to induce memory T lymphocytes.
  - Studies show that CoVepiT provides tissue-resident memory (Trm) sentinel T cell response with long-term protective immunity in barrier tissues such as the respiratory tract and the lung
  - The emergence of new mutated coronavirus variants strengthens the multi-epitope approach against 11 viral proteins to generate a T lymphocyte response.
- On April 1, 2021, OSE Immunotherapeutics announced the authorization of the Federal Agency for Medicines and Health Products (FAMHP) and the Belgian Ethics Committee to start a Phase 1 clinical trial with CoVepiT which will assess the safety, reactogenicity and immunogenicity of the vaccine in healthy adult volunteers.

#### **BI 765063 (OSE-172) (ANTI-SIRP MONOCLONAL ANTIBODY α)**

- Collaboration and license agreement granted to Boehringer Ingelheim (April 2018) for the development, registration and marketing of the product in immuno-oncology. Following authorization from the French and Belgian regulatory authorities in March 2019, the product candidate is in a Phase 1 clinical trial in patients with advanced solid tumors.

#### **OSE-279 (MONOCLONAL ANTI-PD-1 ANTIBODY)**

- OSE-279 is a humanized anti-PD-1 monoclonal antibody expected to enter Phase 1/2 clinical trials in 2021 for a niche indication in immuno-oncology. This would allow the Company to own a patented anti-PD-1 that it could subsequently develop in combination with other products in its portfolio.

#### **CLEC-1 (IMMUNE MYELOID CHECKPOINT)**

- The OSE Immunotherapeutics teams have succeeded in characterizing the CLEC-1 myeloid checkpoint as a new therapeutic target in immuno-oncology and have identified monoclonal antibody antagonists that block this novel “Don't Eat Me” signal. They increase both the phagocytosis of tumor cells by macrophages and the uptake of antigens

by dendritic cells (data presented at the 2020 meeting of the American Association for Cancer Research). The identification of CLEC-1 and its antagonists constitute an exciting innovative step in cancer immunotherapy.

#### **OSE-127/S95011 (INTERLEUKIN-7 RECEPTOR ANTAGONIST)**

- License option granted to Servier (December 2016) for the development and marketing of the product in autoimmune diseases-Entry into a Phase 1 clinical trial in healthy volunteers completed at the end of 2018. Exercise of option 1 of the collaboration and licensing agreement in February 2019.
- Positive Phase 1 clinical trial results showing a good safety and tolerability profile of the product.
- A Phase 2 clinical trial underway since December 2020 in ulcerative colitis led and sponsored by OSE Immunotherapeutics.

#### **FR104 (CD28 ANTAGONIST)**

- The positive results of the Phase 1 clinical proof-of-concept trial of FR104, combined with the preclinical tolerability profile and the efficacy data for a large number of preclinical models of inflammatory and autoimmune diseases support the continuation of the product's clinical development in autoimmune diseases and transplants.
- In December 2020, the French regulatory authorities gave their authorization for a Phase 1/2 clinical trial evaluating FR104 in patients having received a kidney transplant. This study aims to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of FR104 in patients who have received a renal transplant. It is being carried out under a clinical collaboration agreement between OSE Immunotherapeutics and the Center Hospitalier Universitaire de Nantes, which is the sponsor.
- In parallel with the ongoing Phase 1/2 clinical trial of FR104 in kidney transplantation, OSE Immunotherapeutics is planning a new Phase 2 clinical trial of FR104 in an indication of autoimmune disease.

#### **OSE-230 (CHEMR23 AGONIST ANTIBODY)**

- Preclinical efficacy data showed that OSE-230 was the first monoclonal antibody activator of specialized resolution receptors that restore the hemostasis of the pathological tissue, its integrity and its functions (data presented at the annual FOCIS meeting 2020 "Federation of Clinical Immunology Societies"). The product has a strong therapeutic potential in various chronic pathologies.

Given the Company's current activities, it has not provided any specific comments on the trends that may affect its recurring revenues and general operating conditions from the date of the last fiscal year ended December 31, 2020, until the publication date of this Universal Registration Document.

With a cash position of €29.3 million at December 31, 2020 (excluding the 2020 research tax credit of €5.1 million), the Company has the cash required to continue its operations for the 12 months following the publication of its financial statements for the fiscal year ended December 31, 2020.

This capital will enable the Company to accelerate and expand its portfolio of products in the clinical phase with the launch of three programs:

- A Phase 2 study with FR104 in an indication of autoimmune disease,
- The preparation of a clinical trial of OSE-230, a new monoclonal antibody developed for the resolution of chronic inflammation and
- preparing for clinical trials of CLEC-1, the innovative new "Don't Eat Me signal" myeloid checkpoint.

This capital will also finance its development costs for ongoing clinical studies on:

- Tedopi® with the Phase 3 clinical trial of Tedopi® in the treatment of lung cancer (non-small cell or NSCLC) after the failure of a checkpoint inhibitor that has shown positive results, the Phase 2 clinical trial of Tedopi® in pancreatic cancer and the Phase 2 clinical trial in ovarian cancer
- OSE-127/S95011 in its Phase 2 clinical trial step
- BI 765063/OSE-172 in its Phase 1 clinical trial step
- CoVepiT, the COVID-19 vaccine, in its Phase 1 clinical trial step

As well as research on earlier products.

The Company is expected to receive an amount of €5.1 million for the 2020 Research Tax Credit. During 2020 or 2021, the Company is expected to reach further development milestones for OSE-172/BI 765063 under its contract with Boehringer Ingelheim, and OSE-127/S95011 under its contract with Servier, which could generate additional cash flow.

The reader is invited to refer to section 3.5 of this Universal Registration Document covering the activity's financing needs.

## **10.2 Trends, uncertainties, demands, commitments or events that are reasonably likely to have a material effect on the Company's prospects**

N/A.

## **11 Profit/(loss) forecasts or estimates**

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The Company does not make any profit forecast or estimate.

## 12 Administrative, management and supervisory bodies, and senior management

### 12.1 Management and directors

#### 12.1.1 Composition of the Board of Directors

As of the date of this Universal Registration Document, the Board of Directors is comprised of 9 members:

First name — Last name or corporate name of the member	Main position in the Company	Main position(s) outside the Company
Dominique Costantini	- Director of Development - Chairman of the Board of Directors - Director	- Director of Theranexus SAS - Director of Smart Immune
Maryvonne Hiance	- Director of Public Relations - Vice-Chairman of the Board of Directors - Director	- Vice Chairman of France Biotech - Vice Chairman of the Atlanpole Biotherapies cluster - Chairman of HealthTech For Care - Chairman of Olgram - Director of Pherecydes Pharma
Sophie Brouard	- Director	- 1st Class Director of Research, CNRS
Jean-Patrick Demonsang	- Director	- Chairman of Demonsang Consulting SAS - Chairman of the Supervisory Board of G1J Ile-de-France
Brigitte Dréno	- Director	- Consulting Firms: BMS, Fabre Oncology
Didier Hoch	- Director	- President of the Supervisory Board of Pherecydes Pharma - Director of the University of the Underground Charity Foundation Strategic Advisor for Goliver Therapeutics
Alexis Peyrols	- Chief Executive Officer - Director	- Chairman of Aperana Consulting - CEO of OSE Immunotherapeutics Inc.
Nicolas Poirier	- Chief Scientific Officer - Director representing the employee shareholders	- Member of the Scientific Board of MabDesign and MabSillico
Gérard Tobelem	- Director	- Director of Dendrogenix

#### BIOGRAPHIES OF THE MEMBERS OF THE BOARD OF DIRECTORS

The 9 members of the Board of Directors combine international expertise in drug development, marketing, industry and finance with experience working with Nasdaq- and Euronext-listed biotechnology companies.

##### Dominique Costantini — Chairman of the Board of Directors

Since co-founding OSE in 2012, Dominique Costantini has raised private equity funds in 2014, completed the Company's IPO in 2015, acquired Effimune in 2016 to lead the Company's development programs and contributed to the partnership agreements implemented in 2016 and 2018. She is the founder and former Chief Executive Officer of BioAlliance Pharma (1997–2011), which was renamed Onxeo in 2014 and is listed on Euronext Paris. Dominique has designed, developed and secured approval for innovative cancer therapies. She raised funds from 1999 to 2005 and completed an IPO for BioAlliance Pharma on Euronext in late 2005. Three successful stock market fundraisings were then based on product development benchmarks: two innovative products were approved in Europe and the United States. She has established international

industrial partnerships, signing contracts worth more than €130 million. BioAlliance Pharma is the only French biotech company to have had two products registered with the FDA. Dominique gained more than 15 years of operational management experience in the pharmaceutical industry while working at HMR (now Sanofi). She led R&D and drug marketing activities from research to market in fields including immunology, endocrinology, inflammation, infection and oncology. Medical Doctor, Immunology – René Descartes University – Paris V.

#### **Alexis Peyrols — Chief Executive Officer and Director**

EDHEC and Executive MBA from Imperial College in London; Alexis joined OSE Pharma as Chief Financial Officer in September 2013. He was appointed Chief Executive Officer of OSE Immunotherapeutics on March 28, 2018. Alexis has more than 20 years of international management experience, mainly in healthcare, having worked for Sanofi in Japan and in eastern Europe, where he served as Financial Control Manager for the Baltic States and then Head of Activities for Business Development in Eastern Europe. He then joined Guerbet, where he served as Financial Control Manager and then Chief Executive Officer for Latin America based in Brazil, where he managed all the marketing and manufacturing operations.

#### **Maryvonne Hiance — Vice Chairman of the Board of Directors, Director**

Maryvonne, who was previously the Chairman and co-founder of Effimune, is an engineer who specializes in nuclear science. For 14 years she managed a neutron studies program at Framatome (Areva). Over the past 20 years, she has led several innovative biotechnology companies: SangStat Atlantic, whose parent company, SangStat Medical Corporation, was acquired by Genzyme in 2003 for its product portfolio in immunosuppression and transplantation; she also led innovative companies, DrugAbuse Sciences and TcLand. Maryvonne founded and managed Strategic Ventures, a consulting firm that works with technology companies. Maryvonne Hiance has been a member of the French Strategic Council for Innovation and has served as advisor to the French SMEs and Industry Ministry. She is Vice Chairman of France Biotech, the French Association of Life Sciences entrepreneurs.

#### **Sophie Brouard — Director**

Sophie Brouard is an immunologist and veterinarian who specializes in transplants. She completed postdoctoral studies at Harvard Medical School in Boston. She is a director of research at CNRS, co-director of an INSERM research unit specializing in immunotherapy of autoimmune diseases and grafts and leads an INSERM research unit in Nantes on transplantation and its mechanisms. This current research work focuses on understanding the rejection mechanism during a transplant in order to find biomarkers of the survival of the transplant. She also chairs the Executive Committee of the Centaure Foundation. Centaure is a world-renowned foundation and pioneer in pancreas transplants that performs around two-thirds of the simultaneous liver and pancreas transplants in France. This accomplishment is due to the strong commitment of the surgical and research teams. Centaure has also won worldwide recognition for its work on the immunological mechanisms of diabetes, in experimental models and its therapy trials in diabetic patients. Centaure combines three key centers of excellence — Nantes, Lyon and Paris—enabling them to collaborate on research in transplantation, in connection with an international committee of Europeans and Americans.

#### **Jean-Patrick Demonsang — Director**

Jean-Patrick Demonsang joined the Board of Directors of OSE Pharma in 2014. During his tenure as Chairman and Chief Executive Officer of Seventure Partners until 2013, he supported the activities of more than 150 companies. Seventure is now a leading venture capital firm in France, managing more than €500 million with a team of 12 experts in two investment sectors: information technologies and life sciences, in France and Europe.

Jean-Patrick Demonsang is also an entrepreneur who has created and led several SMEs, and he is currently leading an entrepreneurial project involving a theme park in the south of France. Jean-Patrick holds an MBA from HEC and a degree in physics.

**Brigitte Dréno — Director**

Professor Brigitte Dréno is head of the Dermatology Department at the Nantes University Hospital Center, which develops research expertise and groundbreaking treatments in skin oncology. Brigitte Dréno is also the Director of the Biotherapy Clinical Investigation Center and Director of the Unit of Cell and Gene Therapy, and as such closely oversees all immuno-oncology advances. She is Vice Dean of the Medical School. In collaboration with the academic leadership, she supports OSE Immunotherapeutics' R&D initiatives on the Nantes University campus.

**Didier Hoch — Director**

Didier Hoch is a medical doctor and Chairman of the Biovision Forum and of Big Booster, a start-up accelerator. He also serves as a director for listed companies, including Gentilicel and, previously, DBV Technologies. From 2000 to 2010, he was Chairman of Sanofi-Pasteur-MSD, a joint venture between Sanofi and Merck dedicated to vaccines. He also held a variety of managerial positions at Rhône Poulenc Rorer and then Aventis where he was Vice Chairman for Middle East & Africa. He previously served as Chairman of the European Vaccine Manufacturers' Association and Chairman of the LEEM Biotechnology Committee.

**Nicolas Poirier — Director representing the employee shareholders of OSE Immunotherapeutics**

Nicolas Poirier has been chief scientific officer of OSE Immunotherapeutics since 2016. He joined the company in 2009 as project leader and then as director of scientific programs. Nicolas Poirier holds a Ph.D. in immunology and has a strong expertise in the development of immunotherapies. His role has been to implement innovative therapeutic strategies on new targets and pathways in immunology addressing severe pathologies with high therapeutic need, thus making a robust contribution to the Company's growth. He is the author of several high-level international publications in the area of immunotherapy.

**Gérard Tobelem — Director**

Gérard Tobelem won the first Diderot Innovation prize in 2006. He has held industrial, medical and scientific positions, including as Executive Chairman of the French Blood Establishment. Gérard Tobelem has held strategic roles at the French Ministry of Higher Education and Research. He has advised a variety of international pharmaceutical companies on their Research & Development strategies. Until 2018, he was non-executive Chairman of the Board of Directors of Theradiag S A. Previously, he taught hematology at Paris 7 University and was head of the Department of Blood Disorders at Lariboisière Hospital in Paris.

**Addresses of directors**

- Dominique Costantini – 286, boulevard Raspail – 75015 Paris
- Maryvonne Hiance – 35, rue Edison – 44000 Nantes
- Alexis Peyrols – 158, rue Diderot – 94300 Vincennes
- Sophie Brouard – Les Vaux – 44240 Sucé sur Erdre
- Jean-Patrick Demonsang – 149, rue Louis Rouquier – 92300 Levallois-Perret
- Brigitte Dréno – 10, rue Voltaire – 44000 Nantes
- Didier Hoch – 1508, route de Bellegarde – La Sauzée – 42210 Saint Cyr Les Vignes
- Nicolas Poirier - 4, impasse de la Rochère - 44119 Grandchamps des Fontaines
- Gérard Tobelem – 113, rue Monge – 75005 Paris

#### CAPITAL AND VOTING RIGHTS HELD BY MEMBERS OF THE BOARD OF DIRECTORS

After potential exercise of all the instruments carrying rights to shares of the Company, shares held in the Company by the directors at March 31, 2021, would be as follows:

- After the exercise of all dilutive instruments, Alexis Peyroles will hold (directly and through his company Aperana Consulting), 768,499 shares representing 4.27% of the capital and 5.07% of the voting rights
- Dominique Costantini will hold 1,978,663 shares representing 11.00% of the capital and 16.62% of the voting rights
- Maryvonne Hiance (directly and through her family holding company), will hold 424,084 shares representing 2.36% of the capital and 3.48% of the voting rights
- Sophie Brouard (directly and through her family holding company), will hold 202,904 shares representing 1.13% of the capital and 1.71% of the voting rights
- Jean-Patrick Demonsang will hold 30,000 shares representing 0.17% of the capital and 0.25% of the voting rights
- Brigitte Dréno will hold 10,000 shares representing 0.06% of the capital and 0.05% of the voting rights
- Didier Hoch will hold 7,334 shares representing 0.04% of the capital and 0.06% of the voting rights
- Nicolas Poirier will hold 92,802 shares representing 0.52% of the capital and 0.49% of the voting rights
- Gérard Tobelem will hold 31,250 shares representing 0.17% of the capital and 0.26% of the voting rights

#### LIST OF CORPORATE OFFICES AND POSITIONS HELD BY THE MEMBERS OF THE BOARD OF DIRECTORS IN ALL COMPANIES IN THE LAST FIVE YEARS

First name — Last name or corporate name of the member	Other current offices held in other companies	Other offices and positions held in other companies during the last five years and not held as of the date of this Universal Registration Document:
Dominique Costantini	<ul style="list-style-type: none"> <li>- Director of Theranexus SAS</li> <li>- Director of Smart Immune</li> </ul>	<ul style="list-style-type: none"> <li>- Director of Abivax</li> <li>- Director of Theradiag SA</li> <li>- Director of Carthera SAS</li> <li>- Director of Sensorion</li> </ul>
Maryvonne Hiance	<ul style="list-style-type: none"> <li>- Vice Chairman of France Biotech</li> <li>- Vice Chairman of the Atlanpole Biotherapies cluster</li> <li>- Chairman of HealthTech For Care</li> <li>- Chairman of Olgram</li> <li>- Director of Pherecydes Pharma</li> </ul>	<ul style="list-style-type: none"> <li>- Chairman of France Biotech</li> <li>- Director of APAVE</li> <li>- Chairman of the Strategic Advisory Board of Olmix, Bréhan</li> <li>- Strategic Adviser for Goliver, Nantes</li> </ul>
Sophie Brouard	<ul style="list-style-type: none"> <li>- 1st Class Director of Research, CNRS</li> </ul>	<ul style="list-style-type: none"> <li>- Director of the Centaure Foundation</li> <li>- Director of the French Society of Immunology (SFI)</li> <li>- Vice Chairman of Life Sciences and Health for the Pays de la Loire region</li> </ul>
Jean-Patrick Demonsang	<ul style="list-style-type: none"> <li>- Chairman of Demonsang Consulting SAS</li> <li>- Chairman of the Supervisory Board of G1J Ile-de-France</li> </ul>	<ul style="list-style-type: none"> <li>- Chairman of Parexi SAS</li> <li>- Chief Executive Officer of Genode Partners SAS</li> </ul>
Brigitte Dréno	<ul style="list-style-type: none"> <li>- Consulting Firms: BMS, Fabre Oncology</li> </ul>	<ul style="list-style-type: none"> <li>- Deputy Vice-President for Scientific and Technical Culture at the University of Nantes</li> </ul>
Didier Hoch	<ul style="list-style-type: none"> <li>- President of the Supervisory Board of Pherecydes Pharma</li> <li>- Director of the University of the Underground Charity Foundation</li> <li>- Strategic Advisor for Goliver Therapeutics</li> </ul>	<ul style="list-style-type: none"> <li>- Independent Director of DBV Technology, Gentichel, Germitech</li> <li>- Member of the Strategic Board—Committee Advisory Board of Myastérix, Curavac Director of the Foundation for the Université Grenoble Alpes</li> </ul>
Nicolas Poirier	<ul style="list-style-type: none"> <li>- Member of the Scientific Board of MabDesign and MAbSillico</li> </ul>	<ul style="list-style-type: none"> <li>- None</li> </ul>
Alexis Peyroles	<ul style="list-style-type: none"> <li>- Chairman of Aperana Consulting</li> <li>- CEO of OSE Immunotherapeutics Inc.</li> </ul>	<ul style="list-style-type: none"> <li>- None</li> </ul>
Gérard Tobelem	<ul style="list-style-type: none"> <li>- Director of Dendrogenix</li> </ul>	<ul style="list-style-type: none"> <li>- Director of SupBiotech</li> <li>- Director of the Louis Dreyfus business foundation</li> <li>- Chairman of Théradiag SA</li> </ul>

## 12.1.2 Composition of the operational management team

### COMPOSITION OF THE EXECUTIVE MANAGEMENT

Dominique Costantini serves as Chairman of the Board of Directors. Dominique Costantini previously served as Chief Executive Officer of the Company until April 12, 2018.

Alexis Peyroles is the Company's Chief Executive Officer. He was previously the Chief Operating Officer until April 12, 2018, responsible for operations, finance and the Company's agreements and licenses.

### BIOGRAPHIES OF THE MEMBERS OF THE EXECUTIVE MANAGEMENT

Please refer to paragraph 14.1.1 of the Universal Registration Document.

#### Alexis Peyroles—Chief Executive Officer

EDHEC and Executive MBA from Imperial College in London; Alexis joined OSE Pharma as Chief Operating Officer. He became Chief Executive Officer of OSE Immunotherapeutics on April 12, 2018. Alexis Peyroles has successfully established OSE's strategic collaborations and licensing agreements by bringing together all the components of the business lines needed to sign such partnerships. Through his 20-plus years of international management experience in the pharmaceutical industry (at Sanofi and Guerbet) and in biotechnology in Europe, Japan and South America, he has developed his skills in strategy, finance, pharmaceutical marketing and agreements and licenses. Since the inception of OSE, his strategic and operational skills have been pivotal to the growth of the Company, its initial public offering, acquisitions and the partnerships shaping the future of OSE with key value-creating steps.

#### Alexis Peyroles is supported by an operational management team that includes:

- **Dominique Costantini** (MD), Director of Development, brings to the OSE team her broad expertise in this field.
- **Maryvonne Hiance**, Director of Public Affairs, brings to the Company her networks and strong involvement with public authorities and, more broadly, with institutional players, as well as her personal experience.
- **Anne-Laure Autret-Cornet**, Chief Financial Officer

Anne-Laure Autret-Cornet graduated from ESSCA Management School and has received the certificate "Corporate Finance" from HEC Paris in 2020. Specialized in Audit-Finance, Anne-Laure has acquired a seven-year experience within Deloitte before joining Effimune in 2013 as Administrative and Financial Manager. Upon the merger with OSE Pharma in 2016, Anne-Laure was appointed Chief Financial Officer of OSE Immunotherapeutics.

Damien Vieillard (replacement during maternity leave of Anne-Laure Autret-Cornet) is graduated from Noema Business Scholl with a speciality in financing engineering. He benefits from experience in the field of audit finance acquired at PriceWaterhouseCoopers and pharmaceutical companies (Sanofi and Ipsen).

- **Jean-Pascal Conduzorgues** (PharmD), Industrial Director and Qualified Pharmacist

With a doctorate in pharmacy, he has vast experience as a qualified person (QP), a pharmaceutical qualification required for drugs in Europe. He organizes the subcontractors needed to coordinate the pharmaceutical cases. He was a founder, manager and qualified person of the Montpellier-based CRID Pharma, which became Amatsi and then recently Eurofins, which he headed for 20 years. This company is a pharmaceutical services company specializing in pharmaceutical development (formulation, analytical development, approval of manufacturing processes, ICH stability studies, quality control and pharmaceutical writing) and in drug management for clinical trials. In 2011 he merged CRID Pharma with Avogadro to form Amatsi, a 175-person group located in France and the United States offering all services related to drug development. Since 2013 Jean-Pascal Conduzorgues has had his own consulting firm, Ibero, where he assists with pharmaceutical planning and initiatives by biotechnology companies he chooses to support as a shareholder and consultant, as is the case for OSE Immunotherapeutics.

- **Nicolas Poirier (PhD), Chief Scientific Officer**

Nicolas Poirier has been chief scientific officer of OSE Immunotherapeutics since 2016. He joined the company in 2009 as project leader and then as director of scientific programs. Nicolas Poirier holds a Ph.D. in immunology and has a strong expertise in the development of immunotherapies. His role has been to implement innovative therapeutic strategies on new targets and pathways in immunology addressing severe pathologies with high therapeutic need, thus making a robust contribution to the Company's growth. He is the author of several high-level international publications in the area of immunotherapy.

Specific operational departments handle medical, translational, medical-marketing, pharmaceutical and legal activities.

### **12.1.3 Disclosures about the Management team and directors**

In the last five years, none of the members of the Company's Board of Directors have been:

- Convicted of fraud or subject to an incrimination or official public sanction by the statutory or regulatory authorities;
- involved in any bankruptcies, receiverships or liquidations as a manager or corporate officer;
- Prevented from acting as a member of an administrative, management or supervisory body or from participating in the management or conduct of business of an issuer;
- subject to an incrimination and/or official public sanction by the statutory or regulatory authorities (including designated professional organizations).

In the last five years, neither Dominique Costantini nor Alexis Peyroles has been:

- convicted of fraud, or subject to an incrimination or official public sanction by the statutory or regulatory authorities;
- involved in any bankruptcies, receiverships or liquidations as a manager or corporate officer;
- prevented from acting as a member of an administrative, management or supervisory body or from participating in the management or conduct of business of an issuer;
- subject to any incrimination and/or official public sanction by the statutory or regulatory authorities (including designated professional organizations).

## **12.2 Potential conflicts of interest of the members of the Board of Directors and Executive Management**

To the best of the Company's knowledge, no current or potential conflict of interest exists between the duties with regard to the Company and the personal interests and/or duties of the persons comprising the administrative or management bodies or the executive management as referred to above in paragraph 12.1 "Management and directors".

Dominique Costantini signed a part-time, open-ended employment contract on July 1, 2014. Her employment contract was amended in April 2015 to increase her hours to 133 working hours per month, for gross annual compensation of €180,000 excluding variable compensation. Dominique Costantini agreed an addendum to her employment contract on October 1, 2016, making it full-time with gross annual compensation of €205,314, which increased to gross annual compensation of €275,000 on July 1, 2019, then to gross annual compensation of €302,500 on July 1, 2020. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets. The Company is continuing this contract due to Dominique Costantini's seniority and her unique technical roles and expertise in drug development.

Alexis Peyroles, Chief Executive Officer, signed an open-ended employment contract on July 1, 2014, modified by an addendum effective July 1, 2018, as Director of Operations with a gross annual salary of €250,000, then again modified by an addendum effective July 1, 2019, for an annual gross salary of €350,000. Variable compensation equal to up to 50% of the gross annual compensation is provided for based on the achievement of certain targets, with 50% of it in the form of free shares. The Company is continuing this contract due to Alexis Peyroles' seniority and his unique technical roles in operational management and international business collaborations.

Maryvonne Hiance, Vice-Chairman of OSE Immunotherapeutics, has an operational role as Strategic Advisor within the Executive Management under a contract dated May 31, 2016. At its meeting on June 26, 2019, the Board of Directors wished to amend the title and position in her employment contract to Director of Public Affairs; this change was made without a salary raise. Compensation under this employment contract is calculated on the basis of €120,000 in gross annual salary. The employment contract took effect on May 31, 2016, concurrently with the completion of the merger. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets. The Company continues this contract due to Maryvonne Hiance's seniority, her unique technical roles in industrial strategy, her networks and strong involvement with public authorities and, more broadly, with institutional players.

Nicolas Poirier, elected as the director representing the employee shareholders on June 26, 2019, is employed as Chief Scientific Officer under an employment contract dated May 31, 2016. Compensation in respect of this employment contract has been calculated on the basis of the gross annual sum of €180,000, increased to a gross annual sum of €200,000 on July 1, 2020. Variable compensation is also provided for. Since his appointment as the director representing the employee shareholders was based on his position as a pre-existing employee, Nicolas Poirier's employment contract is considered a standard agreement entered into under normal conditions.

## 13 Compensation and benefits

### 13.1 Total gross compensation for members of the Board of Directors and General Management

In accordance with the law of July 3, 2008, the disclosures presented herein are established by referring to the corporate governance code and additional recommendations regarding communication on the compensation of executive corporate officers of listed companies as defined by Middlenext. The Middlenext Code used as a reference by the Company can be consulted at the address [http://www.middlenext.com/IMG/pdf/Code\\_de\\_gouvernance\\_site.pdf](http://www.middlenext.com/IMG/pdf/Code_de_gouvernance_site.pdf). Tables no. 1, no. 2, no. 3, no. 4, no. 8, no. 9, no. 10 and no. 11 of the "AMF Recommendation on corporate officers' compensation disclosures to be included in the registration documents" of December 22, 2008 are presented below.

For the 2020 fiscal year, the only executive corporate officers were Dominique Costantini and Alexis Peyroles. The only compensation paid to executive corporate officers during 2020 was attendance fees for their terms of office as directors.

Dominique Costantini has held an open-ended employment contract since July 1, 2014 for her position as Director of Development. She agreed an addendum to her employment contract on October 1, 2016, making it 151.67 hours per month with gross annual compensation of €205,314, which increased to gross annual compensation of €275,000 on July 1, 2019, then to gross annual compensation of €302,500 on July 1, 2020. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

Alexis Peyroles, Chief Executive Officer, signed an open-ended employment contract on July 1, 2014, modified by an addendum effective July 1, 2018, as Director of Operations with a gross annual salary of €250,000, then again modified by an addendum effective July 1, 2019, for an annual gross salary of €350,000. Variable compensation equal to up to 50% of the gross annual compensation is provided for based on the achievement of certain targets, with 50% of it in the form of free shares.

A report setting out the principles and criteria for determining, distributing and allocating the fixed, variable and exceptional items making up the total compensation and benefits of any kind or members of the Board of Directors and Executive Management for the 2020 fiscal year is presented in Appendix C of this Universal Registration Document. This report will be submitted for approval to the Annual General Shareholders' Meeting scheduled for June 24, 2021 in resolutions [7 to 10]. The reader is referred to that report.

**TABLE 1: SUMMARY TABLE OF COMPENSATION AND SHARE SUBSCRIPTION WARRANTS ALLOCATED TO EACH EXECUTIVE CORPORATE OFFICER**

	2020 fiscal year	2019 fiscal year
<b>Dominique Costantini</b>		
<b>Chairman of the Board of Directors since March 28, 2018</b>		
Compensation due for the fiscal year (table 2)	€385,875 Gross Wages	€319 969 Gross Wages
Valuation of multi-annual variable compensation allocated during the year	N/A	N/A
Valuation of the share subscription warrants* and founders' share warrants allocated during the fiscal year (Table 4)	€25,900	N/A
Valuation of free shares allocated (table 6)	N/A	N/A
<b>TOTAL</b>	<b>€411,775</b>	<b>€319,969</b>

<b>Alexis Peyrols Chief Executive Officer</b>		
Compensation due for the fiscal year (table 2)	€454,362 Gross Wages	€393,136 Gross Wages
Valuation of multi-annual variable compensation allocated during the year	N/A	N/A
Valuation of the share subscription warrants and founders' share warrants allocated during the fiscal year (Table 4)	N/A	N/A
Valuation of free shares allocated (table 6)	€836,486 Gross	€609,635
<b>TOTAL</b>	<b>1.290,848€</b>	<b>1.002,771 €</b>

**TABLE 2: SUMMARY TABLE OF THE REMUNERATION OF EACH EXECUTIVE CORPORATE OFFICER**

Executive CorOfficer	Compensation for the 2020 fiscal year (In K)		Compensation for the 2019 fiscal year (in K)	
	Amounts due	Amounts paid	Amounts due	Amounts paid
Fixed compensation	293,565	293,565	240,157	240,157
Annual variable compensation	75,625	75,625 <sup>2</sup>	68,750	68,750
Multi-year variable compensation	N/A	N/A	N/A	N/A
Exceptional compensation	N/A	N/A	N/A	51,328
Directors' fees	16,685	16,685	11,062	11,062
Benefits in kind	0	0	0	0
<b>TOTAL</b>	<b>385,875</b>	<b>385,875</b>	<b>319,969</b>	<b>319,969</b>

<sup>1</sup> Dominique Costantini's employment contract was amended in October 2016 to bring her to full-time (151.67 working hours per month), for gross annual compensation of €205,314 excluding variable compensation, then amended on July 1, 2019, to bring the gross annual compensation to €275,000 excluding variable compensation, then amended on July 1, 2020, to increase the gross annual compensation to €302,500 excluding variable compensation.

Dominique Costantini's bonus for fiscal year 2019 was paid at the beginning of fiscal year 2020. Dominique Costantini, having achieved the targets for the 2019 fiscal year, was paid a bonus of three months' wages in January 2020, i.e. €68,750.

<sup>2</sup> Variable compensation was paid in January 2021.

Executive Officer	Compensation for the 2020 fiscal year In euros		Compensation for the 2019 fiscal year In euros	
Alexis Peyrolles	454,362€ Gross <sup>1</sup>		393,136€ Gross <sup>1</sup>	
	Amounts due	Amounts paid	Amounts due	Amounts paid
Fixed compensation	350,177	350,177	300,000	300,000
Annual variable compensation	87,500	87,500 <sup>2</sup>	83,125	83,125
Multi-year variable compensation	N/A	N/A	N/A	N/A
Exceptional compensation	N/A	N/A	N/A	N/A
Directors' fees	16,685	16,685	10,011	10,011
Benefits in kind	0	0	0	0
<b>TOTAL</b>	<b>454,362</b>	<b>454,362</b>	<b>393,136</b>	<b>393,136</b>

<sup>1</sup> Alexis Peyrolles' contract provided for compensation of €150,000 gross per year. This compensation was increased to €250,000 as of June 13, 2018, then to €350,000 as of July 1, 2019. Variable compensation equal to up to 50% of the gross annual compensation is provided for based on the achievement of certain targets, with 50% of it in the form of free shares.

<sup>2</sup> Variable compensation was paid in January 2021.

**TABLE 3: TABLE ON DIRECTORS' FEES AND OTHER COMPENSATION RECEIVED BY NON-EXECUTIVE CORPORATE OFFICERS**

Last Name First Name Name Corporate name	Position on the Board and Board Committees	Directors' fees (for the fiscal year 2020)	Other compensation (for the 2020 fiscal year)	Directors' fees (for the fiscal year 2019)	Other compensation (for the 2019 fiscal year)
Gérard Tobelem	Director Appointments and Compensation Committee (Chairman)	€34,286		€24,000	
Jean-Patrick Demonsang	Director Audit Committee (Chairman)	€34,286		€24,000	
Walter Flamenbaum	Director	N/A		€8,706	
Didier Hoch	Director	€30,857		€20,571	
Sophie Brouard	Director	€25,714		€15,429	
Maryvonne Hiance	Director Vice-Chairman of the Board of Directors	€22,724		€14,775	

Brigitte Dréno	Director	€21,429		€12,000	
Nicolas Poirier	Director representing employee shareholders	€18,937		€8,837	

**TABLE 4: SUBSCRIPTION OR PURCHASE STOCK OPTIONS GRANTED TO EACH EXECUTIVE CORPORATE OFFICER BY THE COMPANY OR ANY GROUP COMPANIES DURING THE FISCAL YEARS ENDED DECEMBER 31, 2019, AND 2020**

Executive corporate officer name	Plan date	Plan number	Valuation of share subscription warrants and founders' share warrants according to the method used in the consolidated financial statements	Number of share subscription warrants and founders' warrants allocated during the fiscal year	Exercise price	Exercise period
Dominique Costantini	June 17, 2020	Founders' share warrants 2020	€25,900	10,000 founders' share warrants	€6.14	6/17/2025
Maryvonne Hiance	June 17, 2020	Founders' share warrants 2020	€25,900	10,000 founders' share warrants	€6.14	6/17/2025
Gérard Tobelem	June 26, 2019	Founders' share warrants 2019	€13,200	10,000 founders' share warrants	€3.58	6/26/2024
	June 17, 2020	Founders' share warrants 2020	€25,900	10,000 founders' share warrants	€6.14	6/17/2025
Jean-Patrick Demonsang	June 26, 2019	Founders' share warrants 2019	€13,200	10,000 founders' share warrants	€3.58	6/26/2024
	June 17, 2020	Founders' share warrants 2020	€25,900	10,000 founders' share warrants	€6.14	6/17/2025
Walter Flamenbaum	June 26, 2019	Founders' share warrants 2019	€13,200	10,000 founders' share warrants	€3.58	6/26/2024
Didier Hoch	June 26, 2019	Founders' share warrants 2019	€13,200	10,000 founders' share warrants	€3.58	6/26/2024
	June 17, 2020	Founders' share warrants 2020	€25,900	10,000 founders' share warrants	€6.14	6/17/2025

Sophie Brouard	June 26, 2019 June 17, 2020	Founders' share warrants 2019 Founders' share warrants 2020	€13,200 €25,900	10,000 founders' share warrants 10,000 founders' share warrants	€3.58 €6.14	6/26/2024 6/17/2025
Brigitte Dréno	June 26, 2019 June 17, 2020	Founders' share warrants 2019 Founders' share warrants 2020	€13,200 €25,900	10,000 founders' share warrants 10,000 founders' share warrants	€3.58 €6.14	6/26/2024 6/17/2025
<b>TOTAL</b>			<b>€260,500</b>	<b>130,000 founders' share warrants</b>		

**TABLE 5: STOCK SUBSCRIPTION OR PURCHASE OPTIONS EXERCISED BY EACH EXECUTIVE CORPORATE OFFICER DURING THE FISCAL YEARS ENDED DECEMBER 31, 2019, AND 2020**

None

**TABLE 6: FREE SHARES AWARDED TO EACH EXECUTIVE CORPORATE OFFICER DURING THE FISCAL YEARS ENDED DECEMBER 31, 2019, AND 2020**

Executive corporate officer name	Plan number and date	Number of shares awarded during the 2019/2020 fiscal years	Valuation of shares according to the method used in the consolidated financial statements	Vesting date	Availability date	Performance conditions
Maryvonne Hiance	June 26, 2019	25,000	€88,000	June 26, 2020	June 26, 2021	Attendance
Alexis Peyroles	June 26, 2019	150,000	€528,000	June 26, 2020	June 26, 2021	Attendance
	December 10, 2019	22,625	€81,224	December 10, 2021	December 10, 2022	Attendance
	June 17, 2020	150,000	€498,707	June 17, 2021	June 17, 2022	Attendance
	December 8, 2020	11,363	€5,184	December 8, 2021	December 8, 2022	Attendance
Nicolas Poirier	March 12, 2019 June 17, 2020	25,000 100,000	€88,000 €332,471	March 12, 2020 June 17, 2021	March 12, 2021 June 17, 2022	Attendance Attendance
<b>TOTAL</b>		<b>483,988</b>	<b>€1,621,586</b>			

**TABLE 7: FREE SHARES THAT BECAME AVAILABLE TO EACH EXECUTIVE CORPORATE OFFICER DURING THE FISCAL YEARS ENDED DECEMBER 31, 2019, AND 2020**

Corporate officer name	Plan number and date	Number of shares that became available during the year	Vesting conditions
Maryvonne Hiance	March 28, 2017	10,926 (at March 28, 2019)	Attendance
Nicolas Poirier	March 28, 2017	1,822 (at March 28, 2019)	Attendance
Nicolas Poirier	June 14, 2017	8,603 (as of July 18, 2019)	Attendance
Alexis Peyroles	June 13, 2018	150,000 (at June 13, 2020)	Attendance
Alexis Peyroles	December 5, 2018	18,712 (on December 5, 2020)	Attendance
Nicolas Poirier	December 5, 2018	20,000 (at December 5, 2020)	Attendance

**TABLE 8: HISTORY OF THE ALLOCATION OF SUBSCRIPTION OR PURCHASE STOCK OPTIONS GRANTED TO CORPORATE OFFICERS**

**AS OF THE DATE OF THIS UNIVERSAL REGISTRATION DOCUMENT:**

	Founders' share warrants 2020	Founders' share warrants 2019	Founders' share warrants 2018	Share subscription warrants 2018	Share subscription warrants 2017	Effimune share subscription warrants	2015 founders' share warrants	2015 share subscription warrants	2014 share subscription warrants
Date of General Shareholders' Meeting or Board Directors having allocated the plan	Extraordinary General Shareholders' Meeting on 6/26/2019	Extraordinary General Shareholders' Meeting of 6/13/2018	Extraordinary General Shareholders' Meeting of 6/14/2017	Extraordinary General Shareholders' Meeting of 6/14/2017	Extraordinary General Shareholders' Meeting of 5/31/2016	Extraordinary General Shareholders' Meeting of 5/31/2016	Extraordinary General Shareholders' Meeting 9/17/2014	Extraordinary General Shareholders' Meeting 9/17/2014	Extraordinary General Shareholders' Meeting of 6/02/2014
Maximum number of warrants authorized by General Shareholders' Meetings	500,000 instruments	500,000 instruments	500,000 instruments	500,000 instruments	400,000 instruments	67,820 (Entitling the holder to 130,892 shares under the exchange parity defined as part of the merger with Effimune on 5/31/2016)	300,000 instruments	300,000 instruments	800,000 decreased to 500,000 by the EGM of 9/17/2014

	Founders' share warrants 2020	Founders' share warrants 2019	Founders' share warrants 2018	Share subscription warrants 2018	Share subscription warrants 2017	Effimune share subscription warrants	2015 founders' share warrants	2015 share subscription warrants	2014 share subscription warrants
Number of instruments issued	70,000	60,000	25,900	42,850	52000	67,820 (Entitling the holder to 130,892 shares under the exchange parity defined as part of the merger with Effimune on 5/31/2016)	65,000	136,222	481,982
Dominique Costantini	10,000		25,900						11,250
Jean-Patrick Demonsang	10,000	10,000							13,000
Gérard Tobelem	10,000	10,000		42,850					13,417
Maryvonne Hiance	10,000					5,000 (Entitling the holder to 9,650 shares under the exchange parity defined as part of the merger with Effimune on 5/31/2016)			
Didier Hoch	10,000	10,000				3,000 (Entitling the holder to 6,369 shares under the exchange parity defined as part of the merger with Effimune on 5/31/2016)			
Sophie Brouard	10,000	10,000				1,000 (Entitling the holder to 1,930 shares under the exchange parity defined as part of the merger with			

	Founders' share warrants 2020	Founders' share warrants 2019	Founders' share warrants 2018	Share subscription warrants 2018	Share subscription warrants 2017	Effimune share subscription warrants	2015 founders' share warrants	2015 share subscription warrants	2014 share subscription warrants
						Effimune on 5/31/2016)			
Brigitte Dréno	10,000	10,000							
Alexis Peyrolles							65,000		85,000
Starting point for exercising warrants	Allocation date	Allocation date	Allocation date	Allocation date	Allocation date	Allocation date 10/01/2017 10/01/2018 10/01/2019	Allocation date	Allocation date	
Expiration date	6/17/2025	6/26/2024	6/13/2023	6/13/2023	07/17/2021	6/27/2016 (tranche 1) 12/08/2016 (tranche 2) 7/01/2019 (tranche 3) 11/25/2019 (tranche 4)	4/01/2019 4/01/2020 4/01/2021	3/30/2020	6/30/2019
Warrant subscription or purchase price	€0	€0	€0	€0.70	€0.60	€0.60 (Tranches 1 and 2) €0.70 (Tranches 3 and 4)	€0	€1.08	€0.10
Warrant subscription or purchase price	0	0	0	0	42,000	23,620 (Entitling the holder to 45,586 shares under the exchange parity defined as part of the merger with Effimune on 5/31/2016)	0	136,222	400,982
Warrant exercise terms	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares
Exercise price	€6.14	€3.58	€4.17	€4.17	€4.65	€5 (Tranches 1 and 2) €7 (Tranches 3 and 4)	€10.80	€10.80	€8
Number of shares subscribed on the date of this Universal	0	0	0	0	0	45,586	0	0	156,250

	Founders' share warrants 2020	Founders' share warrants 2019	Founders' share warrants 2018	Share subscription warrants 2018	Share subscription warrants 2017	Effimune share subscription warrants	2015 founders' share warrants	2015 share subscription warrants	2014 share subscription warrants
Registration Document									
Cumulative number of canceled or lapsed share subscription or purchase warrants	0	0	0	0	10,000	10,000 (Entitling the holder to 19,300 shares under the exchange parity defined as part of the merger with Effimune on 5/31/2016)	0	0	13,000
Remaining subscription warrants to be issued on the date of this Universal Registration Document	0	0	25,900	42,850	0	0	0	0	0

**TABLE 9: STOCK SUBSCRIPTION OR PURCHASE OPTIONS GRANTED TO THE FIRST 10 EMPLOYEES WHO ARE NOT CORPORATE OFFICERS AND OPTIONS EXERCISED BY THEM**

Stock subscription or purchase options granted to the first ten employees who are not corporate officers and options exercised by them	Options granted during the fiscal year by the issuer and any Company included in the options' allocation scope, to the first ten employees of the issuer and of any Company included in this scope, to whom the number of options thus granted is the highest (aggregate information)	Options held on the issuer and the Companies referred to above, exercised, during the year, by the ten employees of the issuer and these Companies, whose number of options thus purchased or subscribed is the highest (aggregate information)	Total number of options allocated/shares subscribed or purchased	Weighted average price
41,155 Free Share Allocation plan for 2017		N/A	40,151 vested on 7/18/2018	N/A
150,000 Free Share Allocation plan for 2018-2		N/A	141,800 vested on 3/26/2020	N/A
150,000 Free Share Allocation plan for 2019		N/A	145,300 acquired on 6/27/2020	N/A
250,000 Free Share Allocation plan for 2020			244,500 Free Share Allocated plan allocated on 12/18/2020	€5.76
<b>TOTAL</b>			<b>571,751</b>	

**TABLE 10: HISTORY OF FREE SHARE ALLOCATIONS**

As of the date of this Universal Registration Document:

The Board of Directors issued 98,000 free shares on May 31, 2016
The Board of Directors issued 13,851 free shares on September 8, 2016
The Board of Directors issued 150,000 free shares on December 13, 2016
The Board of Directors issued 25,040 free shares on March 28, 2017
An issue of 40,151 free shares was carried out by the Chief Executive Officer on July 18, 2018, on the delegation of the Board of Directors on June 14, 2017 (total of 41,155 free shares for the benefit of non-corporate officer employees).
An issue of 150,000 free shares was carried out by the Board of Directors on June 13, 2018, to Alexis Peyroles.
An issue of 38,712 free shares was carried out by the Board of Directors on December 5, 2018, to Alexis Peyroles and Nicolas Poirier.

- A budget of 150,000 free shares for the benefit of non-executive employees was decided by the Board of Directors on December 5, 2018, and 149,200 were allocated by the Chief Executive Officer on March 12, 2019 (resulting in the acquisition of 141,800 shares recognized by the Board of Directors on March 26, 2020);
- A budget of 150,000 free shares was approved by the Board of Directors on June 26, 2019, for Alexis Peyroles (resulting in the acquisition of 150,000 free shares recognized by the Chief Executive Officer on June 27, 2020);
- A budget of 148,400 free shares for the benefit of non-corporate officer employees was approved by the Board of Directors and 148,400 were allocated by the Chief Executive Officer on June 26, 2019 (resulting in the acquisition of 145,300 free shares by the Chief Executive Officer on June 27, 2020);
- An allocation of 22,625 free shares was approved by the Board of Directors on December 10, 2019, to Alexis Peyroles for his variable compensation (resulting in the acquisition of 22,625 free shares recognized by the Chief Executive Officer on December 18, 2020);
- An allocation of 150,000 free shares was approved by the Board of Directors on June 17, 2020, to Alexis Peyroles;
- An allocation of 100,000 free shares was approved by the Board of Directors on June 17, 2020, to Nicolas Poirier;
- A budget of 250,000 free shares was approved by the Board of Directors for non-corporate officer employees on June 17, 2020, and 244,500 were allocated by the Chief Executive Officer on December 18, 2020;
- An allocation of 11,363 free shares was approved by the Board of Directors on December 8, 2020, for Alexis Peyroles as part of his variable compensation.

HISTORY OF FREE SHARE ALLOCATIONS												
INFORMATION ON FREE SHARES ALLOCATED												
Meeting date	6/26/19	6/13/18	6/13/18	6/14/17	6/13/18	6/14/17	6/14/17	9/17/14	5/31/16	5/31/16	5/31/16	5/31/16
Date of the Board of Directors meeting	6/17/20	12/08/20	6/17/20	12/10/19	6/26/19	12/05/18	6/13/18	5/31/16	9/08/16	12/13/16	3/28/17	6/14/17 (delegation to the Chief Executive Officer on 6/18/2017 )
Total number of free shares	400,000	11,363	100,000	22,625	300,000	38,712	150,000	98,000	13,851	150,000	25,040	41,155
<b>of which the number allocated to:</b>												
Maryvonne Hiance, Director								40,000	0	0	10,926	0
Alexis Peyroles Chief Operating Officer	150,000	11,363		22,625	150,000	18,712	150,000	0	12,162	150,000	0	0
Nicolas Poirier, director			100,000			20000						

representing employee shareholder s											
Share vesting date	6/17/21	12/8/21	6/17/21	12/10/20	6/26/20	12/05/19	6/13/19	6/01/18	9/09/17	12/13/17 (100,000 Free Share Allocation plan) 6/13/2018 (50,000 Free Share Allocation plan)	3/29/18 7/18/18
Lock-up period end date	6/17/22	12/08/22	6/17/22	12/10/21	6/26/21	12/05/20	6/13/20	6/01/20	9/09/18	12/13/18 (100,000 Free Share Allocation plan) 6/13/2019 (50,000 Free Share Allocation plan)	3/29/19 7/18/19
Number of shares vested on 03/31/2020	0	0	0	22,625	150,000	38,712	150,000	98,000	13,851	150,000	25,040 40,151
Cumulative number of canceled or lapsed shares	0	0	0	0	0	0	0	0	0	0	0
Free shares remaining at the balance sheet date					-	-	-	-	-	-	-

**TABLE 11: DETAILS OF THE COMPENSATION CONDITIONS AND OTHER BENEFITS GRANTED TO EXECUTIVE CORPORATE OFFICERS**

Executive corporate officers	Date of first appointment	End of term	Service agreement		Employment contract		Supplementary pension plan		Compensation or benefits due or likely to be due as a result of a termination or change of position		Compensation relating to a non-compete clause	
			Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
<b>Dominique Costantini</b> <i>Chairman of the Board</i> <i>Director</i>	4/27/2012	GSM for the fiscal year ended 12/31/2020		X	X			X		X		X
<b>Alexis Peyrols</b> <i>Chief Executive Officer</i> <i>Director</i>	5/31/2016	GSM for the fiscal year ended 12/31/2021		X	X			X		X		X

Director											
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No maintenance of employment contracts, or severance pay in the event of termination of the employment contract are provided for as of the date of this Universal Registration Document.

### **13.2 Amounts provisioned or recognized by the Company for the purpose of paying pensions, retirement or other benefits**

The Company has not provisioned any amounts to pay pensions, retirement and other benefits to corporate officers and/or executive corporate officers who do not otherwise benefit (or have benefited) from a departure or sign-on bonus within the Company.

The share subscription warrants and founders' share warrants granted to corporate officers or executive corporate officers are subject to a detailed breakdown in chapter 15.2 of this Universal Registration Document.

## 14 Operating procedures of the administrative and management bodies

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### **14.1 Operating procedures and terms of office of the members of the Board of Directors and Executive Management**

The directors' terms of office are as follows:

First name — Last name or corporate name of the member	Date of first appointment	End of term	Main position in the Company
Dominique Costantini	April 27, 2012	GSM called to approve the financial statements for the fiscal year ended December 31, 2020, i.e., three years	Chairman of the Board of Directors, Director
Alexis Peyroles	May 31, 2016	GSM approving the financial statements December 31, 2021, i.e., 3 years	Director, Chief Executive Officer
Maryvonne Hiance	May 31, 2016	GSM called to approve the financial statements for the fiscal year ended December 31, 2021, i.e., six years	Vice-Chairman of the Board of Directors
Sophie Brouard	May 31, 2016	GSM called to approve the financial statements for the fiscal year ended December 31, 2021, i.e., six years	Director
Jean-Patrick Demonsang	April 10, 2014	GSM called to approve the financial statements for the fiscal year ended December 31, 2022, i.e., 3 years	Director
Brigitte Dréno	June 14, 2017	GSM called to approve the financial statements for the fiscal year ended December 31, 2022, i.e., 3 years	Director
Didier Hoch	May 31, 2016	GSM called to approve the financial statements for the fiscal year ended December 31, 2021, i.e., six years	Director
Nicolas Poirier	June 26, 2019	GSM called to approve the financial statements for the fiscal year ended December 31, 2021, i.e., three years	Director representing the employee shareholders
Gérard Tobelem	April 10, 2014	GSM called to approve the financial statements for the fiscal year ended December 31, 2022, i.e., three years	Director

The operating rules for the administrative bodies are set out in the bylaws in force.

### **14.1.1 Board of Directors (Articles 19 to 22 of the bylaws)**

#### **ARTICLE 19 — BOARD OF DIRECTORS (EXCERPT)**

- (i) Except as permitted by law, the Company is administered by a Board of Directors with a minimum of three and a maximum of eighteen members.
- (ii) During the Company's life span, directors are appointed or reappointed by the Ordinary General Shareholders' Meeting. Notwithstanding, in the event of a merger, directors may be appointed by the Extraordinary General Shareholders' Meeting approving the transaction.
- (iii) Directors may or may not be Company shareholders.
- (iv) The directors' term of office is three years and ends at the conclusion of the Ordinary General Shareholders' Meeting called to approve the financial statements of the fiscal year ended and held during the year in which the term of the relevant director expires.  
Directors may be re-elected. They may be dismissed at any time by the Ordinary General Shareholders' Meeting.  
No one may be appointed director if they are older than 70 and their appointment would mean that more than one-third of the members of the Board of Directors would be over 70. If this proportion is exceeded, the oldest director is deemed to have resigned automatically at the end of the Ordinary General Shareholders' Meeting called to approve the financial statements of the fiscal year during which this threshold was crossed.  
Directors may be natural persons or legal entities. Upon their appointment, directors who are legal entities must appoint a permanent representative who is subject to the same conditions and obligations and who incurs the same liabilities as if he or she were a director in his or her own name, without affecting the joint liability of the legal entity he or she is representing.  
When the legal entity director ends the term of office of its permanent representative, it must immediately notify the Company, via registered letter, of its decision and provide the name of its new permanent representative. The same applies in the event of the death or resignation of the permanent representative.  
The permanent representative of a legal entity director is subject to the same age requirements as apply to natural person directors.
- (v) In the event of a vacancy due to death or the resignation of one or more directors, the Board of Directors may make provisional appointments between two General Shareholders' Meetings in order to maintain the same number of directors.  
Provisional appointments made in this way by the Board of Directors are subject to ratification by the next Ordinary General Shareholders' Meeting. Failing ratification, the decisions made and actions taken still remain valid.  
When the number of directors falls below the legal minimum, the directors still in office must immediately convene the Ordinary General Shareholders' Meeting to fill the number of directors.  
A director who is appointed to replace another director stays in office only for the predecessor's remaining term.  
Natural person directors may not simultaneously serve on more than five boards of directors or supervisory boards of limited companies (société anonyme) headquartered in metropolitan France, except where permitted by law.  
A Company employee may only be appointed as director if his or her contract corresponds to active employment. The employee does not lose the benefit of this employment contract. The number of directors with an employment contract with the Company may not exceed one-third of the directors in office.

#### **ARTICLE 20 — CHAIRMANSHIP OF THE BOARD OF DIRECTORS**

The Board of Directors elects a Chairman from among its natural person members and determines the Chairman's compensation. It sets the term of the Chairman's duties, which may not exceed the Chairman's term as a director. The Chairman may be re-elected.

The Board of Directors may dismiss the Chairman at any time.

No one older than 70 may be appointed Chairman of the Board of Directors. If the Chairman of the Board of Directors turns 70 while in office, he or she will be deemed to have resigned and a new Chairman will be appointed in accordance with the terms and conditions stipulated in this article.

The Chairman represents the Board of Directors. The Chairman organizes and leads the work of the Board of Directors and reports on it to the General Shareholders' Meeting. The Chairman ensures that the Company bodies operate smoothly and, in particular, ensures that the directors are able to perform their duties.

In the event of a temporary impediment or the death of the Chairman, the Board of Directors may appoint a director to serve as Chairman.

In the event of a temporary impediment, this appointment is granted for a limited period and may be renewed.

In the event of death, it applies until the new Chairman is elected.

## ARTICLE 21 — MEETINGS AND PROCEEDINGS OF THE BOARD OF DIRECTORS

### BOARD MEETINGS

The Board of Directors meets as often as the corporate interest requires and is convened by the Chairman. If no meeting is held for more than two months, a group of directors comprising at least one-third of the members of the Board of Directors may convene the Board, providing a specific agenda.

Either the Chief Executive Officer, when he or she is not serving as Chairman of the Board of Directors, or the Chief Operating Officers may ask the Chairman to convene the Board of Directors to discuss an established agenda.

The meeting is held at the registered office or any other location.

Notices of meeting may be issued by any means, including verbally.

The Chairman of the Board of Directors chairs the meetings. In the event that the Chairman is unable to perform his or her duties, at each meeting the Board appoints one of its members in attendance to chair the meeting.

At each meeting, the Board may appoint a secretary who does not need to be a Board member.

A register signed by all the members present at the Board meeting is kept.

Directors and any other person called on to attend the meetings of the Board of Directors are bound to secrecy with regard to confidential information that is described as such by the Chairman.

### QUORUM AND MAJORITY

The Board of Directors may validly deliberate only if at least half of the directors are present or deemed to be present, subject to the arrangements stipulated in the Rules of Procedure in the event that videoconferencing or another telecommunication medium is used.

Unless stipulated otherwise in these bylaws and subject to the arrangements stipulated in the Rules of Procedure in the event that videoconferencing or another telecommunication medium is used, Board resolutions are passed by a majority vote of the members present or deemed present.

In the event of a tie, the Chairman of the meeting has the casting vote.

For the purposes of calculating the quorum and majority, directors participating in the Board of Directors' meeting through videoconference or another telecommunication medium in accordance with the terms and conditions outlined in the Board's Rules of Procedure are deemed to be present. Nonetheless, actual presence or presence through a representative is required for any Board proceedings on the approval of the separate financial statements and the group's management report, and for any decisions relating to the dismissal of the Chairman of the Board of Directors, the Chief Executive Officer and the Chief Operating Officer.

## REPRESENTATION

Any director may give another director, in writing, may give a proxy to represent him or her at a Board meeting.

Each director may represent only one other director during a single Board meeting.

These provisions apply to the permanent representative of a legal entity.

## MINUTES OF THE PROCEEDINGS

The Board of Directors proceedings are reported in minutes issued in a special register, listed and initialed, and kept at the registered office in accordance with the regulatory provisions.

The minutes are signed by the Chairman of the meeting and by a director.

Copies or extracts from the minutes of the Board of Directors proceedings are legally certified by the Chairman or the Chief Executive Officer.

## NON-VOTING MEMBERS

During the Company's life span, the Ordinary General Shareholders' Meeting may appoint nonvoting members from among or outside the shareholders.

There may be no more than three nonvoting members.

Nonvoting members are appointed for a one-year term. Their duties end at the conclusion of the Ordinary General Shareholders' Meeting called to approve the financial statements for the fiscal year ended and held during the year in which their term of office expires.

Any outgoing nonvoting member may be re-elected provided that they meet the criteria of this article.

Nonvoting members may be dismissed and replaced at any time by the Ordinary General Shareholders' Meeting without any compensation being due to them. The duties of the nonvoting members also end in the event of death or impediment for a nonvoting member who is a natural person, and in the event of a winding up or initiation of collective insolvency proceedings for a legal entity nonvoting member, or in the event of resignation.

Nonvoting members may be natural persons or legal entities. If the nonvoting member is a legal entity, upon its appointment, it must appoint a permanent representative who is subject to the same conditions and obligations and who incurs the same civil and criminal liabilities as if he or she were a nonvoting member in his or her own name, without affecting the joint liability of the legal entity he or she is representing.

The role of the nonvoting members is to ensure the strict enforcement of the bylaws and present their remarks during the Board of Directors' meetings.

Nonvoting members have an overall advisory and supervisory role in the Company. As part of their role, they may share remarks with the Board and ask to review corporate documents at the Company's registered office.

Nonvoting members must be invited to every Board of Directors' meeting in the same way as the directors.

Nonvoting members have only advisory authority on an individual or collective basis and do not have voting rights on the Board.

Failure to summon the nonvoting member or to send documents to the nonvoting member(s) prior to the meeting of the Board of Directors may in no way be a reason to invalidate the decisions made by the Board of Directors.

## ARTICLE 22 — POWERS OF THE BOARD OF DIRECTORS

(i) The Board of Directors determines the Company's business strategies and ensures that they are implemented.

Subject to the powers expressly granted by law to shareholders' meetings and to the extent of the corporate purpose, it examines any issue affecting the proper functioning of the Company and through its proceedings resolves matters that concern it.

In relations with third parties, the Company is bound even for actions by the Board of Directors that do not fall within the corporate purpose unless it proves that the third party knew that the action in question exceeded this purpose or that it could not be unaware of this given the circumstances, it being stated that the mere publication of the bylaws is not sufficient to constitute this proof.

- (ii) The Board of Directors may at any time perform the audits and verifications it deems appropriate.

All directors must receive the information required for completing their assignments and they may obtain all documents they consider necessary from the Executive Management.

- (iii) The Board of Directors may give any agent of its choice any delegation of authority within the bounds of its powers under the law and these bylaws.

It may decide to create working committees tasked with studying the issues the Board or the Chairman of the Board submits to it.

- (iv) The Board of Directors is not qualified to vote on or authorize a bonds issue; these bylaws reserve that power for the General Shareholders' Meeting.

### **14.1.2 Executive Management (Articles 23 to 26 of the bylaws)**

#### **ARTICLE 23 — METHODS OF EXECUTIVE MANAGEMENT**

The Company is responsible for its Executive Management, either through the Chairman of the Board of Directors or through another natural person appointed by the Board of Directors who assumes the title of Chief Executive Officer.

The Board of Directors chooses which of these executive management methods to implement. The Board decides on the method of the Executive Management through a majority vote of the directors who are present and deemed present, subject to the special provisions of Article 21 in the event that there are directors participating in the Board meeting via videoconference or another telecommunication medium.

The Board of Directors' choice is communicated to the shareholders and third parties in accordance with the regulations in force.

The option chosen by the Board of Directors may be reassessed only upon the re renewal or replacement of the Chairman of the Board of Directors or when the Chief Executive Officer's term of office expires.

A change in the method of Executive Management does not require an amendment of the bylaws.

#### **ARTICLE 24 — EXECUTIVE MANAGEMENT**

Based on the method selected by the Board of Directors, the Chairman or the Chief Executive Officer takes responsibility for the Company's Executive Management.

The Chief Executive Officer is appointed by the Board of Directors, which sets the length of his or her term of office, determines his or her compensation and, where necessary, the limitations of his or her powers.

The Chief Executive Officer may be dismissed by the Board of Directors at any time. If the Chief Executive Officer who is not the Chairman is dismissed, he or she may be due to damages if the dismissal is decided without just cause.

#### **ARTICLE 25 — POWERS OF THE CHIEF EXECUTIVE OFFICER**

The Chief Executive Officer is vested with the broadest powers to act in any situation on behalf of the Company.

The Chief Executive Officer exercises his or her powers within the limits of the corporate purpose, and subject to the powers expressly granted by law to the General Shareholders' Meetings and the Board of Directors.

The Chief Executive Officer represents the Company in its dealings with third parties. The Company is bound even for actions by the Chief Executive Officer that do not fall within the corporate purpose unless it proves that the third party knew that the

action in question exceeded this purpose or that it could not be unaware of this given the circumstances, it being stated that the mere publication of the bylaws is not sufficient to constitute this proof.

#### **ARTICLE 26 — CHIEF OPERATING OFFICERS**

At the suggestion of the Chief Executive Officer, whether this position is held by the Chairman of the Board of Directors or another person, the Board of Directors may appoint one or more natural persons, selected or not from among the directors and shareholders, responsible for assisting the Chief Executive Officer and given the title Chief Operating Officer.

There may be a maximum of five Chief Operating Officers.

In agreement with the Chief Executive Officer, the Board of Directors determines the scope and duration of the powers granted to the Chief Operating Officers and sets their compensation.

With regard to third parties, the Chief Operating Officer or Chief Operating Officers have the same powers as the Chief Executive Officer.

In the event of a termination of, or inability to perform, the duties of the Chief Executive Officer, the Chief Operating Officers retain their duties and powers until a new Chief Executive Officer is appointed, unless decided otherwise by the Board of Directors.

The Chief Operating Officers may be dismissed at any time on a proposal by the Chief Executive Officer. The dismissal of the Chief Operating Officers may give rise to damages if it is decided without just cause.

#### **14.2 Information on the service contracts between the members of the Board of Directors and the Executive Management and the Company or one of its subsidiaries**

Dominique Costantini, Chief Executive Officer, Chairman and Director of Development, signed an initial employment contract as Director of Development in 2014. Her contract was amended in October 2016 to bring her to full-time (151.67 working hours per month), for gross annual compensation of €205,314 excluding variable compensation, then amended on July 1, 2019 to increase the gross annual compensation to €275,000 excluding variable compensation, then amended again on July 1, 2020 to increase the gross annual compensation to €302,500 excluding variable compensation. Dominique Costantini's bonus for fiscal year 2019 was paid at the beginning of fiscal year 2020. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

Maryvonne Hiance, Vice-Chairman, holds an operational role as Director of Public Affairs in the Executive Management in accordance with a contract updated following the merger dated May 31, 2016. The compensation under this employment contract is calculated on the basis of €120,000 in gross annual salary. The employment contract took effect on May 31, 2016. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

Alexis Peyrols, Director and Chief Executive Officer, initially signed a permanent employment contract on July 1, 2014, amended on October 1, 2016 and July 1, 2018 as Director of Operations, with a gross annual remuneration of €350,000 (for 151.67 hours of monthly work). Variable compensation up to 50% of the fixed compensation, half of which is payable in shares, is provided for based on the achievement of certain targets.

Nicolas Poirier, elected as the director representing the employee shareholders on June 26, 2019, is employed as Chief Scientific Officer under an employment contract dated May 31, 2016. Compensation under this employment contract is calculated on the basis of a gross annual amount of €180,000 increased to a gross annual amount of €200,000 from July 1, 2020. Variable compensation is also provided for.

## 14.3 Committees

In accordance with Articles 6 and 7 of the Rules of Procedure, the Board has appointed a Compensation and Appointments Committee and an Audit Committee made up of Board members.

The composition of these Committees provides for a term of two years. Committee members are paid €3,000 per year and their Chairman is paid €5,000 per year.

Travel and lodging costs incurred by each Committee participant for meetings held outside of Europe will be covered for an amount of €2,500 per meeting, while costs incurred for meetings in Europe will be covered up to €500 per meeting.

### 14.3.1 Audit Committee

#### COMPOSITION

The Audit Committee comprises Jean-Patrick Demonsang (Committee Chairman) and Didier Hoch, whose terms of office were renewed at the Board of Directors meeting on June 26, 2019, for a two-year period.

Jean-Patrick Demonsang and Didier Hoch are both independent members.

#### OPERATING PROCEDURES

##### DUTIES

The Audit Committee is responsible for overseeing issues relating to the preparation and audit of accounting and financial information. It is responsible for continually assessing the existence and effectiveness of the Company's financial control and risk control procedures, and has as its duties:

###### Internal control

- Ensuring that the internal control and risk management systems are effective;
- Verifying the smooth operation with assistance from the Finance Department;
- Reviewing the schedule of internal and external audits;
- Ensure that the Statutory Auditors conduct the statutory audit of the separate financial statements and, where applicable, the consolidated financial statements.

###### Statutory financial statements and financial information

After regularly reviewing the financial position, the cash position and the commitments appearing in the Company's separate financial statements:

- Reviewing the accounting and financial documents, annual and interim financial statements;
- Overseeing the process of issuing the statutory and consolidated/combined financial statements and the process of preparing the financial information;
- Reviewing the internal control measures;
- Reviewing the material risks for the Company, particularly off-balance sheet risks and commitments;
- Validating the relevance of accounting rules and choices;
- Verifying the relevance of the financial information reported by the Company.

###### Risk management

- Reviewing any item likely to have material, financial and accounting impacts;
- Reviewing the status of major litigation;
- Review off-balance sheet risks and commitments;
- Reviewing the relevance of the risk monitoring procedures;
- Reviewing any related-party agreements.

#### Statutory Auditors

- Leading the selection of the Statutory Auditors, managing their compensation and ensuring their independence;
- Ensuring the proper implementation of their assignment;
- Monitoring the statutory audit of the separate financial statements and, where applicable, the consolidated financial statements by the Statutory Auditors;
- Establishing the rules for using the Statutory Auditors for tasks other than the audit of the financial statements and ensuring the proper implementation of their assignment;
- Issue a recommendation on the proposals for the appointment and potential reappointment of the Statutory Auditors presented to the General Shareholders' Meeting, their fees and any issue related to their independence.

#### **INTERNAL RULES**

The operating procedures of the Audit Committee are governed by Article 7 of the Internal Rules of the Board of Directors. These Rules of Procedure may be viewed at the Company's registered office upon prior written request.

#### **WORK IN 2020**

The Audit Committee met twice in 2020, to review and approve the statutory and consolidated financial statements for fiscal year 2019 (March 23, 2020) and to review and approve the consolidated financial statements for first-half 2020 (September 15, 2020).

### **14.3.2 Appointments and Compensation Committee**

#### **COMPOSITION**

The Appointments and Compensation Committee consists of Gérard Tobelem (Committee Chairman) and Maryvonne Hiance, whose terms of office were renewed at the Board of Directors meeting on June 26, 2019, for a two-year period.

The independent member is Gérard Tobelem.

#### **OPERATING PROCEDURES**

#### **DUTIES**

The Appointments and Compensation Committee issues recommendations to the Board of Directors on the following topics:

- Advice and assistance regarding compensation, the pension and welfare benefit plan, supplementary pensions, benefits in kind, various cash entitlements of the executive corporate officers, allocations of free or performance shares, stock subscriptions or purchase options;
- The determination of the procedures for setting the variable portion of the compensation of the executive corporate officers, and overseeing the enforcement of these procedures;
- The distribution of the directors' fees, where necessary, to the directors taking into account their attendance record and tasks accomplished on the Board of Directors;
- Any extraordinary compensation of the directors for specific assignments or duties given to them by the Board;
- Any changes to the composition of the Board of Directors or the Executive Management;
- Prevention of conflicts of interest on the Board of Directors;
- Oversight of the establishment of structures and procedures making it possible to apply proper governing practices within the Company;
- Ensuring compliance with ethical principles within the Company and in its relations with third parties;
- Discussions on the classification of independent director for each director when the director is first appointed and every year before the publication of the Universal Registration Document, and presentation of the report of its recommendations to the Board of Directors.

In addition, the Executive Management proposes to it the various stock subscription or purchase option plans, equity warrant plans, founders' warrant allocation plans or free share allocation plans.

## **INTERNAL RULES**

The operating procedures of the Appointments and Compensation Committee is governed by Article 6 of the Board of Directors' Internal Rules. These Internal Rules may be viewed at the Company's registered office upon prior written request.

## **WORK IN 2020**

The Appointments and Compensation Committee met twice in 2020: on June 17 to review the compensation of management and award-free shares to employees and founders' warrants, and on December 8 to award free shares and set the targets for the Chief Executive Officer and the Chairman of the Board of Directors.

### **14.3.3 Scientific Advisory Board**

As an addition and without forming a committee, strictly speaking, on November 29, 2013, the Company created a Scientific Advisory Board. The role of this Scientific Advisory Board is to contribute the skills of prominent partners to the Company's business, based on the scientific topics to be addressed.

This Scientific Advisory Board is chaired by Wolf Hervé Fridman, director of the Cordeliers Research Center.

The Scientific Advisory Board integrates high-level expertise with the therapeutic indications on which OSE Immunotherapeutics positions itself. Its main role is to formulate and validate the scientific information published by OSE Immunotherapeutics and to contribute any scientific information that may help the development of the Company's projects. Therefore, this Scientific Advisory Board is not intended to meet regularly, but rather to be available to the management to provide active support for the innovations being developed. Practically speaking, the Company management calls on the Chairman of the Scientific Board, Wolf Hervé Fridman, who draws on the skills of outside consultants and experts in their fields to contribute high-level expertise based on the required topics.

## **14.4 Statement on corporate governance**

The Company refers to the Corporate Governance Code for Small and Midcap Companies as published in December 2009 by MiddleNext and approved as a standard-setting code by the French Financial Markets Authority, insofar as the principles it contains will be compatible with the organization, size, resources and shareholding structure of the Company, particularly in the context of preparing the corporate governance report stipulated in the provisions of Article L. 225-37 of the French Commercial Code.

<b>Recommendations of the MiddleNext Code</b>	<b>Already adopted</b>	<b>To be adopted</b>	<b>Will not be adopted</b>	<b>Not applicable</b>
<b>I. Executive power</b>				
R13: Definition and transparency of the compensation of executive corporate officers*	X			
R15: Combination of corporate officers and employment contracts**	X			
R16: Severance payments ***				X
R17: Supplementary pension schemes****				X
R18: Stock options and free shares*****			X	
<b>II. Supervisory power</b>				
R1: Board of Directors' ethics policy	X			
R3: Composition of the Board, independent directors	X			
R4: Board member information	X			
R5: Board and committee meetings	X			

R6: Creation of committees	X			
R7: Implementation of Rules of Procedure	X			
R8: Choice of directors	X			
R9: Directors' terms of office	X			
R10: Directors' compensation	X			
R11: Implementation of an assessment of the Board's work*****	X			

\* Dominique Costantini has an open-ended employment contract as Director of Development. The Company is continuing this technical contract for Director of Early Development despite the appointment of Dominique Costantini as Chairman of the Board of Directors due to her seniority and the unique technical duties she performs pertaining to drug development expertise.

\*\* Alexis Peyrols combines his duties as Chief Executive Officer with an employment contract for Chief Operating Officer. Given the specific nature of his duties and the distinction with the position of Chief Executive Officer, the Board of Directors has decided to continue Alexis Peyrols' contract due to his seniority and the unique technical duties he performs pertaining to managing operations and international business collaborations.

\*\*\* The Company has not implemented a pension scheme as referred to in Article L. 137-11 of the French Social Security Code (defined benefit plan).

\*\*\*\* The Company does not currently plan to implement a supplementary retirement scheme.

\*\*\*\*\* The Company has no stock options. The 2012, 2014, 2015 and 2016 equity warrants, and 2015, 2016, 2017, 2018 and 2019 founder warrants were granted to management, consultants and employees. Thanks to their technical knowledge, resources or expertise, these people have provided or continue to provide the Company with tools and resources that have helped it grow both scientifically and as a business. These equity warrants and founder warrants do not correspond to a compensation instrument as no performance criterion would be relevant to express the Company's medium- or long-term interest.

The other financial instruments used by the Company (free shares, founders' warrants) are meant to retain key Company employees to help the organization operate smoothly and grow.

\*\*\*\*\*The performance of the Board of Directors is assessed every three years in the form of a self-assessment carried out under the guidance of an outside consultant. This assessment addresses the Board's composition, organization and operating procedures. In addition, once a year, the Board puts a discussion of its operating procedures on the agenda of one of its meetings.

Furthermore, through a decision dated March 27, 2015, the Board of Directors wished to establish Rules of Procedure in order to specify, supplement and implement the rules for its organization and operation that apply to it under the law (and to its committees), the Company's regulations and bylaws, and the ethical rules that apply to all the directors and the corporate governance principles by which it refers (Corporate Governance Code for Small and Midcaps, MiddleNext, December 2009).

## 14.5 Changes to the corporate governance

None

## **15 Employees**

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### **15.1 Human resources**

#### **15.1.1 Number of employees**

At December 31, 2020, the workforce included 51 employees.

As of the date of this Universal Registration Document, the Company's workforce is 56 employees (excluding interns):

The clinical and regulatory Research & Development Division has 47 persons.

The Administrative Division has 9 persons.

### **15.2 Employee shareholding and stock options**

#### **15.2.1 Stock subscription warrants (BSA) and Company founder warrants (BSPCE)**

As of the date of this Universal Registration Document, the various share subscription warrants and founders' share warrants plans allow for subscription of new common shares in exchange for one warrant.

##### **ISSUANCE OF 2015 FOUNDERS' SHARE WARRANTS**

On March 27, 2015 and then on March 28, 2017, the Board of Directors decided to issue 65,000 founders' share warrants to Alexis Peyroles under the following conditions:

- 15,000 could be subscribed as of October 1, 2017
- 25,000 could be subscribed as of October 1, 2018
- 25,000 could be subscribed as of October 1, 2019

As of December 31, 2019, no founders' share warrants had been subscribed, and 45,000 had lapsed.

##### **ISSUANCE OF 2017 SHARE SUBSCRIPTION WARRANTS**

On July 18, 2017, the Chief Executive Officer, by delegation of the Board of Directors on June 14, 2017, himself making use of the delegation from the General Shareholders' Meeting of May 31, 2016, decided to issue 52,000 2017 share subscription warrants for the benefit of consultants (see section 19.1.4 "potential capital" *below*), which can be subscribed until July 17, 2018.

42,000 2017 share subscription warrants were subscribed, 10,000 having lapsed.

##### **ISSUANCE OF 2018 SHARE SUBSCRIPTION WARRANTS**

On June 13, 2018, the Board of Directors, making use of the delegation of the General Shareholders' Meeting on June 14, 2017, decided to issue 42,850 2018 share subscription warrants for the benefit of Gérard Tobelem, which can be subscribed until June 13, 2023. This date is that of the 2016 share subscription warrants.

### ISSUANCE OF 2018 FOUNDERS' SHARE WARRANTS

On June 13, 2018, the Board of Directors, making use of the delegation from the General Shareholders' Meeting of June 14, 2017, decided to issue 25,900 2018 founders' share warrants for the benefit of Dominique Costantini. This issue served to offset the 2017 founders' share warrants which could not have been subscribed or exercised before the end of the exercise period on March 28, 2018 given the market price.

### ISSUANCE OF 2019 FOUNDERS' SHARE WARRANTS

On June 26, 2019, the Board of Directors, making use of the delegation from the General Shareholders' Meeting of June 13, 2018, decided to issue 60,000 2019 founders' share warrants, i.e. 10,000 founders' share warrants for the benefit of each non-salaried non-executive director in office on June 26, 2019.

### ISSUANCE OF 2020 FOUNDERS' SHARE WARRANTS

On June 17, 2020, the Board of Directors, making use of the delegation from the General Shareholders' Meeting of June 26, 2019, decided to issue 70,000 2020 founders' share warrants, i.e. 10,000 founders' share warrants for the benefit of each non-salaried non-executive director in office on June 17, 2020.

#### *15.2.1.1 Plan details*

	Founders' share warrants 2020	Founders' share warrants 2019	Founders' share warrants 2018	Share subscription warrants 2018	Share subscription warrants 2017	2015 founders' share warrants
Date of General Shareholders' Meeting or Board of Directors having allocated the plan	Extraordinary General Shareholders' Meeting on 6/26/2019  Board of Directors meeting on 6/17/2020	Extraordinary General Shareholders' Meeting on 6/13/2018  Board of Directors meeting on 6/26/2019	Extraordinary General Shareholders' Meeting on 6/14/2017  Board of Directors meeting on 6/13/2018	Extraordinary General Shareholders' Meeting on 6/14/2017	Extraordinary General Shareholders' Meeting on 5/31/2016	Extraordinary General Shareholders' Meeting on 9/17/2014  Board of Directors meeting on 3/27/2015 and on 3/28/2017
Maximum number of warrants authorized by General Shareholders' Meetings	70,000	60,000	500,000	500,000	400,000	300,000
Number of warrants issued	70,000	60,000	25,900	42,850	52,000	65,000
Starting point for exercising warrants	Allocation date	Allocation date	Allocation date	Allocation date	Allocation date	See 15.2.1 above
Expiration date	6/17/2025	6/26/2024	6/13/2023	6/13/2023	7/17/2021	See 15.2.1 above
Warrant subscription or purchase price	€0	€0	€0	€0.70	€0.60	€0
Number of warrants subscribed	0	0	0	0	30,000	65,000

	<b>Founders' share warrants 2020</b>	<b>Founders' share warrants 2019</b>	<b>Founders' share warrants 2018</b>	<b>Share subscription warrants 2018</b>	<b>Share subscription warrants 2017</b>	<b>2015 founders' share warrants</b>
<b>Warrant exercise terms</b>	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares	Subscribe common shares
<b>Exercise price</b>	€6.14	€3.58	€4.17	€4.17	€4.65	€10.80
<b>Number of shares subscribed on the date of this Universal Registration Document</b>	0	0	0	0	0	0
<b>Cumulative number of canceled or lapsed share subscription or purchase warrants</b>	0	0	0	0	0	0
<b>Remaining subscription warrants to be issued on the date of this Universal Registration Document</b>	0	0	0	0	0	0

### 15.2.2 Free share allocations

See Tables 6, 7 and 10 in section 13.1 of this Universal Registration Document.

## 15.3 Incentive and profit-sharing contracts

The Company's employees do not benefit from any incentive or profit-sharing contracts.

## 16 Main shareholders

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### 16.1 Changes in shareholding

#### 16.1.1 Changes in shareholding over 2 years

To the knowledge of the Board of Directors, the change in the shareholding structure is as follows:

Name	December 31, 2018			December 31, 2019			December 31, 2020		
	Number of shares	% Capital	% voting rights	Number of shares	% Capital	% voting rights	Number of shares	% capital	% voting rights
Groupe Emile Loria	3,563,697	24.05 %	17.69%	3,557,530	23.71%	17.21%	3,199,353	13.74%	10.49%
Guy Chatelain	230,490	1.56%	1.14%	212,490	1.42%	1.03%	195,490	1.09 %	0.90%
Dominique Costantini	1,937,083	13.07 %	18.64%	1,978,663	13.19%	18.65%	1,978,663	11.00 %	16.62%
Alexis Peyroles (1)	429,576	2.90%	3.14%	595,874	3.97%	3.69%	768,499	4.27 %	5.07%
Maryvonne Hiance (2)	399.084	2.69%	3.64%	399,084	2.66%	3.60%	424.084	2.36 %	3.48%
Nicolas Poirier	22,802	0.15%	0.13%	42,802	0.29%	0.22%	92,802	0.52 %	0.49%
Public	8,234,280	55.58 %	55.60%	7,913,851	52.74%	52.9%	11,324,147	62.97 %	59.86%
<b>Total</b>	<b>14,817,012</b>	<b>100%</b>	<b>100%</b>	<b>15,005,724</b>	<b>100%</b>	<b>100%</b>	<b>17,983,038</b>	<b>100%</b>	<b>100%</b>

(1) Directly and indirectly through the intermediary of his asset management company Aperana Consulting.

(2) Directly and indirectly through her asset management company HIANCE MD2A.

#### 16.1.2 Distribution of capital on the registration date of this Universal Registration Document

To date, the share capital stands at €3,596,607.60, divided into 17,983,038 shares, fully subscribed.

### 16.2 Double voting rights

In accordance with Article L. 225-123 of the French Commercial Code, and unless specified otherwise by the bylaws, shareholders who have owned registered shares for more than two years automatically receive double voting rights. Because no special provision has been stipulated in the bylaws, double voting rights have entered into force for shareholders who met the legal conditions within two years from the Company's first listing, i.e. March 30, 2017.

### **16.3 Control of the issuer**

As of the date of this Universal Registration Document, the Company is not controlled by one shareholder or a group of shareholders.

Out of the nine members of the Board of Directors, five are independent, the duties of the Chairman and Chief Executive Officer are segregated within the Company, and at the Board of Directors meeting on March 27, 2015, the Company created two special committees, an Audit Committee and an Appointments and Compensation Committee, which are described above in paragraph 16.3 of this document. The Company has not implemented any other measures to ensure that this control is not exercised improperly.

### **16.4 Agreements that may lead to a change in control**

N/A.

## 17 Related-party transactions

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### 17.1 Significant agreements with related parties

#### 17.1.1 Agreement between Company subsidiaries and shareholders

##### **OSE PHARMA INTERNATIONAL (OPI)**

OSE Pharma International, a limited company (*société anonyme*) with its registered office in Switzerland (known as OPI SA) has share capital of 100,000 Swiss francs and was created in February 2012. Its corporate purpose is the acquisition, holding, operation, development and marketing of intellectual property rights in biotechnology; research and development of products and treatments resulting from such rights, the conduct of studies and clinical trials, the granting of licenses; the identification and the building of relationships involving partners and scientific, financial, manufacturing and governmental investors; investment in companies active in the same sector (in compliance with the Swiss Federal Law on Acquisition of Real Estate by Persons Resident Abroad - LFAIE); all of which in the Americas. Its main asset is worldwide rights relating to the composition of peptides. It has no employees.

In July 2012, OPI (represented by Guy Chatelain) signed a licensing and marketing contract with OSE Pharma for the Tedopi® project (OSE-2101). This first contract gives OSE Pharma the commercial rights to market the product in Europe as well as responsibility for international development in Europe and the USA. OSE Pharma will set up an international development team and will seek to obtain the green light from the two Registration Agencies (EMA and FDA) in both Europe and the USA. The two companies, both controlled by Emile Loria since 2012, have always had the same common goal, i.e. the international clinical development of Tedopi®, for which OSE Pharma is responsible. Initial meetings between the two agencies verified that the international development strategy could be conducted as a Phase 3 trial with a common trial protocol.

The understanding between OSE Pharma and OPI has been identified as a crucial requirement for the continuation and success of the project, both in terms of funding and in terms of potential industrial partnerships across all territories and the expansion of the project to cover other cancers of interest. Since OSE Pharma is responsible for clinical development and has the required management team and expert know-how, this company acquired OPI in April 2014.

In April 2014, OSE Pharma acquired, via the acquisition of OPI, the assets, worldwide rights and know-how of OSE-2101 technology for all cancers of interest expressing HLA-A2. OPI SA in Geneva is now a subsidiary of OSE Pharma, and OPI shareholders are now OSE Pharma shareholders.

#### 17.1.2 Transactions with related parties

##### **Dominique Costantini**

Dominique Costantini, Chairman of the Board of Directors, has had an open-ended employment contract since July 1, 2014, amended on October 1, 2016, as Head of Development and on July 1, 2020, receiving gross annual compensation of €302,500 (for 151.67 working hours per month) since July 1, 2020. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

At December 31, 2020, Dominique Costantini received €379,000 gross, including a €68,750 bonus for 2019.

The Board of Directors meeting of June 17, 2020, granted 10,000 founders' warrants 2020 to each director, including to Ms. Costantini.

##### **Alexis Peyrols**

Alexis Peyrols, the Company's Chief Executive Officer, has had an open-ended employment contract since July 1, 2014, amended through an addendum on October 1, 2016, and July 1, 2018, as Chief Operating Officer, receiving gross annual

compensation of €350,000 (for 151.67 working hours per month). Variable compensation amounting to 50% of the fixed compensation, half of which is payable in shares, is provided for based on the achievement of certain targets.

At December 31, 2020, Alexis Peyroles received €449,987 gross, including a €83,125 bonus for 2019.

**Maryvonne Hiance**

Maryvonne Hiance, Vice-Chairman of the Board of Directors, has had an open-ended employment contract since May 31, 2016, as Head of Public Relations, receiving gross annual compensation of €120,000 (for 151.67 working hours per month). Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

At December 31, 2020, Maryvonne Hiance received €174,957 gross, including a €30,000 bonus for 2019.

The Board of Directors meeting of June 17, 2020, granted 10,000 founders' warrants 2020 to each director, including to Ms. Hiance.

**Mr. Nicolas Poirier**

Nicolas Poirier, elected as the director representing the employee shareholders on June 26, 2019, is employed as Chief Scientific Officer under an employment contract dated May 31, 2016. Compensation in respect of this employment contract has been calculated on the basis of the gross annual sum of €180,000, increased to a gross annual sum of €200,000 on July 1, 2020. Variable compensation is also provided for.

The Board of Directors meeting of June 17, 2020, wished to grant to Nicolas Poirier an incentive in the form of 100,000 free shares for his leadership of the Research team (one year vesting period).

**Dear shareholders**

Members of the Board of Directors received a total of €158,500 net in directors' fees from the Company for 2020.

## **18 Financial information concerning the issuer's assets, liabilities, financial position and profit or loss**

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### **18.1 Historical financial information**

Fiscal year 2018 historical financial information (combined financial statements and consolidated financial statements) as well as auditors' reports, appear in the Company's 2018 Registration Document, registered with the AMF on April 26, 2019, under number D. 19-0424 and incorporated for reference purposes.

Fiscal year 2019 historical financial information (combined financial statements and consolidated financial statements) as well as auditors' reports, appear in the Company's 2019 Universal Registration Document, registered with the AMF on April 15, 2020, under number D. 20-0298 and incorporated for reference purposes.

### **18.1.1 Historical financial information**

#### **18.1.1.1 Statutory Auditors' report on the consolidated financial statements for the fiscal year ended on December 31, 2020**

RBB BUSINESS ADVISORS

ERNST & YOUNG et Autres

**OSE Immunotherapeutics**  
Exercice clos le 31 décembre 2020

Rapport des commissaires aux comptes sur les comptes consolidés

RBB BUSINESS ADVISORS  
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414 202 341 R.C.S. Paris

ERNST & YOUNG et Autres  
Tour First  
TSA 14444  
92037 Paris-La Défense cedex  
S.A.S. à capital variable  
438 476 913 R.C.S. Nanterre

Commissaire aux Comptes  
Membre de la compagnie  
régionale de Paris

Commissaire aux Comptes  
Membre de la compagnie  
régionale de Versailles et du Centre

## OSE Immunotherapeutics

Exercice clos le 31 décembre 2020

### Rapport des commissaires aux comptes sur les comptes consolidés

A l'Assemblée Générale de la société OSE Immunotherapeutics,

#### Opinion

En exécution de la mission qui nous a été confiée par vos assemblées générales, nous avons effectué l'audit des comptes consolidés de la société OSE Immunotherapeutics relatifs à l'exercice clos le 31 décembre 2020, tels qu'ils sont joints au présent rapport.

Nous certifions que les comptes consolidés sont, au regard du référentiel IFRS tel qu'adopté dans l'Union européenne, réguliers et sincères et donnent une image fidèle du résultat des opérations de l'exercice écoulé ainsi que de la situation financière et du patrimoine, à la fin de l'exercice, de l'ensemble constitué par les personnes et entités comprises dans la consolidation.

L'opinion formulée ci-dessus est cohérente avec le contenu de notre rapport au comité d'audit.

#### Fondement de l'opinion

##### ■ Référentiel d'audit

Nous avons effectué notre audit selon les normes d'exercice professionnel applicables en France. Nous estimons que les éléments que nous avons collectés sont suffisants et appropriés pour fonder notre opinion.

Les responsabilités qui nous incombent en vertu de ces normes sont indiquées dans la partie « Responsabilités des commissaires aux comptes relatives à l'audit des comptes consolidés » du présent rapport.

##### ■ Indépendance

Nous avons réalisé notre mission d'audit dans le respect des règles d'indépendance prévues par le Code de commerce et par le Code de déontologie de la profession de commissaire aux comptes sur la période du 1<sup>er</sup> janvier 2020 à la date d'émission de notre rapport, et notamment nous n'avons pas fourni de services interdits par l'article 5, paragraphe 1, du règlement (UE) n° 537/2014.

Opinion

*"In compliance with engagement entrusted to us by your General Meetings, we have audited the consolidated financial statements of OSE Immunotherapeutics for the fiscal year ended December 31, 2020 as attached to the present report.*

*We certify that, in accordance with the IFRS as adopted by the European Union, the consolidated financial accounts are fair and true and give an accurate view of the results of the Company's operations for the past year, of its financial position and of its assets and liabilities as at December 31, 2020, of the parties and entities included in the consolidation.*

*The opinion expressed above is consistent with our report to the Audit Committee."*

## Justification des appréciations - Points clés de l'audit

La crise mondiale liée à la pandémie de Covid-19 crée des conditions particulières pour la préparation et l'audit des comptes de cet exercice. En effet, cette crise et les mesures exceptionnelles prises dans le cadre de l'état d'urgence sanitaire induisent de multiples conséquences pour les entreprises, particulièrement sur leur activité et leur financement, ainsi que des incertitudes accrues sur leurs perspectives d'avenir. Certaines de ces mesures, telles que les restrictions de déplacement et le travail à distance, ont également eu une incidence sur l'organisation interne des entreprises et sur les modalités de mise en œuvre des audits.

C'est dans ce contexte complexe et évolutif que, en application des dispositions des articles L. 823-9 et R. 823-7 du Code de commerce relatives à la justification de nos appréciations, nous portons à votre connaissance les points clés de l'audit relatifs aux risques d'anomalies significatives qui, selon notre jugement professionnel, ont été les plus importants pour l'audit des comptes consolidés de l'exercice, ainsi que les réponses que nous avons apportées face à ces risques.

Les appréciations ainsi portées s'inscrivent dans le contexte de l'audit des comptes consolidés pris dans leur ensemble et de la formation de notre opinion exprimée ci-avant. Nous n'exprimons pas d'opinion sur des éléments de ces comptes consolidés pris isolément.

### ■ Reconnaissance des produits d'exploitation issus des accords de collaboration

*Cf. notes 3.5., 3.16. et 4.8.1. de l'annexe aux comptes consolidés.*

Risque identifié	Notre réponse
<p>Le chiffre d'affaires du groupe est principalement issu des accords de collaboration mis en place avec des sociétés pharmaceutiques partenaires. Ces accords incluent diverses composantes, d'une part, des montants facturables à la signature, puis des montants facturables lors du franchissement de certains objectifs de développement prédefinis ou bien encore d'objectifs commerciaux ou réglementaires.</p> <p>Comptablement, les montants facturables au titre de la signature du contrat sont soit immédiatement enregistrés en chiffre d'affaires lorsque le groupe n'a pas d'engagements de développement futurs, soit, lorsque le groupe n'a pas transféré l'ensemble des droits, étalés sur la durée estimée de l'implication du groupe dans les développements futurs, laquelle fait l'objet de révisions périodiques. Les montants facturables à franchissement d'un objectif défini contractuellement sont comptabilisés en chiffre d'affaires à la date à laquelle la condition contractuelle est remplie.</p> <p>La comptabilisation de ces contrats s'appuie donc sur des estimations et hypothèses de la direction concernant notamment :</p> <ul style="list-style-type: none"> <li>➤ l'estimation des dates de franchissement des objectifs ;</li> <li>➤ le montant estimé des frais de recherche et développement à engager après la signature.</li> </ul>	<p>Nos travaux ont porté sur l'intégralité des contrats en cours et clos au cours de la période. Nos contrôles ont plus particulièrement consisté à :</p> <ul style="list-style-type: none"> <li>➤ analyser les clauses contractuelles et les traitements comptables applicables aux montants facturables à la signature et aux montants facturables au franchissement d'objectifs ;</li> <li>➤ étudier les hypothèses utilisées dans la reconnaissance du chiffre d'affaires, notamment les dates de finalisation des travaux de recherche et développement du groupe ;</li> <li>➤ étudier le montant des frais de recherche et développement encouru, par rapprochement des coûts avec le grand livre analytique ;</li> <li>➤ étudier le montant des frais de recherche et développement restant à encourir par entretiens avec la direction financière et par examen du budget qui a été validé par le conseil d'administration ;</li> <li>➤ rapprocher le budget avec celui de l'année précédente et analyser les variations ;</li> <li>➤ vérifier l'exactitude arithmétique du calcul du chiffre d'affaires.</li> </ul>

Dès lors, nous avons considéré que la reconnaissance du chiffre d'affaires issu des accords de collaboration, représentant l'essentiel du chiffre d'affaires du groupe, est un point clé de notre audit.

■ Evaluation des actifs incorporels relatifs à la R&D (FR104 et OSE-127)

*Cf. notes 3.5., 3.7., 3.8. et 4.1.1. de l'annexe aux comptes consolidés.*

Risque identifié	Notre réponse
<p>La valeur nette comptable des actifs incorporels relatifs à la recherche et au développement en cours (R&amp;D) s'élève au 31 décembre 2020 à M€ 52,6.</p> <p>Ces actifs immobilisés sont constitués de deux molécules, FR104 et OSE-127 (ex. Effi-7), issues de l'acquisition de la société Effimune.</p> <p>Les actifs incorporels en cours sont soumis à un test de dépréciation lorsque des circonstances indiquent que la recouvrabilité de leur valeur comptable est mise en doute ou a minima une fois par an. Une perte de valeur est comptabilisée à concurrence de l'excédent de la valeur comptable sur la valeur recouvrable de l'actif.</p> <p>Comme explicité dans la note 4.1.1., ces tests de dépréciation sur les molécules FR104 et OSE-127 ont été réalisés en utilisant la méthode de l'actualisation des flux futurs de trésorerie afin d'analyser la valeur d'utilité des actifs.</p> <p>Ces flux de trésorerie prévisionnels prennent en considération plusieurs hypothèses clés : horizon temporel, probabilités de réussite, taux d'actualisation, taux d'imposition. Les conclusions de ces tests ont conduit à une absence de dépréciation.</p> <p>Nous avons considéré que la détermination de la valeur recouvrable des actifs incorporels relatifs à la R&amp;D est un point clé de notre audit en raison (i) de leur importance dans les comptes du groupe, (ii) des estimations nécessaires pour déterminer les flux futurs de trésorerie et (iii) des estimations et hypothèses, notamment en ce qui concerne les probabilités de réussite et le taux d'actualisation, utilisées pour déterminer leur valeur d'utilité.</p>	<p>Notre approche d'audit concernant les actifs incorporels relatifs à la R&amp;D repose principalement sur des analyses sur (i) le <i>business plan</i> établi par la direction du groupe et incluant différentes hypothèses opérationnelles ainsi que les probabilités de réalisation de ces flux de trésorerie prévisionnels et (ii) le modèle financier contribuant à déterminer la valeur recouvrable de chacun des actifs utilisés par le groupe.</p> <p>Nous avons focalisé notre attention sur les éléments suivants :</p> <ul style="list-style-type: none"> <li>▶ les principales hypothèses opérationnelles incluses dans le <i>business plan</i> : nous avons pris connaissance des estimations et hypothèses retenues et les avons rapprochées avec les informations prévisionnelles communiquées par les sociétés pharmaceutiques partenaires. Nous avons également vérifié l'exactitude arithmétique du <i>business plan</i> produit par la direction. Nous avons rapproché ce <i>business plan</i> avec le budget approuvé par le conseil d'administration ;</li> <li>▶ la probabilité de réussite : nous avons examiné les différentes probabilités de succès retenues et comparé celles-ci aux pratiques observées dans le secteur des biotechnologies ;</li> <li>▶ le taux d'actualisation retenu : nous avons apprécié le taux retenu, en incluant dans notre équipe d'audit des experts en évaluation financière ;</li> <li>▶ le taux d'imposition : nous avons apprécié le taux d'imposition retenu en incluant dans notre équipe d'audit des experts en fiscalité ;</li> <li>▶ les tests de sensibilité : nous avons examiné l'analyse de sensibilité de la valeur d'utilité effectuée par la direction à une variation des principales hypothèses retenues ;</li> <li>▶ enfin nous avons vérifié que les notes XX de l'annexe donnaient une information appropriée.</li> </ul>

- Caractère exhaustif des dépenses de recherche et développement sous-traitées (études cliniques)

*Cf. notes 3.5. et 4.8.2. de l'annexe aux comptes consolidés.*

Risque identifié	Notre réponse
<p>Le groupe poursuit des programmes de recherche précliniques et cliniques en collaboration avec des centres de recherche et d'essais cliniques sous contrat. Au 31 décembre 2020, les frais de sous-traitance de recherche et développement s'élèvent à M€ 21,7.</p> <p>Les dépenses de recherche et développement engagées à ce titre sont systématiquement reconnues en charges selon l'avancement des projets. A la clôture, sur la base des informations transmises par les prestataires ou par les calendriers de réalisation prévus aux contrats, la direction détermine les avancements au prorata temporis de chacune des prestations de recherche.</p> <p>Compte tenu de l'importance des dépenses de recherche et développement et de leur méthode d'estimation à la clôture de l'exercice, nous avons considéré leur caractère exhaustif comme étant un point clé de notre audit.</p>	<p>Nos travaux ont notamment consisté à prendre connaissance des éléments justifiant les estimations clés utilisées par la direction pour déterminer le montant des charges à provisionner dans les comptes à la clôture de l'exercice. Dans ce cadre, nous avons :</p> <ul style="list-style-type: none"> <li>▶ pris connaissance du processus de contrôle interne de suivi de l'avancement des charges mis en place par la société afin d'identifier et d'estimer les coûts à provisionner à la clôture de l'exercice ;</li> <li>▶ étudié les contrats significatifs conclus avec les centres de recherche et d'essais cliniques, ainsi que les éléments établis par la direction justifiant des coûts des essais réalisés ;</li> <li>▶ étudié les débouclages des provisions de l'année précédente afin d'examiner la cohérence des estimations faites par la direction ;</li> <li>▶ examiné la cohérence du stade d'avancement des projets et le calcul de la charge afférente, au regard des informations transmises par les centres de recherche et d'essais cliniques ou par l'analyse réalisée par la direction sur la base de calendriers de réalisation prévus aux contrats ;</li> <li>▶ analysé, le cas échéant, les factures émises en période subséquente afin d'examiner l'absence de décalage avec les estimations réalisées.</li> </ul>

#### Vérifications spécifiques

Nous avons également procédé, conformément aux normes d'exercice professionnel applicables en France, aux vérifications spécifiques prévues par les textes légaux et réglementaires des informations relatives au groupe, données dans le rapport de gestion du conseil d'administration.

Nous n'avons pas d'observation à formuler sur leur sincérité et leur concordance avec les comptes consolidés.

#### Autres vérifications ou informations prévues par les textes légaux et réglementaires

- Format de présentation des comptes consolidés destinés à être inclus dans le rapport financier annuel

Conformément au III de l'article 222-3 du règlement général de l'AMF, la direction de votre société nous a informés de sa décision de reporter l'application du format d'information électronique unique tel que défini par le règlement européen délégué n° 2019/815 du 17 décembre 2018 aux exercices

ouverts à compter du 1<sup>er</sup> janvier 2021. En conséquence, le présent rapport ne comporte pas de conclusion sur le respect de ce format dans la présentation des comptes consolidés destinés à être inclus dans le rapport financier annuel mentionné au I de l'article L. 451-1-2 du Code monétaire et financier.

■ Désignation des commissaires aux comptes

Nous avons été nommés commissaires aux comptes de la société OSE Immunotherapeutics par votre assemblée générale du 17 septembre 2014 pour le cabinet RBB BUSINESS ADVISORS et par décision de l'associé unique du 27 avril 2012 pour le cabinet ERNST & YOUNG et Autres.

Au 31 décembre 2020, le cabinet RBB BUSINESS ADVISORS était dans la septième année de sa mission sans interruption et le cabinet ERNST & YOUNG et Autres dans la neuvième année, dont six années depuis que les titres de la société ont été admis aux négociations sur un marché réglementé.

**Responsabilités de la direction et des personnes constituant le gouvernement d'entreprise relatives aux comptes consolidés**

Il appartient à la direction d'établir des comptes consolidés présentant une image fidèle conformément au référentiel IFRS tel qu'adopté dans l'Union européenne ainsi que de mettre en place le contrôle interne qu'elle estime nécessaire à l'établissement de comptes consolidés ne comportant pas d'anomalies significatives, que celles-ci proviennent de fraudes ou résultent d'erreurs.

Lors de l'établissement des comptes consolidés, il incombe à la direction d'évaluer la capacité de la société à poursuivre son exploitation, de présenter dans ces comptes, le cas échéant, les informations nécessaires relatives à la continuité d'exploitation et d'appliquer la convention comptable de continuité d'exploitation, sauf s'il est prévu de liquider la société ou de cesser son activité.

Il incombe au comité d'audit de suivre le processus d'élaboration de l'information financière et de suivre l'efficacité des systèmes de contrôle interne et de gestion des risques, ainsi que le cas échéant de l'audit interne, en ce qui concerne les procédures relatives à l'élaboration et au traitement de l'information comptable et financière.

Les comptes consolidés ont été arrêtés par le conseil d'administration.

**Responsabilités des commissaires aux comptes relatives à l'audit des comptes consolidés**

■ Objectif et démarche d'audit

Il nous appartient d'établir un rapport sur les comptes consolidés. Notre objectif est d'obtenir l'assurance raisonnable que les comptes consolidés pris dans leur ensemble ne comportent pas d'anomalies significatives. L'assurance raisonnable correspond à un niveau élevé d'assurance, sans toutefois garantir qu'un audit réalisé conformément aux normes d'exercice professionnel permet de systématiquement détecter toute anomalie significative. Les anomalies peuvent provenir de fraudes ou résulter d'erreurs et sont considérées comme significatives lorsque l'on peut raisonnablement s'attendre à ce qu'elles puissent, prises individuellement ou en cumulé, influencer les décisions économiques que les utilisateurs des comptes prennent en se fondant sur ceux-ci.

Comme précisé par l'article L. 823-10-1 du Code de commerce, notre mission de certification des comptes ne consiste pas à garantir la viabilité ou la qualité de la gestion de votre société.

Dans le cadre d'un audit réalisé conformément aux normes d'exercice professionnel applicables en France, le commissaire aux comptes exerce son jugement professionnel tout au long de cet audit. En outre :

- ▶ il identifie et évalue les risques que les comptes consolidés comportent des anomalies significatives, que celles-ci proviennent de fraudes ou résultent d'erreurs, définit et met en œuvre des procédures d'audit face à ces risques, et recueille des éléments qu'il estime suffisants et appropriés pour fonder son opinion. Le risque de non-détection d'une anomalie significative provenant d'une fraude est plus élevé que celui d'une anomalie significative résultant d'une erreur, car la fraude peut impliquer la collusion, la falsification, les omissions volontaires, les fausses déclarations ou le contournement du contrôle interne ;
- ▶ il prend connaissance du contrôle interne pertinent pour l'audit afin de définir des procédures d'audit appropriées en la circonstance, et non dans le but d'exprimer une opinion sur l'efficacité du contrôle interne ;
- ▶ il apprécie le caractère approprié des méthodes comptables retenues et le caractère raisonnable des estimations comptables faites par la direction, ainsi que les informations les concernant fournies dans les comptes consolidés ;
- ▶ il apprécie le caractère approprié de l'application par la direction de la convention comptable de continuité d'exploitation et, selon les éléments collectés, l'existence ou non d'une incertitude significative liée à des événements ou à des circonstances susceptibles de mettre en cause la capacité de la société à poursuivre son exploitation. Cette appréciation s'appuie sur les éléments collectés jusqu'à la date de son rapport, étant toutefois rappelé que des circonstances ou événements ultérieurs pourraient mettre en cause la continuité d'exploitation. S'il conclut à l'existence d'une incertitude significative, il attire l'attention des lecteurs de son rapport sur les informations fournies dans les comptes consolidés au sujet de cette incertitude ou, si ces informations ne sont pas fournies ou ne sont pas pertinentes, il formule une certification avec réserve ou un refus de certifier ;
- ▶ il apprécie la présentation d'ensemble des comptes consolidés et évalue si les comptes consolidés reflètent les opérations et événements sous-jacents de manière à en donner une image fidèle ;
- ▶ concernant l'information financière des personnes ou entités comprises dans le périmètre de consolidation, il collecte des éléments qu'il estime suffisants et appropriés pour exprimer une opinion sur les comptes consolidés. Il est responsable de la direction, de la supervision et de la réalisation de l'audit des comptes consolidés ainsi que de l'opinion exprimée sur ces comptes.

#### ■ Rapport au comité d'audit

Nous remettons au comité d'audit un rapport qui présente notamment l'étendue des travaux d'audit et le programme de travail mis en œuvre, ainsi que les conclusions découlant de nos travaux. Nous portons également à sa connaissance, le cas échéant, les faiblesses significatives du contrôle interne que nous avons identifiées pour ce qui concerne les procédures relatives à l'élaboration et au traitement de l'information comptable et financière.

Parmi les éléments communiqués dans le rapport au comité d'audit figurent les risques d'anomalies significatives, que nous jugeons avoir été les plus importants pour l'audit des comptes consolidés de l'exercice et qui constituent de ce fait les points clés de l'audit, qu'il nous appartient de décrire dans le présent rapport.

Nous fournissons également au comité d'audit la déclaration prévue par l'article 6 du règlement (UE) n° 537/2014 confirmant notre indépendance, au sens des règles applicables en France telles qu'elles sont fixées notamment par les articles L. 822-10 à L. 822-14 du Code de commerce et dans le Code de déontologie de la profession de commissaire aux comptes. Le cas échéant, nous nous entretenons avec le comité d'audit des risques pesant sur notre indépendance et des mesures de sauvegarde appliquées.

Paris et Paris-La Défense, le 13 avril 2021

Les Commissaires aux Comptes

RBB BUSINESS ADVISORS

ERNST & YOUNG et Autres



Jean-Baptiste Bonnefoux

Cédric Garcia

**18.1.1.2 Statutory Auditors' report on the separate financial statements for the fiscal year ended on December 31, 2020**

RBB BUSINESS ADVISORS

ERNST & YOUNG et Autres

**OSE Immunotherapeutics**  
Exercice clos le 31 décembre 2020

Rapport des commissaires aux comptes sur les comptes annuels

RBB BUSINESS ADVISORS 133 bis, rue de l'Université 75007 Paris S.A. au capital de € 150 000 414 202 341 R.C.S. Paris	ERNST & YOUNG et Autres Tour First TSA 14444 92037 Paris-La Défense cedex S.A.S. à capital variable 438 476 913 R.C.S. Nanterre
Commissaire aux Comptes Membre de la compagnie régionale de Paris	Commissaire aux Comptes Membre de la compagnie régionale de Versailles et du Centre

## OSE Immunotherapeutics

Exercice clos le 31 décembre 2020

### Rapport des commissaires aux comptes sur les comptes annuels

A l'Assemblée Générale de la société OSE Immunotherapeutics,

#### Opinion

En exécution de la mission qui nous a été confiée par vos assemblées générales, nous avons effectué l'audit des comptes annuels de la société OSE Immunotherapeutics relatifs à l'exercice clos le 31 décembre 2020, tels qu'ils sont joints au présent rapport.

Nous certifions que les comptes annuels sont, au regard des règles et principes comptables français, réguliers et sincères et donnent une image fidèle du résultat des opérations de l'exercice écoulé ainsi que de la situation financière et du patrimoine de la société à la fin de cet exercice.

L'opinion formulée ci-dessus est cohérente avec le contenu de notre rapport au comité d'audit.

#### Fondement de l'opinion

##### ■ Référentiel d'audit

Nous avons effectué notre audit selon les normes d'exercice professionnel applicables en France. Nous estimons que les éléments que nous avons collectés sont suffisants et appropriés pour fonder notre opinion.

Les responsabilités qui nous incombent en vertu de ces normes sont indiquées dans la partie « Responsabilités des commissaires aux comptes relatives à l'audit des comptes annuels » du présent rapport.

##### ■ Indépendance

Nous avons réalisé notre mission d'audit dans le respect des règles d'indépendance prévues par le Code de commerce et par le Code de déontologie de la profession de commissaire aux comptes sur la période du 1<sup>er</sup> janvier 2020 à la date d'émission de notre rapport, et notamment nous n'avons pas fourni de services interdits par l'article 5, paragraphe 1, du règlement (UE) n° 537/2014.

Opinion

*"In compliance with engagement entrusted to us by your General Meetings, we have audited the annual accounts of OSE Immunotherapeutics for the fiscal year ended December 31, 2020 as attached to the present report.*

*We certify that, in accordance with the French accounting principles, the annual accounts are fair and true and give an accurate view of the results of the Company's operations for the past year, of its financial position and of its assets and liabilities as at December 31, 2020.*

*The opinion expressed above is consistent with our report to the Audit Committee."*

### Justification des appréciations - Points clés de l'audit

La crise mondiale liée à la pandémie de Covid-19 crée des conditions particulières pour la préparation et l'audit des comptes de cet exercice. En effet, cette crise et les mesures exceptionnelles prises dans le cadre de l'état d'urgence sanitaire induisent de multiples conséquences pour les entreprises, particulièrement sur leur activité et leur financement, ainsi que des incertitudes accrues sur leurs perspectives d'avenir. Certaines de ces mesures, telles que les restrictions de déplacement et le travail à distance, ont également eu une incidence sur l'organisation interne des entreprises et sur les modalités de mise en œuvre des audits.

C'est dans ce contexte complexe et évolutif que, en application des dispositions des articles L. 823-9 et R. 823-7 du Code de commerce relatives à la justification de nos appréciations, nous portons à votre connaissance les points clés de l'audit relatifs aux risques d'anomalies significatives qui, selon notre jugement professionnel, ont été les plus importants pour l'audit des comptes annuels de l'exercice, ainsi que les réponses que nous avons apportées face à ces risques.

Les appréciations ainsi portées s'inscrivent dans le contexte de l'audit des comptes annuels pris dans leur ensemble et de la formation de notre opinion exprimée ci-dessous. Nous n'exprimons pas d'opinion sur des éléments de ces comptes annuels pris isolément.

#### ■ Reconnaissance des produits d'exploitation issus des accords de collaboration

*Cf. note « Produits d'exploitation » de l'annexe aux comptes annuels.*

Risque identifié	Notre réponse
Les produits d'exploitation de votre société sont principalement issus des accords de collaboration mis en place avec des sociétés pharmaceutiques partenaires. Ces accords incluent diverses composantes, d'une part des montants facturables à la signature, puis des montants facturables lors du franchissement de certains objectifs de développement prédéfinis ou bien encore d'objectifs commerciaux ou réglementaires.	Nos travaux ont porté sur l'intégralité des contrats en cours et clos au cours de la période. Nos contrôles ont ainsi consisté à : <ul style="list-style-type: none"> <li>▶ étudier les hypothèses utilisées dans la reconnaissance du chiffre d'affaires, notamment les dates de finalisation des travaux de recherche et développement de votre groupe ;</li> <li>▶ étudier le montant des frais de recherche et développement encouru, par rapprochement des coûts avec le grand livre analytique ;</li> <li>▶ étudier le montant des frais de recherche et développement restant à encourir, par entretiens avec la direction financière et par examen du budget qui a été validé par votre conseil d'administration ;</li> <li>▶ rapprocher le budget avec celui de l'année précédente et analyser les variations ;</li> <li>▶ vérifier l'exactitude arithmétique du calcul du chiffre d'affaires.</li> </ul>
Comptablement, les montants facturables au titre de la signature du contrat sont soit immédiatement enregistrés en produits lorsque votre société n'a pas d'engagements de développement futurs, soit, lorsque votre société n'a pas transféré l'ensemble des droits, étais sur la durée estimée de l'implication de votre groupe dans les développements futurs, laquelle fait l'objet de révisions périodiques. Les montants facturables au franchissement d'un objectif défini contractuellement sont comptabilisés en produits à la date à laquelle la condition contractuelle est remplie.	
La comptabilisation de ces contrats s'appuie donc sur des estimations et hypothèses de la direction concernant notamment : <ul style="list-style-type: none"> <li>▶ l'estimation des dates de franchissement des objectifs ;</li> <li>▶ le montant estimé des frais de recherche et développement à engager après la signature.</li> </ul>	

Dès lors, nous avons considéré que la reconnaissance des produits d'exploitation issus de ces contrats de collaboration constituait un point clé de l'audit.

#### ■ Evaluation du fonds commercial

*Cf. note « Immobilisations incorporelles » de l'annexe aux comptes annuels.*

Risque identifié	Notre réponse
Comme mentionné dans la note « Immobilisations incorporelles » des parties « Règles et méthodes comptables » et « Notes relatives à certains postes du bilan » de l'annexe aux comptes annuels, le fonds commercial est inscrit au bilan pour une valeur nette comptable de K€ 42 734. Il est comptabilisé au coût d'acquisition.	Notre appréciation de la valeur du fonds commercial est fondée sur le processus mis en place par votre société pour déterminer la valeur d'utilité de cet actif. Nos travaux ont notamment consisté à : <ul style="list-style-type: none"> <li>▶ prendre connaissance de la méthodologie retenue par la direction pour évaluer la valeur d'utilité de cet actif ;</li> <li>▶ analyser le <i>business plan</i> élaboré par la direction, en rapprochant les éléments prévisionnels utilisés du budget approuvé par votre conseil d'administration ;</li> <li>▶ examiner les différentes probabilités de succès retenues et comparer celles-ci aux pratiques observées dans le secteur des biotechnologies ;</li> <li>▶ apprécier le taux d'actualisation retenu, en incluant des experts en évaluation financière dans notre équipe d'audit. Des tests de sensibilité ont ainsi été réalisés par la société et examinés par nos soins ;</li> <li>▶ apprécier le taux d'imposition retenu en incluant des experts en fiscalité dans notre équipe d'audit ;</li> <li>▶ vérifier les calculs réalisés par la direction de la société dans le <i>business plan</i> et le modèle financier établi ;</li> <li>▶ étudier les tests de sensibilité : nous avons apprécié l'analyse de sensibilité de la valeur d'utilité effectuée par la direction à une variation des principales hypothèses retenues ;</li> <li>▶ vérifier que les notes X.a) et Y.b) donnaient une information appropriée.</li> </ul>
Ce fonds commercial a été affecté aux molécules, FR104 et OSE-127, issues de l'acquisition de la société Effimune.	
Lorsque la valeur actuelle de cet actif est inférieure à la valeur comptable, une dépréciation est constituée du montant de la différence.	
Comme explicité dans la note « Immobilisations incorporelles », ce test de dépréciation a été réalisé en utilisant la méthode de l'actualisation des flux futurs de trésorerie afin d'analyser la valeur d'utilité des actifs.	
Ces flux de trésorerie prévisionnels prennent en considération plusieurs hypothèses clés : horizon temporel, probabilités de réussite, taux d'actualisation, taux d'imposition. La réalisation de ces tests a conduit la direction à conclure à une absence de dépréciation.	
Compte tenu de l'importance du fonds commercial et de l'impact significatif qu'aurait une évolution des estimations et hypothèses, notamment en ce qui concerne les probabilités de réussite et le taux d'actualisation, sur la valeur d'utilité, nous avons considéré l'évaluation du fonds commercial comme un point clé de l'audit.	

#### ■ Evaluation des titres de participation

*Cf. note « Immobilisations financières » de l'annexe aux comptes annuels.*

Risque identifié	Notre réponse
Comme mentionné dans les notes « Immobilisations financières » des parties « Règles et méthodes comptables » et « Notes relatives à certains postes du bilan » de l'annexe aux comptes annuels, les titres de participation sont inscrits au bilan pour une valeur nette	Notre appréciation de l'évaluation de la valeur des titres de participation est fondée sur le processus mis en place par la société pour déterminer la valeur d'utilité de ces actifs.

comptable de K€ 50 000. Ils sont comptabilisés à la date d'entrée au coût d'acquisition ou à la valeur d'apport.

Les titres de participation sont constitués essentiellement des titres d'OSE Pharma International (OPI) qui possède les droits sur la molécule OSE-2101.

Lorsque la valeur actuelle de ces actifs est inférieure à la valeur comptable, une dépréciation est constituée du montant de la différence.

La valeur actuelle de ces actifs, comme exposé dans la note « Immobilisations financières », est établie sur la base d'éléments prévisionnels via la réalisation de flux futurs de trésorerie (DCF) issus des business plans établis par la direction.

Les flux de trésorerie pour tester les titres de participation de l'entité OPI incluent les projections de la direction pour la molécule OSE-2101 dont l'entité OPI détient les droits d'exploitation.

Ces flux de trésorerie prévisionnels prennent en considération plusieurs hypothèses clés : horizon temporel, probabilités de réussite, taux d'actualisation, taux d'imposition. La réalisation de ces tests a conduit la direction à conclure à une absence de dépréciation.

Les perspectives de rentabilité et les incertitudes inhérentes à certaines hypothèses requièrent l'exercice du jugement de la direction afin de confirmer l'évaluation faite de la valeur nette comptable des titres de participation.

Compte tenu de l'importance des titres de participation et de l'impact significatif qu'aurait une évolution des estimations et hypothèses, notamment en ce qui concerne les probabilités de réussite et le taux d'actualisation sur leur valeur actuelle, nous avons considéré l'évaluation des titres de participation comme un point clé de l'audit.

Nos travaux ont notamment consisté à :

- ▶ prendre connaissance de la méthodologie retenue par la direction pour évaluer la valeur d'utilité de ces actifs ;
- ▶ analyser le *business plan* élaboré par la direction, ces évaluations reposant sur des éléments prévisionnels ;
- ▶ apprécier les différentes probabilités de réussite retenues et comparer celles-ci aux pratiques observées dans le secteur des biotechnologies, notamment dans le domaine de l'oncologie ;
- ▶ étudier la pertinence du taux d'actualisation retenu, en incluant des experts en évaluation financière dans notre équipe d'audit. Des tests de sensibilité ont ainsi été réalisés par la direction de la société et examinés par nos soins ;
- ▶ apprécier le taux d'imposition retenu en incluant des experts en fiscalité dans notre équipe d'audit ;
- ▶ vérifier les calculs réalisés par la direction de la société dans le *business plan* et le modèle financier établi.

#### ■ Caractère exhaustif des dépenses de recherche et développement sous-traitées (études cliniques)

*Cf. « Frais de recherche et développement » de l'annexe aux comptes annuels.*

Risque identifié	Notre réponse
Votre société poursuit des programmes de recherche en collaboration avec des centres de recherche sous contrat. Au 31 décembre 2020, les frais de sous-traitance de recherche et développement s'élèvent à K€ 27 521.	Nos travaux ont notamment consisté à prendre connaissance des éléments justifiant les estimations clés utilisées par la direction pour déterminer le montant des charges à provisionner dans les comptes à la clôture de l'exercice. Dans ce cadre, nous avons :
Les dépenses de recherche et développement engagées à ce titre sont systématiquement comptabilisées en charges selon l'avancement des projets. A la clôture de l'exercice, sur la base des informations transmises par les prestataires ou par les calendriers de réalisation prévus	<ul style="list-style-type: none"> <li>▶ pris connaissance du processus de contrôle interne de suivi de l'avancement des charges mis en place par votre société afin d'identifier et d'estimer les coûts à provisionner à la clôture de l'exercice ;</li> </ul>

aux contrats, la direction détermine les avancements au prorata temporis de chacune des prestations de recherche.

Compte tenu de l'importance des dépenses de recherche et développement et de leur méthode d'estimation à la clôture de l'exercice, nous avons considéré leur évaluation comme étant un point clé de l'audit.

- ▶ étudié les contrats significatifs conclus avec les centres de recherche et d'essais cliniques, ainsi que les éléments établis par la direction justifiant des coûts des essais réalisés ;
- ▶ étudié, le cas échéant, les débouclages de provisions de l'année précédente afin d'examiner la cohérence des estimations passées de la direction ;
- ▶ examiné la cohérence du stade d'avancement des projets et le calcul de la charge afférante, au regard des informations transmises par les prestataires ou par l'analyse réalisée par la direction sur la base de calendriers de réalisation prévus aux contrats ;
- ▶ analysé, si elles ont été émises, les factures émises en période subséquente afin d'examiner l'absence de décalage avec les estimations réalisées.

#### Vérifications spécifiques

Nous avons également procédé, conformément aux normes d'exercice professionnel applicables en France, aux vérifications spécifiques prévues par les textes légaux et réglementaires.

- Informations données dans le rapport de gestion et dans les autres documents sur la situation financière et les comptes annuels adressés aux actionnaires

Nous n'avons pas d'observation à formuler sur la sincérité et la concordance avec les comptes annuels des informations données dans le rapport de gestion du conseil d'administration et dans les autres documents sur la situation financière et les comptes annuels adressés aux actionnaires.

Nous attestons de la sincérité et de la concordance avec les comptes annuels des informations relatives aux délais de paiement mentionnées à l'article D. 441-6 du Code de commerce.

- Informations relatives au gouvernement d'entreprise

Nous attestons de l'existence, dans la section du rapport de gestion du conseil d'administration consacrée au gouvernement d'entreprise, des informations requises par les articles L. 225-37-4, L. 22-10-10 et L. 22-10-9 du Code de commerce.

Concernant les informations fournies en application des dispositions de l'article L. 22-10-9 du Code de commerce sur les rémunérations et avantages versés ou attribués aux mandataires sociaux ainsi que sur les engagements consentis en leur faveur, nous avons vérifié leur concordance avec les comptes ou avec les données ayant servi à l'établissement de ces comptes et, le cas échéant, avec les éléments recueillis par votre société auprès des entreprises contrôlées par elle qui sont comprises dans le périmètre de consolidation. Sur la base de ces travaux, nous attestons l'exactitude et la sincérité de ces informations.

Concernant les informations relatives aux éléments que votre société a considéré susceptibles d'avoir une incidence en cas d'offre publique d'achat ou d'échange, fournies en application des dispositions de l'article L. 22-10-11 du Code de commerce, nous avons vérifié leur conformité avec les documents dont elles sont issues et qui nous ont été communiqués. Sur la base de ces travaux, nous n'avons pas d'observation à formuler sur ces informations.

■ Autres informations

En application de la loi, nous nous sommes assurés que les diverses informations relatives à l'identité des détenteurs du capital ou des droits de vote vous ont été communiquées dans le rapport de gestion.

**Autres vérifications ou informations prévues par les textes légaux et réglementaires**

■ Format de présentation des comptes annuels destinés à être inclus dans le rapport financier annuel

Conformément au III de l'article 222-3 du règlement général de l'AMF, la direction de votre société nous a informés de sa décision de reporter l'application du format d'information électronique unique tel que défini par le règlement européen délégué n° 2019/815 du 17 décembre 2018 aux exercices ouverts à compter du 1<sup>er</sup> janvier 2021. En conséquence, le présent rapport ne comporte pas de conclusion sur le respect de ce format dans la présentation des comptes annuels destinés à être inclus dans le rapport financier annuel mentionné au I de l'article L. 451-1-2 du Code monétaire et financier.

■ Désignation des commissaires aux comptes

Nous avons été nommés commissaires aux comptes de la société OSE Immunotherapeutics par votre assemblée générale du 17 septembre 2014 pour le cabinet RBB BUSINESS ADVISORS et par décision de l'associé unique du 27 avril 2012 pour le cabinet ERNST & YOUNG et Autres.

Au 31 décembre 2020, le cabinet RBB BUSINESS ADVISORS était dans la septième année de sa mission sans interruption et le cabinet ERNST & YOUNG et Autres dans la neuvième année, dont six années depuis que les titres de la société ont été admis aux négociations sur un marché réglementé.

**Responsabilités de la direction et des personnes constituant le gouvernement d'entreprise relatives aux comptes annuels**

Il appartient à la direction d'établir des comptes annuels présentant une image fidèle conformément aux règles et principes comptables français ainsi que de mettre en place le contrôle interne qu'elle estime nécessaire à l'établissement de comptes annuels ne comportant pas d'anomalies significatives, que celles-ci proviennent de fraudes ou résultent d'erreurs.

Lors de l'établissement des comptes annuels, il incombe à la direction d'évaluer la capacité de la société à poursuivre son exploitation, de présenter dans ces comptes, le cas échéant, les informations nécessaires relatives à la continuité d'exploitation et d'appliquer la convention comptable de continuité d'exploitation, sauf s'il est prévu de liquider la société ou de cesser son activité.

Il incombe au comité d'audit de suivre le processus d'élaboration de l'information financière et de suivre l'efficacité des systèmes de contrôle interne et de gestion des risques, ainsi que le cas échéant de l'audit interne, en ce qui concerne les procédures relatives à l'élaboration et au traitement de l'information comptable et financière.

Les comptes annuels ont été arrêtés par le conseil d'administration.

### Responsabilités des commissaires aux comptes relatives à l'audit des comptes annuels

#### ■ Objectif et démarche d'audit

Il nous appartient d'établir un rapport sur les comptes annuels. Notre objectif est d'obtenir l'assurance raisonnable que les comptes annuels pris dans leur ensemble ne comportent pas d'anomalies significatives. L'assurance raisonnable correspond à un niveau élevé d'assurance, sans toutefois garantir qu'un audit réalisé conformément aux normes d'exercice professionnel permet de systématiquement détecter toute anomalie significative. Les anomalies peuvent provenir de fraudes ou résulter d'erreurs et sont considérées comme significatives lorsque l'on peut raisonnablement s'attendre à ce qu'elles puissent, prises individuellement ou en cumulé, influencer les décisions économiques que les utilisateurs des comptes prennent en se fondant sur ceux-ci.

Comme précisé par l'article L. 823-10-1 du Code de commerce, notre mission de certification des comptes ne consiste pas à garantir la viabilité ou la qualité de la gestion de votre société.

Dans le cadre d'un audit réalisé conformément aux normes d'exercice professionnel applicables en France, le commissaire aux comptes exerce son jugement professionnel tout au long de cet audit.

En outre :

- ▶ il identifie et évalue les risques que les comptes annuels comportent des anomalies significatives, que celles-ci proviennent de fraudes ou résultent d'erreurs, définit et met en œuvre des procédures d'audit face à ces risques, et recueille des éléments qu'il estime suffisants et appropriés pour fonder son opinion. Le risque de non-détection d'une anomalie significative provenant d'une fraude est plus élevé que celui d'une anomalie significative résultant d'une erreur, car la fraude peut impliquer la collusion, la falsification, les omissions volontaires, les fausses déclarations ou le contournement du contrôle interne ;
- ▶ il prend connaissance du contrôle interne pertinent pour l'audit afin de définir des procédures d'audit appropriées en la circonstance, et non dans le but d'exprimer une opinion sur l'efficacité du contrôle interne ;
- ▶ il apprécie le caractère approprié des méthodes comptables retenues et le caractère raisonnable des estimations comptables faites par la direction, ainsi que les informations les concernant fournies dans les comptes annuels ;
- ▶ il apprécie le caractère approprié de l'application par la direction de la convention comptable de continuité d'exploitation et, selon les éléments collectés, l'existence ou non d'une incertitude significative liée à des événements ou à des circonstances susceptibles de mettre en cause la capacité de la société à poursuivre son exploitation. Cette appréciation s'appuie sur les éléments collectés jusqu'à la date de son rapport, étant toutefois rappelé que des circonstances ou événements ultérieurs pourraient mettre en cause la continuité d'exploitation. S'il conclut à l'existence d'une incertitude significative, il attire l'attention des lecteurs de son rapport sur les informations fournies dans les comptes annuels au sujet de cette incertitude ou, si ces informations ne sont pas fournies ou ne sont pas pertinentes, il formule une certification avec réserve ou un refus de certifier ;
- ▶ il apprécie la présentation d'ensemble des comptes annuels et évalue si les comptes annuels reflètent les opérations et événements sous-jacents de manière à en donner une image fidèle.

■ Rapport au comité d'audit

Nous remettons au comité d'audit un rapport qui présente notamment l'étendue des travaux d'audit et le programme de travail mis en œuvre, ainsi que les conclusions découlant de nos travaux. Nous portons également à sa connaissance, le cas échéant, les faiblesses significatives du contrôle interne que nous avons identifiées pour ce qui concerne les procédures relatives à l'élaboration et au traitement de l'information comptable et financière.

Parmi les éléments communiqués dans le rapport au comité d'audit figurent les risques d'anomalies significatives, que nous jugeons avoir été les plus importants pour l'audit des comptes annuels de l'exercice et qui constituent de ce fait les points clés de l'audit, qu'il nous appartient de décrire dans le présent rapport.

Nous fournissons également au comité d'audit la déclaration prévue par l'article 6 du règlement (UE) n° 537/2014 confirmant notre indépendance, au sens des règles applicables en France telles qu'elles sont fixées notamment par les articles L. 822-10 à L. 822-14 du Code de commerce et dans le Code de déontologie de la profession de commissaire aux comptes. Le cas échéant, nous nous entretenons avec le comité d'audit des risques pesant sur notre indépendance et des mesures de sauvegarde appliquées.

Paris et Paris-La Défense, le 13 avril 2021

Les Commissaires aux Comptes

RBB BUSINESS ADVISORS

ERNST & YOUNG et Autres



Jean-Baptiste Bonnefoux

Cédric Garcia

### **18.1.2 Change of accounting reference date**

Not applicable

### **18.1.3 Accounting standards**

See Part 3 of Section 18.1.6 "Consolidated financial statements"

### **18.1.4 Change of accounting standards**

Not applicable

### **18.1.5 Separate financial statements for the fiscal year ended on December 31, 2020**

<b>Assets in €K</b>	<b>31/12/2020</b>	<b>31/12/2019</b>
<b>Non-current assets</b>		
Intangible assets	42,734	42,734
Tangible assets	947	1,010
Non-current financial assets	50,814	50,436
<b>Total non-current assets</b>	<b>94,494</b>	<b>94,179</b>
<b>Current assets</b>		
Stocks and receivables		
Receivables	9,167	6,605
Marketable securities	83	97
Cash and cash equivalents	29,276	25,730
Prepaid expenses	2,496	1,787
<b>Total current assets</b>	<b>41,021</b>	<b>34,219</b>
<b>Total assets</b>	<b>135,515</b>	<b>128,403</b>

<b>Liabilities in K€</b>	<b>31/12/2020</b>	<b>12/31/2019</b>
Stated capital	3,597	3 001
share premium	132,170	115,339
Legal reserve		
Retained earnings	(13,261)	(13,387)
Net result	(17,398)	125
	<b>Total shareholders' equity</b>	<b>105 107</b>
Conditioned advances	9,232	9,252
	<b>Total other equity</b>	<b>9,232</b>
Provision for risks	529	726
Provision for charges	531	377
	<b>Total provision for risks and charges</b>	<b>1,060</b>
Current financial liabilities	6,978	308
Other current financial liabilities	250	
Trade payables	10,278	6,915
Fiscal and social debts	1,902	1,493
Other debts and accruals		
Deferred income	704	4,239
	<b>Total current debts</b>	<b>20 112</b>
Exchange difference	3	14
	<b>Total liabilities</b>	<b>135,515</b>
		<b>128,403</b>

### Income statement

<b>P&amp;L in K€</b>	<b>31/12/2020</b>	<b>31/12/2019</b>
Turnover	9,743	10,602
Other revenues	1,301	16,653
<b>Total Revenues</b>	<b>11,044</b>	<b>27,254</b>
Other purchase and external expenses	25,949	23,629
Staff cost	6,710	5,687
Tax expenses	131	129
Depreciation for amortisation and provision	427	1,013
Other expenses	252	181
<b>Total Operating costs</b>	<b>33,469</b>	<b>30,639</b>
<b>Operating Profit/Loss</b>	<b>(22,425)</b>	<b>(3,384)</b>
Financial products	24	190
Financial expenses	288	16
<b>Financial result</b>	<b>(264)</b>	<b>173</b>
<b>Profit/Loss Before Tax</b>	<b>(22,689)</b>	<b>(3,211)</b>
Exceptional product	552	370
Exceptional expenses	332	23
Income Tax	(5,070)	(2,989)
<b>Net Profit/Loss</b>	<b>(17,398)</b>	<b>125</b>

### 18.1.6 Consolidated financial statement for the fiscal year ended on December 31, 2020

#### *Consolidated statement of financial position*

(Amount in €k)

ASSETS in €k	Note	12/31/2020	12/31/2019
Intangible assets			
R&D	1.1	52,600	52,600
Tangible assets	1.2	947	1,009
Right-of-use assets	1.3	2,848	1,692
Financial assets	1.4	581	287
Deferred tax assets	10.1	165	283
<b>Total intangible assets</b>		<b>57,141</b>	<b>55,871</b>
Trade receivables			
Other accounts receivables	2.2	1,074	747
Current financial assets	2.3	9,390	6,474
Cash and cash equivalents	2.1	29,368	25,842
<b>Total tangible assets</b>		<b>39,832</b>	<b>33,062</b>
<b>TOTAL ASSETS</b>		<b>96,973</b>	<b>88,933</b>

LIABILITIES in €K		12/31/2020	12/31/2019
Stated capital	4.1	3,597	3,001
Share premium	4.1	65,449	48,497
Treasury stock	4.4	(93)	(148)
Reserves and retained earnings		8,966	11 838
Consolidated result		(16,555)	(4,652)
	<b>Total shareholders' equity</b>	<b>61,364</b>	<b>58,536</b>
Non-current financial liabilities	5	16,552	9,211
Lease non-current liabilities	5	2,318	1,413
Non-current deferred tax liabilities	10.1	2,080	5,066
Non-current provisions	7	531	377
	<b>Total non-current debts</b>	<b>21,481</b>	<b>16,067</b>
Current financial liabilities	5	50	548
Lease current liabilities	5	594	309
Trade payables	6.1	10,286	6,918
Tax due liabilities	6.2	2	20
Other payables	6.2	2,108	1,723
Other debts and accruals	6.3	1,090	4,832
	<b>Total current debts</b>	<b>14,128</b>	<b>14,330</b>
<b>TOTAL LIABILITIES</b>		<b>96,973</b>	<b>88,933</b>

**Statement of comprehensive income**

P&L IN K€		December 31, 2020	December 31, 2019
Turnover	8.1	10,418	25,952
Other operating income	8.1	13	0
<b>Total Revenues</b>		<b>10,432</b>	<b>25,952</b>
Research and development expenses	8.2	(22,355)	(21,655)
Overhead expenses	8.3	(4,783)	(3,898)
Expenses related to shares payments	8.4	(2,283)	(1,868)
<b>OPERATING PROFIT/LOSS - CURRENT</b>		<b>(18,989)</b>	<b>(1,469)</b>
Other operating products (badwill)		0	0
Other operating expenses		0	(2)
<b>OPERATING PROFIT/LOSS</b>		<b>(18,989)</b>	<b>(1,472)</b>
Financial products	9	31	221
Financial expenses	9	(288)	(213)
<b>PROFIT/LOSS BEFORE TAX</b>		<b>(19,246)</b>	<b>(1,464)</b>
Income Tax	10.3	2,692	(3,188)
<b>NET PROFIT/LOSS</b>		<b>(16,555)</b>	<b>(4,652)</b>
<i>Of which consolidated net result attributable to shareholders</i>		<b>(16,555)</b>	<b>(4,652)</b>
<b>Net earnings attributable to shareholders</b>			
Weighted average number of shares outstanding	12	<b>15,556,046</b>	<b>14,892,496</b>
<b>Basic earnings per share</b>		(1.06)	(0.31)
<b>Diluted earnings per share</b>		(1.06)	(0.31)

IN K€	2020	2019
<b>NET RESULT</b>	<b>(16,555)</b>	<b>(4,652)</b>
<i>Amounts to be recycled in the income statement:</i>		
Unrealized gains on securities available for sale, net of tax		
Currency conversion difference	(4)	(43)
<i>Amounts not to be recycled in the income statement:</i>		
Other comprehensive income in the period	(7)	(80)
<b>GLOBAL PROFIT/LOSS</b>	<b>(16,561)</b>	<b>(4,732)</b>

**Statement of changes in consolidated equity**

In K€	Share capital	Share premium	Currency translation transactions	Own shares	Retained earnings and result	Total consolidated equity
<b>Consolidated equity as at December 31st, 2018</b>	<b>2,963</b>	<b>48,535</b>	<b>(57)</b>	<b>(168)</b>	<b>10,482</b>	<b>61,755</b>

<b>Consolidated result</b>					<b>(4,652)</b>	<b>(4,652)</b>
<i>Actuarial difference</i>			,		<b>(37)</b>	<b>(37)</b>
<i>Currency translation transactions</i>			<b>(43)</b>			<b>(43)</b>
<b>Global consolidated result</b>			<b>(43)</b>	<b>0</b>	<b>(4,689)</b>	<b>(4,732)</b>
Capital variation - free shares	38	(38)				0
Warrant subscription						0
Deferred tax						0
Share based payments					1 511	1 511
Own shares transactions				20	(17)	3
<b>Consolidated equity as at December 31st, 2019</b>	<b>3,001</b>	<b>48,497</b>	<b>(100)</b>	<b>(148)</b>	<b>7,286</b>	<b>58,536</b>
<b>Consolidated result</b>					<b>(16 555)</b>	<b>(16 555)</b>
<i>Actuarial difference</i>					<b>(3)</b>	<b>(3)</b>
<i>Currency translation transactions</i>			<b>(4)</b>			<b>(4)</b>
<b>Global consolidated result</b>			<b>(4)</b>	<b>0</b>	<b>(16,558)</b>	<b>(16,561)</b>
Capital variation - free shares	92	(92)				0
Capital variation	504	18,127				18,630
Capital increase fees		(1,083)				(1,083)
Share based payments					1,787	1 787
Own shares transactions				55		55
<b>Consolidated equity as at December 31st, 2020</b>	<b>3,597</b>	<b>65,449</b>	<b>(104)</b>	<b>(93)</b>	<b>(7,485)</b>	<b>61,364</b>

### Statement of cash flows

In K€	Note	2020	2019
<b>CONSOLIDATED RESULT</b>		<b>(16,555)</b>	<b>(4,652)</b>
+/- Depreciation, amortization & provision expenses	1.2	273	231
+/- Provision for pensions and retirement	7	151	92
+ Amortization on "right-of-use"	1.3	457	251
+/- Shares based payments (1)	8.4	1,787	1,511
<b>CASH FLOW BEFORE TAX</b>		<b>(13,888)</b>	<b>(2,568)</b>
+ Financial charges	5	273	30
- Income tax expenses	10.3	(2,692)	3,188
<b>CASH FLOW FROM OPERATIONS BEFORE NET BORROWING COST AND TAXES (A)</b>		<b>(16,306)</b>	<b>650</b>
- Tax paid		(50)	(70)
+/- Working capital variation (2)		(2,920)	8,555
<b>CASH FLOW FROM OPERATING ACTIVITIES (D)</b>		<b>(19,277)</b>	<b>9,135</b>
- Tangible assets increase	1.2	(210)	(336)
+/- Financial assets variation	2.1	0	2,861
+/- Mutual funds units accounted in current financial assets		0	34
+/- Loans and advances variation	1.4	(294)	(184)
<b>CASH FLOW FROM INVESTING ACTIVITIES (E)</b>		<b>(504)</b>	<b>2,375</b>
+ Capital increase	4.1	18,630	0
+/- Capital increase costs	4.1	(1,203)	0
+ Loan subscription	5	6,960	5,628
- Loan repayment	5	(325)	(455)
- Lease debt repayment (3)	5	(482)	(251)
- Financial charges	5	(273)	(164)
<b>CASH FLOW FROM FINANCING ACTIVITIES (F)</b>		<b>23,306</b>	<b>4,759</b>
+/- Currency translation transactions (G)		0	0
<b>CASH VARIATION H = (D + E + F + G)</b>		<b>3,526</b>	<b>16,269</b>
<b>CASH OPENING BALANCE (I)</b>	2.1	25,842	9,573
<b>CASH CLOSING BALANCE (J)</b>	2.1	29,368	25,842

- (1) €1,787,000 in valuation costs for free shares and founders' warrants allocated as of December 31, 2020.
- (2) The change in working capital requirement was primarily due to the following:
- increase in trade receivables amounting to €277,000
  - increase in other current assets amounting to €2,916,000
  - increase in trade payables amounting to €3,368,000
  - increase in tax and employee-related payables amounting to €385,000
  - decrease in other payables amounting to €3,724,000
- (3) This line relates to the application of IFRS 16 and corresponds to the repayment of lease liabilities amounting to €482,000.
- (4) Of which €1,000 of CCB

## Notes to the consolidated financial statements

### 1- INFORMATION ON THE COMPANY PRESENTING THE FINANCIAL STATEMENTS

OSE Immunotherapeutics (the “Group” or the “Company”) is a biotechnology company focused on developing innovative immunotherapies acting on activator or suppressor cells to stimulate or inhibit the immune response for immuno-oncology and autoimmune diseases and transplantation. It has a portfolio of innovative clinical and preclinical products and agreements with international pharmaceutical groups. The registered office of OSE Immunotherapeutics is in Nantes. Teams are based in Nantes and Paris.

OPI, a wholly-owned subsidiary of OSE Immunotherapeutics, is a company governed by Swiss law, founded in February 2012, which owns the rights to Tedopi® (OSE-2101), which it acquired from Biotech Synergy (US) in April 2012. OPI grants OSE Immunotherapeutics the license to Tedopi® (OSE-2101).

OSE Immunotherapeutics Inc. is a company governed by US law, founded in April 2017, in order to serve as a point of support for international scientific collaboration.

### 2 - HIGHLIGHTS

#### 2.1 COVID-19

The emergence and spread of the Coronavirus in early 2020 have impacted the global economic environment.

At this point, Management cannot reliably assess the impacts that this crisis may have on the Group’s business should it continue. However, Management considers that the medium-term impact should be moderate and should not hinder its ability to continue as a going concern.

The impacts incurred in 2020 are as follows:

Following the lockdown imposed by the Government on March 17, 2020, the Company’s laboratory operations slowed down due to the slowdown in the supply of consumables and limited access to animal facilities. Over a four-week period, the Company introduced limited operations only for a skeleton laboratory staff; The activity of the laboratory was then able to resume normally;

The rate of enrollment in clinical trials was reduced, given the measures taken in hospitals which are focused on fighting COVID-19; This situation has led to the postponement of a milestone initially planned in 2020 for OSE-127/S95011. The clinical trials on OSE-127/S95011 were also several months behind schedule.

Recruitment halted for step 2 of the Atalante trial (see next paragraph).

If the crisis were to continue, the impacts could be the following:

The rate of enrollment of patients in clinical trials may be reduced, given the measures taken in hospitals which are focused on fighting COVID-19.

The Company may also be subject to subcontractor prioritization policies, particularly for clinical batch production of its products.

#### 2.2 SIGNATURE OF A COLLABORATION AGREEMENT WITH MABSILICO

In February 2020, the Company signed a collaboration agreement with the innovative company MAbsilico (Tours, France), specializing in the use of artificial intelligence algorithms to discover and characterize therapeutic antibodies.

#### 2.3 SIGNATURE OF AN AMENDMENT TO THE LICENSE AGREEMENT WITH SERVIER

In March 2020, the Company signed an amendment to the two-step global licensing option agreement on the exclusive rights of OSE-127/S95011, Interleukin-7 receptor antagonist, signed with Servier in December 2016. This amendment modifies the arrangements for the potential exercise of the licensing option agreement’s second step. OSE Immunotherapeutics will thus receive a milestone payment of €5 million from Servier on enrollment of the first patient in Phase 2a clinical study scheduled

to start in Sjögren's Syndrome and an additional payment of €15 million on exercise of the option at the end of the two scheduled Phase 2 studies, with priority being given to the study in Sjögren's Syndrome. The initial agreement provided for a total payment of €20 million at the end of Phase 2 in ulcerative colitis. OSE Immunotherapeutics remains in charge of the Phase 2 clinical trial in ulcerative colitis.

In addition, on December 21, 2020, the Company announced the inclusion of the first patient in the Phase 2 clinical trial evaluating OSE-127/S95011, an IL-7 receptor antagonist, in patients with moderate to severe active ulcerative colitis. This clinical trial is being sponsored by OSE Immunotherapeutics.

#### **2.4 POSITIVE RESULTS OF STEP-1 OF THE PHASE 3 CLINICAL TRIAL OF TEDOPI®**

In March 2020, the Company announced the positive results of the Phase 3 clinical trial of Tedopi®, Atalante 1, in non-small cell lung cancer: Primary endpoint of step-1 achieved with a 12-month survival rate in patients treated with Tedopi® of 46%. In the context of the COVID-19 epidemic, decision taken to voluntarily and definitively discontinue screening and the enrolling new patients in step 2 initially planned in the trial and which will therefore not be conducted. The Company will continue additional analyses of the step 1 data and initiate discussions with the regulatory authorities to determine the best path to take for development of the product, in view of the high therapeutic need of the population of patients suffering from advanced lung cancer following failure of treatment by checkpoint inhibitor.

#### **2.5 LAUNCH OF A VACCINE PROGRAM AGAINST COVID-19**

In April 2020, announcement of a prophylactic vaccine program against COVID-19 which relies on the Company's expertise in selecting and optimizing peptides, and on its patented Memopi® technology to explore a T-cell response immune memory in COVID-19.

In August 2020, publication online on BioRxiv of positive data from a preclinical study and an *ex vivo* study in humans on CoVepiT. The results show that CoVepiT provides tissue-resident memory sentinel T cell response with long-term protective immunity in barrier tissues such as the respiratory tract and the lung, associated with long-term protective immunity.

In November 2020, announcement of the finalization of the *ex vivo* trial in humans conducted with CoVepiT. At the same time, the Company presented the development of its vaccine at the World Immunotherapy Congress. This is the first presentation on a second-generation memory T cell COVID-19 vaccine at a scientific congress.

In December 2020, the Company obtained funding of €5.2 million as part of the PSPC-COVID call for projects, operated on behalf of the French State by Bpifrance as part of the Future Investment Program, managed by the General Secretariat for Investment (SGPI), in order to support the development program of CoVepiT if certain criteria are met.

On April 1, 2021, OSE Immunotherapeutics announced the authorization of the Federal Agency for Medicines and Health Products (FAMHP) and the Belgian Ethics Committee to start a Phase 1 clinical trial that will assess tolerability, reactogenicity and immunogenicity of the vaccine in healthy adult volunteers.

#### **2.6 SIGNATURE OF A FRENCH GOVERNMENT-GUARANTEED LOAN AGREEMENT**

In May 2020, the Company signed a non-dilutive agreement for €7 million in the form of a French Government-Guaranteed loan set up in the context of the COVID-19 pandemic, with a group of French banks (see Note 5). The term of this loan is one year with an option for four additional years that the Company already intends to exercise.

The overall effective rate is 0.25% corresponding to the guarantee fee. If the loan is extended beyond the first year, the interest rate will be set through an amendment.

#### **2.7 FINANCING OF €200,000 OBTAINED FROM NANTES MÉTROPOLE**

In July 2020, the Company obtained funding of up to €200,000 from Nantes Métropole to develop a prophylactic vaccine against the pandemic SARS-CoV-2 virus. This grant was awarded as part of the Metropolitan Fund to support health innovations related to the COVID-19 health crisis.

## 2.8 PUBLICATION ON THE EFFICACY AND MECHANISM OF ACTION OF BI 765063 (OSE-172)

In October 2020, data from preclinical and translational studies, recently published in the Journal of Clinical Investigation (JCI), show, in vivo models in rodents and ex vivo in humans, the efficacy and mechanism of action of BI 765063 (OSE-172), the first selective antagonist of the “Don’t Eat” signal mediated by SIRP $\alpha$ . For the first time, the OSE R&D team has identified the “Don’t Find Me” signal, a complementary mechanism mediated by SIRP $\alpha$  whereby tumor cells evade immune detection by preventing T lymphocytes from entering the heart of the tumor.

## 2.9 SUCCESS OF THE COMPANY’S FIRST FUNDRAISING

On November 18, 2020, the Company announced the successful completion of its capital increase, launched on November 16, by means of a private placement. It was carried out with cancellation of preferential subscription rights through a private placement with 25 qualified French and international investors, a large majority of which were new shareholders, and by the accelerated construction of an order book, for €18.6 million.

This capital increase amounts to €503,517.80 through the issue of 2,517,589 new shares and a share premium of €18,126,640.80.

The costs related to this transaction amounted to €1,203,460 and were fully charged against the share premium.

## 2.10 ANSM AUTHORIZATION TO START A CLINICAL TRIAL WITH FR104

In December 2020, the French National Medicines Safety Agency (Agence Nationale de Sécurité du Médicament) and the Committee for the Protection of People gave their authorization to start a Phase 1/2 clinical trial evaluating FR104, a CD-28 antagonist monoclonal antibody, in patients who have received a kidney transplant. This study will be conducted as part of a collaboration agreement between OSE Immunotherapeutics and the Centre Hospitalier de Nantes, the study sponsor.

## 2.11 CAPITAL INCREASE RELATED TO FREE SHARE PLANS

Following the issue of free shares in 2019, presented in the appendices below, the Company carried out the following capital increase during the fiscal year:

- on March 26, 2020: €28,360 capital increase through the issue of 141,800 new shares;
- on June 27, 2020: €59,060 capital increase through the issue of 295,300 new shares;
- on December 18, 2020: €4,525 capital increase through the issue of 22,625 new shares.

After these transactions, the share capital amounted to €3,596,607.60.

## 2.12 ALLOCATION AND ISSUANCE

During the fiscal year, the Company allocated 505,863 free shares and 70,000 founders' warrants (see Section 4-2 of the consolidated financial statements).

The Board of Directors of December 8, 2020, approved a bank financing with the European Investment Bank of €25 million backed by the issue of a maximum of 1,400,000 share warrants.

## 2.13 BPIFRANCE FINANCING

In December 2020, the Company announced that it received €5.2 million in public funding from Bpifrance for the clinical development of its COVID-19 vaccine.

The French State's funding, totaling €5.8 million for the entire consortium and including €5.2 million for OSE Immunotherapeutics, will in particular support the CoVepiT 1 trial, the production of a clinical batch according to Good Manufacturing Practices and a Phase 1/2 clinical trial which will assess the safety and immunogenicity of CoVepiT in patients from at-risk populations.

For the Company, this financing consists of a grant of €1.6 million and a repayable advance of €3.6 million.

### **3 - ACCOUNTING POLICIES AND PRINCIPLES**

#### **3.1 BASIS OF PREPARATION OF THE CONSOLIDATED FINANCIAL STATEMENTS**

The consolidated financial statements of OSE Immunotherapeutics, the consolidating entity, and its subsidiaries, OPI and OSE Immunotherapeutics Inc (the “Group”), approved by the Board of Directors on March 26, 2021, are presented in thousands of euro (000) and were prepared in accordance with International Financial Reporting Standards (IFRS) as adopted by the European Union.

The Board of Directors adopted the going concern assumption, in view of the following:

- Cash and cash equivalents available at December 31, 2020, stood at €29.4 million and did not include the 2020 research tax credit provision of €5.1 million;
- Obtaining financing from Bpifrance in January 2021 for an amount of €1.3 million;
- The signature of a loan agreement in February 2021 with the European Investment Bank for an amount of €25 million.

As a result, the Company will be able to finance its development costs over the next twelve months.

Lastly, as a listed company, and as authorized by the last General Shareholders’ Meeting, the Company has the option, if needed, to use the financial instruments to which listed companies have access.

#### **3.2 REPORTING DATE**

Consolidated entities’ reporting date is December 31 which is the Group’s reporting date.

#### **3.3 STANDARDS AND INTERPRETATIONS APPLICABLE FROM JANUARY 1, 2020**

The Group applied the following standards and interpretations adopted by the European Union:

- Amendments to IAS 1 and IAS 8 - Definition of “material”
- Amendment to IFRS 3 - Definition of a company
- Amendments to IFRS 9, IAS 39 and IFRS 7 – Reform of interest rate benchmarks - Phase 1
- Amendment to IFRS 16 - COVID-19-related lease concessions

The new standards and interpretations had no impact on the Company’s financial statements.

#### **3.4 STANDARDS, AMENDMENTS AND INTERPRETATIONS ADOPTED BY THE EUROPEAN UNION AND APPLICABLE TO FISCAL YEARS BEGINNING ON OR AFTER JANUARY 1, 2021, AND NOT ADOPTED IN ADVANCE BY THE COMPANY**

The Company did not adopt in advance other standards, amendments, revisions and interpretations of published standards effective for annual periods beginning on or after January 1, 2021. Management does not expect these standards to have a material impact on the Company’s financial statements.

#### **3.5 KEY ACCOUNTING ESTIMATES AND JUDGMENTS**

The preparation of financial statements in accordance with IFRS requires judgments, estimates and assumptions to be made which affect the amounts and disclosures that appear in the financial statements. Actual results may prove to be very different from these estimates depending on the various assumptions or conditions and, where applicable, a sensitivity analysis may be carried out if the difference is significant.

##### ***Estimates and assumptions***

- **Valuation of free share allocation plans (AGA) share subscription warrant plans (BSA) and founders’ warrant allocation plans (BSPCE).**

The fair value of the free share plans, share subscription warrants and founders' warrants allocated is measured on the basis of a valuation model that takes into consideration the probability of the plans' vesting requirements being met.

The fair value of the share subscription warrants and Company founders' warrants granted is measured on the basis of actuarial valuation models. These models require the Company to use certain calculation assumptions such as the expected volatility of the share price (see Note 4.3).

**■ Recognition of corporate tax**

The Company is liable to pay income tax in France for its business activities.

Deferred tax assets mainly relate to tax loss carryforwards which are only recognized to the extent that it is probable that future taxable profits will be available. The Group must use its judgment to determine the probability of the existence of future taxable profits.

These deferred tax assets are recognized within the limit of tax liabilities recognized in the form of deferred tax liabilities, payment of which may be avoided by the Company, and the thresholds provided for by tax legislation (see Note 10).

**■ Revenue recognition**

Within the context of a sale or licensing agreement, the Company may defer recognition of a portion of revenue, irrespective of the payments received (see Note 8.1). Determining the duration of this deferral requires the use of estimates.

**■ Intangible assets arising from the acquisition of Effimune**

The fair value of intangible assets associated with the FR104 and OSE-127 molecules was estimated on the basis of business plans reflecting management's best estimate (see Note 1.1).

**■ Estimation and recognition of R&D expenses provisioned under trade payables**

R&D expenses are systematically recognized as expenses as the research programs progress. Based on the information supplied by service providers or by work schedules provided for in contracts, on the reporting date, Management determines the progress of each of the research services on a pro rata basis and, where necessary, settles the expenses for the fiscal year.

### **3.6 FINANCIAL STATEMENTS AND TRANSACTIONS IN FOREIGN CURRENCIES**

Each consolidated entity decides on the operating currency in line with its own economic environment and the conditions under which it conducts its business transactions.

#### ***Financial statements in foreign currencies***

The financial statements of entities whose operating currency differs from the presentation currency are converted using the closing rate method. This conversion is as follows:

Assets and liabilities are converted into the presentation currency, i.e. into euros at closing rates.

Income and expenses are converted using the average rate for the period. The Group used an annual average, considering this to be an acceptable approximation of the conversion applicable on the date of each transaction.

Foreign exchange gains and losses arising from this conversion are recognized in other comprehensive income under "foreign exchange gains and losses."

### *Transactions in foreign currencies*

Transactions in foreign currencies are converted into the presentation currency at the current rate on the transaction date. Monetary items are converted at the foreign exchange rate on the annual reporting date and the effects of these revaluations are recognized in profit or loss for the period.

### **3.7 INTANGIBLE ASSETS**

Intangible assets are recognized in the statement of financial position when they satisfy IAS 38 recognition criteria.

Intangible assets acquired are recognized at their acquisition cost, on the assumption that recognition criteria (reliable valuation and probability that economic benefits will be generated by the asset) have been met.

### *R&D expenses*

- **Research expenses are systematically recognized as expenses.**

Under IAS 38, development expenses are only recognized as intangible assets if all the following criteria have been met:

- (a) Technical feasibility needed to complete the development project;
- (b) Company's intention to complete the project and use the asset;
- (c) Ability to use the intangible asset;
- (d) Demonstration of the probability of future economic benefits attached to the asset;
- (e) Availability of technical, financial and other resources to complete the project; and
- (f) reliable valuation of development expenses.

Given the uncertainty surrounding the technical feasibility of the completion of the research in progress, the Company's development expenses do not currently meet the IAS 38 criteria and are therefore recognized as expenses over the period during which the research commitment was made.

- **Acquired R&D projects are recognized as intangible assets at their fair value, even in the absence of marketing authorization. These assets fall into two categories:**

- They are classed as assets with a defined useful life when they generate economic benefits. In this case, their fair value as recognized in the statement of financial position less, where applicable, the remaining value, is amortized over the period of use expected by the Company.
- Other cases include non-current assets in development which are not amortized but are subject to annual impairment tests.

### *Patents*

Costs relating to filing existing patents, incurred by the Company until said patents are obtained, are recognized as expenses, in line with the position taken for recognizing R&D expenses.

### **3.8 TESTING NON-CURRENT ASSETS FOR IMPAIRMENT**

Intangible assets and property, plant and equipment with a finite life are tested for impairment when circumstances indicate that the recoverability of their carrying amount has been put into doubt and this test is conducted at least once a year on the reporting date (see Note 4.1.1). An impairment is recognized for the difference between the carrying amount and the recoverable amount of the asset.

The recoverable amount of an asset is its fair value fewer selling costs or, if higher, its value in use.

### 3.9 FINANCIAL ASSETS

Financial assets within the scope of IFRS 9 are classed and measured in three categories:

- Amortized cost;
- Fair value through other comprehensive income;
- Fair value through profit or loss.

Upon initial recognition, financial assets are measured at their fair value plus, in the case of investments which are not recognized at fair value through profit or loss, any directly attributable transaction costs.

The Company determines the classification of its financial assets upon initial recognition and, once authorized and appropriated, reviews this classification at each annual reporting date.

### 3.10 NON-CURRENT FINANCIAL ASSETS

Non-current financial assets include long-term financial assets, in particular:

- Cash SICAVs (money market funds);
- Loans and receivables;
- And the “cash portion” of the liquidity contract associated with share buybacks.

#### *Loans and receivables*

This category of non-current financial assets includes advances and collateral deposits pledged to third parties. Repayable advances and collateral deposits are non-derivative financial assets. They are recognized at amortized cost using the effective interest rate method in accordance with IFRS 9.

Loans and receivables are impaired when a loss event occurs, their carrying amount reduced to the sum of the cash flows expected.

### 3.11 CURRENT FINANCIAL ASSETS

Current financial assets include trade and other receivables, other current assets, cash and cash equivalents and current financial instruments.

These assets are recognized by type, based on the following rules.

#### *Trade receivables*

Trade receivables are initially recorded and recognized at the fair value of the consideration received or receivable. Where applicable, receivables are impaired to take recovery risk into consideration.

#### *Current financial instruments*

The Company classes its investments in current financial instruments in one of these three categories:

- **Investments held to maturity recorded at amortized cost:** during this period, the Company did not hold any such investments.
- **Assets at fair value through profit or loss**

They are held-for-trading assets, i.e. assets acquired by the Company intended for short-term sale. The objective is to realize a capital gain.

These assets are part of a portfolio of financial instruments managed together and for which there is a practice of short-term selling. They are measured at fair value and changes in fair value are recognized through profit or loss.

These financial assets are recognized at their fair value without deducting the transaction costs that may be incurred when they are sold. Realized or unrealized gains or losses, associated with the change in fair value of these assets are recognized through profit or loss under Income from cash or cash equivalents.

- **Financial assets at fair value through other comprehensive income:** during this period, the Company did not hold any such investments.

### **Cash and cash equivalents**

Cash equivalents are highly liquid, short-term investments, which are easily convertible into a known amount of cash, and which are subject to negligible risk of change of value.

Cash and cash equivalents include cash at bank and in hand, as well as cash investments in transferable securities or term deposits maturing in less than three months and with a very low sensitivity to interest rate risk.

When preparing the statement of cash flows, cash and cash equivalents comprise bank sight deposits, highly liquid short-term investments, net of bank overdrafts. In the statement of financial position, bank overdrafts are shown as borrowings under financial liabilities.

### **3.12 CONSOLIDATED SHAREHOLDERS' EQUITY**

Consolidated shareholders' equity is the shareholders' equity of consolidated group entities.

Common shares are classified as equity. Capital transaction costs directly attributable to the issue of new shares or options are recognized in equity as a deduction from the proceeds of the issue.

### **3.13 TREASURY SHARES**

The acquisition cost of the OSE Immunotherapeutics shares held by the Group are recognized as a deduction from consolidated equity.

Since April 8, 2015, for a two-year period, automatically renewable for subsequent one-year periods, OSE Immunotherapeutics has charged an organization with implementing a liquidity contract that complies with the Ethics charter drafted by the French Association of Investment Firms (Association française des entreprises d'investissement) and approved by the AMF in a decision dated March 21, 2011.

At December 31, 2020, OSE Immunotherapeutics securities held through the liquidity account, as well as the profits or losses generated over the fiscal year on transactions conducted by the liquidity contract manager were reclassified as shareholders' equity. The cash portion of the liquidity account is classed under "Other financial assets."

### **3.14 SHARE-BASED PAYMENTS**

The Group introduced compensation plans paid out in equity instruments in the form of share subscription warrants, Company founders' warrants or free shares awarded to employees, management, consultants, service providers and members of the Board of Directors.

In application of IFRS 2, for share-based payment transactions settled in equity instruments, the Company measures the related compensation, at the fair value of the goods and services received, unless such fair value cannot be reliably estimated.

In order to apply these last provisions, the amount of benefits granted is measured using the Bjerksund & Stensland model and is recognized under expenses, over the period in which the rights to benefit from the equity instruments vest, offset by increases in equity.

The fair value of the share subscription warrants granted is determined by applying the option-pricing model described in Note 4.3.

The fair value of the free shares awarded is measured on the basis of a valuation model that takes into consideration the probability of the plans' vesting requirements being met.

### 3.15 FINANCIAL LIABILITIES

A financial liability is defined as a contractual obligation to deliver cash or another financial asset to another entity. A financial instrument can be classed as a financial liability (debt, derivative financial instrument) or an equity instrument.

The acquisition price of a financial liability is the amount actually paid, net of transaction costs (unless measured at fair value through profit or loss) and net of any redemption premiums.

There are three categories of financial liabilities:

- **Liabilities measured at amortized cost**

These include trade payables, tax and social security debts, loans and other financial liabilities, such as repayable advances and bank loans. They are recognized at amortized cost using the effective interest rate method.

The portion of financial liabilities maturing in less than one year is shown under "Current financial liabilities."

- **Liabilities measured at fair value through profit or loss**

The Company did not hold any of this type of investment over the period.

- **Liabilities measured optionally at fair value through profit or loss**

The Company did not hold any of this type of investment over the period.

### 3.16 PUBLIC FUNDING

The Company received public funding in the form of conditional advances and grants. Details of this funding are supplied in Note 5.

Public grants are recognized as assets where there is reasonable assurance that:

- The Company will comply with the conditions attached to the grants; and
- Grants will be received.

Operating subsidies that offset the expenses incurred by the Group are recognized in the income statement, less R&D expenses, as the costs are incurred for the research programs in question.

Interest-free conditional advances are intended to fund research programs. They are repayable, in full, if the project is a success and, in part, if the program fails.

Repayable advances for which the contractual rate does not constitute a market rate are treated as financial liabilities to be measured at amortized cost at each reporting date, by discounting all future cash payments at the prevailing market rate of interest or in the contract.

The difference between the current value of the advance at the market rate and the amount of cash received from the public body constitutes a grant within the meaning of IAS 20. This difference must be recognized as an income-related grant and recognized in the income statement, less R&D expenses, as the costs are incurred for the research programs in question.

These advances are recognized as non-current financial liabilities and current financial liabilities depending on their maturity. In the event of a marked failure, the debt waiver granted is recorded as a subsidy.

### 3.17 PROVISIONS FOR LIABILITIES AND CHARGES

Provisions for liabilities and charges are commitments arising from disputes and other risks, with uncertain timing and amounts, that the Company may face in the course of its activities.

A provision is recognized when the Company has a legal or constructive obligation to a third party arising from a past event and when it is probable or certain that this will result in an outflow of funds to said third party, with no equivalent consideration expected from the latter, and when the future outflows of liquidity can be reliably estimated.

The amount recognized as a provision is the best estimate of the expenditure needed to discharge the obligation, discounted on the reporting date.

#### **Pension-related commitments**

On leaving the Company, employees receive a pension in accordance with legal requirements and the applicable collective agreement.

The valuation and accounting methods used by the Group are those set out by IAS 19 "Employee benefits."

In accordance with this standard:

- Expenses relating to defined-contribution schemes are recognized as the expenses are incurred.
- Commitments for each defined-benefit scheme are determined using the projected unit credit method. These calculations are based on assumptions relating to mortality, staff turnover and projections of wage increases. They take the economic situation in individual countries into consideration.
- Actuarial gains and losses are recognized as other comprehensive income.

#### **3.18 REVENUE**

To date, the Company's revenue is mainly generated by licensing agreements with pharmaceutical companies. Generally speaking, these contracts are made up of different components, such as amounts billable on signing and amounts billable when certain predefined development targets have been met, one-off funding payments to finance R&D expenses and the assignment of royalties on future product sales. Royalties on future product sales are a percentage of the net sales generated by the partner.

Amounts billable on signing the contract, for the assignment of a molecule's intellectual property rights, are immediately recognized as revenue when the contract comes into force where the amounts are non-refundable and the Company has no future development commitments.

Revenue related to development services carried out on behalf of the client acquiring the intellectual property rights, are initially recognized as deferred income and spread over the estimated length of the Company's involvement in future development, which is subject to periodic reviews.

Amounts billable once certain predefined development targets have been met are recognized in full as revenue when these objectives are actually achieved, provided that the Company is not contractually liable for any development services on behalf of the client that has acquired the intellectual property after these objectives have been met. On the downside, all or some of the amounts billed when a development target is met, may be spread over the estimated duration of the Company's involvement in future development, which is subject to periodic reviews.

#### **3.19 LEASES**

OSE Immunotherapeutics has leases (as a tenant) mainly for offices and other equipment.

Under operating leases, within the meaning of IFRS 16, the Group recognizes right of use assets and lease liabilities for all these leases, apart from short-term leases (12 months or less) and those relating to low-value assets.

Payments under these leases not recognized in the statement of financial position are recognized as operating expenses on a straight-line basis over the lease term.

At the start of the lease, the liability for future lease payments is discounted using a marginal borrowing rate corresponding to a risk-free rate adjusted by a margin that is representative of the risk specific to each Group entity.

As lease payments are spread over the lease term, the Company applies a discount rate based on the term of these payments.

Payments taken into consideration when assessing liability for future lease payments excludes non-lease components and includes fixed amounts that OSE Immunotherapeutics expects to pay to the lessor over the probable lease term.

Once the lease has commenced, the liability for future lease payments reduces as lease payments are made and increases as interest is added. The liability is revalued, where applicable, to reflect a new assessment or change to future lease payments.

Once the lease has commenced, the right of use asset, initially valued at cost, is amortized on a straight line basis over the lease term and, where applicable, is subject to an impairment test.

### **3.20 INCOME TAX**

Income tax is the total amount of tax payable by the different Group companies, corrected for deferred tax.

Deferred tax is recognized using the balance sheet approach, in accordance with IAS 12, for all temporary differences arising from the difference between the tax base and the carrying amount of assets and liabilities appearing in the financial statements (apart from, for example, goodwill, etc.). They are not discounted.

Deferred tax assets are recognized to the extent that it is probable that future profits will be sufficient to absorb tax loss carryforwards or up to the amount of deferred tax liabilities, within the limit of current thresholds.

### **3.21 RESEARCH TAX CREDIT**

Research tax credits are granted by the French Government to companies to encourage them to carry out technical or scientific research. Companies that can prove that they have incurred expenses that meet the required criteria receive a tax credit which can be used to pay their corporate tax liability for the fiscal year in which the expenses were incurred and for the three subsequent fiscal years, or if applicable, any surplus can be refunded.

The research tax credit is shown in the income statement, fewer R&D expenses, in accordance with IAS 20.

### **3.22 SEGMENT INFORMATION**

The application of IFRS 8 “Operating segments” did not have any impact on the Group’s segment information. In fact, the Group only considers itself to operate in a single aggregated segment: Research & Development on pharmaceutical products with a view to their future sale.

In addition, most of the research and development activity is located in France alongside the Company’s principal operational decision-makers who measure performance against the cash consumed by its activities.

For these reasons, the Group’s management does not believe it to be opportune to set up separate operating segments in its internal reporting.

### **3.23 OTHER COMPREHENSIVE INCOME**

Income and expenses for the period recognized direct in equity are shown under “Other comprehensive income.”

For the periods presented, this heading includes translation adjustments related to the activities of entities with operations in Switzerland and the United States, as well as actuarial losses on employee benefits.

### **3.24 EARNINGS PER SHARE**

Basic earnings per share are calculated over all the periods shown based on shares outstanding in OSE Immunotherapeutics which is legally considered to be the parent company.

Diluted earnings per share are calculated by adding the weighted average number of shares outstanding to the number of shares that would result from the conversion of all common shares with a potentially dilutive effect.

If taking instruments giving future access to equity (BSA, etc.) into account when calculating diluted earnings per share, generates an anti-dilutive effect, these instruments are not taken into consideration.

At the reporting dates presented, taking into account a net loss, the diluted earnings per share was -€0.93 per share, identical to the diluted earnings (see Note 12).

**4- NOTES TO THE FINANCIAL STATEMENTS**

**NOTE 1: NON-CURRENT ASSETS**

**1.1 INTANGIBLE ASSETS**

In €k	12/31/2019	Increase	Decrease	12/31/2020
R&D expenses acquired	52,600	-	-	52,600
	<b>52,600</b>	-	-	<b>52,600</b>

In 2016, following the acquisition of Effimune, the Company valued two molecules, FR104 and OSE-127. These molecules were valued on the basis of future cash flow estimates.

Impairments tests are carried out once a year on non-current assets with an indefinite useful life or which cannot be amortized.

With regard to FR104 in the course of 2020, OSE Immunotherapeutics focused on conducting the Phase 1/2 clinical trial. In December 2020, the Company received authorization for a Phase 1/2 clinical trial evaluating FR104 in patients who received a kidney transplant. This study is being carried out under a clinical collaboration agreement between OSE Immunotherapeutics and the Centre Hospitalier Universitaire de Nantes. A Phase 2 clinical trial is planned for a niche indication in autoimmune diseases.

In addition, discussions are ongoing for a possible partnership for this product.

Concerning OSE-127/S95011, after the Phase 1 clinical trial results obtained in November 2019, the Company received approval from the ANSM to conduct the Phase 2 trial in ulcerative colitis and the first patients were enrolled in the trial in December 2020. Servier will start a Phase 2 study in Sjögren's Syndrome at the end of the second quarter/beginning of the third quarter of 2021.

The value in use of these two molecules, at December 31, 2020, was measured using the discounted cash flow method (DCF). These are the two main assumptions made:

**OSE127/S95011**

(Based on the license agreement signed with Servier)

- 17-year time horizon (with no terminal value);
- Probabilities of success used consistent with the probabilities of success generally observed in the field of autoimmune diseases (Sjögren's Syndrome and ulcerative colitis - UC);
- 10% tax rate (in accordance with the new tax regime for income from the sale or licensing of patents).
- US/Europe/Japan population with 0.2% of the population affected by Sjögren's Syndrome and 0.3% affected by UC;
- Maximum market share of 10% on Sjögren's Syndrome and 7% on UC.

**FR104**

(Based on a financial proposal for a licensing agreement with a pharmaceutical company)

- 17-year time horizon (with no terminal value);
- Probabilities of success used consistent with the probabilities of success generally observed in the field of autoimmune diseases and in transplantation;
- 10% tax rate (in accordance with the new tax regime for income from the sale or licensing of patents).
- US/Europe/Japan population with 0.3% affected by autoimmune disease;
- Maximum market share of 20% for transplants.

The following sensitivity tests were performed:

- Discount rate: sensitivity analysis carried out within a range of between 14% and 16% with a respective impact of €15 million more, or less, not resulting in any impairment of the net carrying amount of these molecules.
- Probability of success: sensitivity analysis conducted within a range of 10% more, or less, not resulting in an impairment of the net carrying amount of these molecules.
- Market share: sensitivity analysis conducted within a range of 5% more, or less, not resulting in an impairment of the net carrying amount of these molecules.
- Price: sensitivity analysis conducted within a range of 5% more, or less, not resulting in an impairment of the net carrying amount of these molecules.

## 1.2 PROPERTY, PLANT AND EQUIPMENT

Property, plant and equipment break down as follows:

In €k	12/31/2019	Increase	Decrease	12/31/2020
<b><u>Gross values</u></b>				
Buildings	284	46	0	331
Equipment and tools	998	119	0	1,117
Office and computer equipment, furniture	133	45	0	178
	<b>1,416</b>	<b>210</b>	<b>0</b>	<b>1,626</b>
<b><u>Amortization</u></b>				
Buildings	59	48	0	107
Equipment and tools	270	195	0	465
Office and computer equipment, furniture	77	30	0	107
	<b>406</b>	<b>273</b>	<b>0</b>	<b>679</b>
<b><u>Net values</u></b>				
Buildings	225	(1)	0	224
Equipment and tools	729	(76)	0	652
Office and computer equipment, furniture	56	15	0	70
	<b>1,009</b>	<b>(63)</b>	<b>0</b>	<b>947</b>

The Company mainly invested in laboratory and office equipment.

## 1.3 RIGHTS OF USE

OSE Immunotherapeutics identified two new leases (covered by the standard) during 2020 with the following characteristics:

- A lease for real estate in France. The incremental borrowing rate used was 2%.
- A sale-leaseback agreement under property, plant and equipment ("Cytometry" research equipment) initially acquired on May 28, 2020, and sold on June 24, 2020. This is considered a sale under IFRS 15 and a right of use was measured applying an interest rate implicit in the lease of 2.11%.

Rights of use break down as follows:

In €K	12/31/2019	Increase	Decrease	12/31/2020
Nantes Lot 1 Lease	537	0	0	537
Nantes Lot 2 Lease	208	0	0	208
Paris Suffren Lease 1	1,198	0	0	1,198
Paris Suffren Lease 2*	0	1,132	0	1,332
Leasing Cytek Cytometre**	0	281	0	281
	<b>1,943</b>	<b>1,613</b>	<b>0</b>	<b>3,556</b>
<b>Amortization</b>				
Nantes Lot 1 Lease	103	103	0	207
Nantes Lot 2 Lease	26	35	0	61
Paris Suffren Lease 1	122	133	0	25
Paris Suffren Lease 2*	0	148	0	148
Leasing Cytek Cytometre**	0	37	0	37
	<b>251</b>	<b>457</b>	<b>0</b>	<b>708</b>
<b>Net Values</b>				
Nantes Lot 1 Lease	434	(103)	0	331
Nantes Lot 2 Lease	182	(35)	0	147
Paris Suffren 1 Lease	1,076	(133)	0	942
Paris Suffren 2 Lease*	0	1,184	0	1,184
Leasing Cytek Cytometre**	0	245	0	245
	<b>1,692</b>	<b>1,157</b>	<b>0</b>	<b>2,848</b>

\* This column includes the recurring and non-recurring breakdown as well as IFRS 9, IAS 20 and IFRS 16 restatements for the year.

\* effective lease date January 1, 2020

\*\* effective lease date June 24, 2020

#### 1.4 NON-CURRENT FINANCIAL ASSETS

In €k	12/31/2019	Increase	Decrease	12/31/2020
Deposits and guarantees	244	211	0	454
Liquidity contract - cash balances	43	1,430	(1,347)	126
<b>Total non-current financial assets</b>	<b>287</b>	<b>1,641</b>	<b>(1,347)</b>	<b>581</b>

## NOTE 2: CURRENT ASSETS

### 2.1 AVAILABLE CASH AND CASH EQUIVALENTS AND CURRENT FINANCIAL ASSETS

In €k	12/31/2019	Increase	Decrease	12/31/2020
Bank accounts	3,082	7,218	(23)	10,277
Term deposit	22,760	19,008	(22,677)	19,091
<b>Cash on deposit</b>	<b>25,842</b>	<b>26,226</b>	<b>(22,700)</b>	<b>29,368</b>
Current financial liabilities (bank accounts)	(2)	(0)	1	(1)
<b>Net cash</b>	<b>25,840</b>	<b>26,226</b>	<b>(22,699)</b>	<b>29,367</b>

The Company invests in non-risky term accounts that meet the definition of cash equivalents (available in the short term).

### 2.2 TRADE RECEIVABLES

In €k	12/31/2020	12/31/2019
Trade receivables	1,074	747
<b>Total net trade receivables</b>	<b>1,074</b>	<b>747</b>

The change in the level of trade receivables is mainly due to the re-invoicing of development costs and un-invoiced revenue to Boehringer Ingelheim for the product OSE-172/BI 765063 (874 thousand euros) and to Servier (€874,000) and to Servier (€189,000).

### 2.3 OTHER CURRENT ASSETS

Other current assets break down as follows:

In €k	12/31/2020	12/31/2019
Value-Added Tax (1)	1,049	978
Trade debtors (2)	100	77
Prepaid expenses (3)	2,496	1,787
Prepaid income (4)	571	546
Government - tax receivable (5)	54	28
Research tax credit (5)	5,120	3,059
<b>Total</b>	<b>9,390</b>	<b>6,474</b>

- (1) Value-added tax includes VAT refund claims of €173,000 for FNP VAT of €266,000 and €587,000 for deductible VAT on services.
- (2) "Trade debtors" mainly comprises €99,000 of trade discounts and rebates receivable.
- (3) Prepaid expenses are mainly composed of R&D expenses, including mainly €641,000 on OSE127 progress, €401,000 on OSE279 progress and €692,000 on OSE172 progress.
- (4) "Prepaid income" mainly comprises grants receivable amounting to €450,000.
- (5) The Research Tax Credit item comprises the tax receivable relating to the 2020 research tax credit.

**NOTE 3: FINANCIAL ASSETS AND LIABILITIES AND IMPACT ON INCOME**

The Company's financial assets were measured as follows as at December 31, 2020:

In €k	12/31/2020		JV per income statement	Loans and receivables	Liabilities at amortized cost
	Statement of Financial Position	JV			
Non-current financial assets	581	581			581
Rights of use	2,848	2,848			2,848
Trade receivables	1,074	1,074			1,074
Other current assets	6,895	6,895			6,895
Current financial assets	-	-			-
Cash and cash equivalents	29,368	29,368			29,368
<b>Total financial assets</b>	<b>40,765</b>	<b>40,765</b>			<b>40,765</b>
Non-current financial liabilities	16,552	16,552			16,552
Non-current lease liabilities	2,318	2,318			2,318
Current financial liabilities	50	50			50
Current lease liabilities	594	594			594
Trade payables	10,286	10,286			10,286
<b>Total financial liabilities</b>	<b>29,799</b>	<b>29,799</b>			<b>29,799</b>

Impacts on the income statement at December 31, 2020		
In €k	Interest	Change in fair value
Assets in JV through income statement	0	0
Loans and receivables		
Assets at amortized cost		
Cash and cash equivalents	12	
<b>Total</b>	<b>12</b>	<b>0</b>
Lease liabilities at amortized cost		59
JV liabilities through income statement	0	
Liabilities measured at amortized cost	272	(58)
<b>Total</b>	<b>272</b>	<b>2</b>

#### NOTE 4: CAPITAL

##### 4.1 ISSUED CAPITAL

Date	Nature of transactions	Capital in €	Issue premium in €	Number of shares created	Number of shares making up the capital	Nominal value in €	Stated capital in €
	<b>At December 31, 2018</b>	<b>2,963,402</b>	<b>48,535,112</b>	<b>4,768,071</b>	<b>14,817,012</b>	<b>0.20</b>	<b>2,963,402</b>
June	Capital increase - Free Shares	30,000	(30,000)	150,000	14,967,012	0.20	2,993,402
December	Issue of 38,712 free shares	7,742	(7,742)	38,712	15,005,724	0.20	3,001,144
	<b>At December 31, 2019</b>	<b>3,001,144</b>	<b>48,497,370</b>	<b>4,956,783</b>	<b>15,005,724</b>	<b>0.20</b>	<b>3,001,144</b>
March	Capital increase - Free Shares (1)	28,360	(28,360)	141,800	15,147,524	0.20	3,029,504
June	Capital increase - Free Shares (2)	30,000	(30,000)	150,000	15,297,524	0.20	3,059,504
June	Capital increase - Free Shares (3)	29,060	(29,060)	145,300	15,442,824	0.20	3,088,564
November	Capital increase (4)	503,518	18,126,641	2,517,589	17,960,413	0.20	3,592,082
November	Capital increase expenses net of tax (4)	0	(1,083,114)	0	17,960,413	0.20	3,592,082
December	Capital increase – Free Shares (5)	4,525	(4,525)	22,625	17,983,038	0.20	3,596,607
	<b>At December 31, 2020</b>	<b>3,596,607</b>	<b>65,448,952</b>	<b>7,934,097</b>	<b>17,983,038</b>	<b>0.20</b>	<b>3,596,607</b>

- (1) Capital increase through the acquisition and issuance of 141,800 free shares.
- (2) Capital increase through the acquisition and issuance of 150,000 free shares.
- (3) Capital increase through the acquisition and issuance of 145,300 free shares.
- (4) Capital increase through the issuance of 2,517,589 shares
- (5) Capital increase through the acquisition and issuance of 22,625 free shares.

On December 31, 2020, the share capital stood at €3,596,607. It is divided into 17,983,038 fully subscribed and paid up common shares with a par value of €0.20.

##### 4.2 EQUITY INSTRUMENTS AUTHORIZED BUT NOT ISSUED

The Combined General Shareholders' Meeting of June 14, 2017, gave the Board of Directors full authority to increase the capital, on one or more occasions, by a maximum of 500,000 new shares:

At December 31, 2019, the Board of Directors had not yet allocated 69,913 of the 500,000 equity instruments.

The Combined General Shareholders' Meeting of June 13, 2018, gave the Board of Directors full authority to increase the capital, on one or more occasions, by a maximum of 500,000 new shares:

On December 31, 2019, the Board of Directors had not yet allocated 140,000 of the 500,000 equity instruments.

The Combined General Shareholders' Meeting of June 26, 2019, gave the Board of Directors full authority to increase the capital, on one or more occasions, by a maximum of 500,000 new shares:

At December 31, 2019, the Board of Directors had not yet allocated 500,000 of the 500,000 equity instruments.

The Combined General Shareholders' Meeting of June 16, 2020, gave the Board of Directors full authority to increase the capital, on one or more occasions, by a maximum of 500,000 new shares:

On June 17, 2020, the Board of Directors decided to:

- issue 100,000 free shares to Nicolas Poirier (under the authority granted on June 13, 2018).
- allocate 150,000 free shares to Alexis Peyroles (under the authority granted on June 26, 2019)
- issue 70,000 (2020) founders' warrants to non-salaried, non-executive directors (i.e., 10,000 founders' warrants per director) (under the authority granted on June 26, 2019)

On June 8, 2020, the Board of Directors decided to:

- issue 11,363 free shares to Alexis Peyroles (under the authority granted on June 13, 2018)
- allocate 244,500 free shares to employees (under the delegation of authority of June 26, 2019)

As of December 31, 2020, there remain:

- 28,637 equity instruments under the authority of the Combined General Shareholders' Meeting on June 13, 2018.
- 35,500 equity instruments under the authority of the Combined General Shareholders' Meeting on June 26, 2019.
- 500,000 equity instruments under the authority of the Combined General Shareholders' Meeting of June 16, 2020.

#### **4.3 SHARE SUBSCRIPTION WARRANTS, FOUNDERS' WARRANTS AND FREE SHARES**

##### **4.3.1 Share subscription warrants/founders' warrants**

The Company issued the following share subscription warrant and founders' warrant plans:

Type	Creation date	Exercise price	Subscription period	Total created	Subscriptions during the fiscal year							Total subscribed and/or exercised at 12/31/2020	
					2013 and before	2014	2015	2016	2017	2018	2019		
<b>Share subscription warrants and founders' share warrants</b>													
2012 share subscription warrants	11/29/13	€1	11/29/2013-02/28/2014	40,000	17,000	23,000						40,000	
Share subscription warrants 2014 1	06/02/14	€8	06/02/2014-06/30/2014	118,649	-	118,649						118,649	
Share subscription warrants 2014 2	07/01/14	€8	07/01/2014-07/16/2014	33,333	-	33,333						33,333	
2014 3 share subscription warrants	3/27/15	€8	03/27/2015-09/30/2016	120,000	-	-	100,000	10,000				110,000	
Share subscription warrants 2014 4	3/27/15	€8	Undetermined	125,000	-	-	36,744	88,256				125,000	
Share subscription warrants 2014 5	3/27/15	€8	04/01/2016-10/01/2016	25,000	-	-	-	25,000				25,000	
Share subscription warrants 2014 7	12/01/15	€8	12/01/2015-09/30/2016	50,000				39,000				39,000	
EFFIMUNE share subscription warrants 2010-2	10/29/10	€5.8	12/08/2011-12/07/2016	23,620	23,620							23,620	
EFFIMUNE share subscription warrants 2014-2	07/01/14	€7	07/01/2014-06/30/2019	30,700				30,700				30,700	
EFFIMUNE share subscription warrants 2014-1	11/25/14	€7	11/25/2014-11/24/2019	3,500				3,500				3,500	
Share subscription warrants 2015	3/27/15	€10.8	03/27/2015-05/30/2015	136,222	-	-	136,222					136,222	
Share subscription warrants 2017	7/18/17	€4.65	07/18/2017-07/17/2021	52,000				30,000	12,000			42,000	
Founders' share warrants 2018	6/13/18	€4.17	06/13/2018-06/13/2023	25,900					25,900			25,900	
Share subscription warrants 2018	6/13/18	€4.17	06/13/2018-06/13/2023	42,850								-	
Founders' share warrants 2019	6/26/19	€3.58	06/26/2019-06/26/2024	60,000					60,000			60,000	
Founders' share warrants 2020	6/17/20	€6.14	06/17/2020-06/17/2025	70,000						70,000		70,000	
<b>Total share subscription warrants and founders' share warrants</b>				<b>996,774</b>	<b>40,620</b>	<b>174,982</b>	<b>272,966</b>	<b>196,456</b>	<b>30,000</b>	<b>37,900</b>	<b>60,000</b>	<b>70,000</b>	<b>882,924</b>

The table below specifies the assumptions used for the valuation of the share subscription warrant and founders' warrant plans set up for previous years:

	2014 3 share subscription warrants	2014 5 share subscription warrants	2014 7 share subscription warrants	2015 share subscription warrants	2017 share subscription warrants	2018 share subscription warrants	2018 founders' share warrants	2019 founders' share warrants
Date of GM establishing plan	3/27/2015	3/27/2015	12/01/2015	3/27/2015	5/31/2016	6/14/2017	6/14/2017	6/13/2018
Number of authorized shares	120,000	25,000	50,000	136,222	52,000	42,850	25,900	60,000
Subscription price	€0.10	€0.10	€0.10	€1.08	€0.60	€0.70	€0.00	€0.00
Subscription date	3/27/2015	04/01/2016	12/01/2015	5/30/2015	7/18/2017	6/13/2018	6/13/2018	6/26/2019
Vesting of share subscription warrants	on subscription	on subscription	on subscription	on subscription	on subscription	on subscription	on subscription	on subscription
Exercise price	€8/share	€8/share	€8/share	€10.80/share	€4.65/share	€4.17/share	€4.17/share	€3.58/share
Option type	American	American	American	American	American	American	American	American
Spot rate	€10.12	€10.12	€8.56	€10.12	€4.05	€4.09	€4.09	€3.52
Maturity	5 years	5 years	3.5 years	5 years	4 years	5 years	5 years	5 years
Volatility	52.94%	54.70%	55.88%	51.26%	46.98%	47.08%	47.08%	44.67%
EUR interest rate	-0.0375%	0.3543%	-0.0318%	0.4690%	0.1494%	0.3812%	0.3812%	-0.2062%
Dividend yield	3/27/2015	0%	0%		0%	0%	0%	0%
Estimated fair value per share subscription warrant	on subscription	4.95	3.59	4.14	1.30	1.64	1.64	1.32
Number of options subscribed	110,000	25,000	39,000	136,222	42,000	0	25,900	60,000
Subscription price	0.10	€0.10	€0.10	€1.08	€0.60	€0.70	0.00	0.00
<i>Number of options exercised</i>	-	-	0	0	-	-	-	-
Contractual expiration date	6/30/2019	6/30/2019	6/30/2019	3/30/2020	7/17/2021	6/13/23	6/13/23	6/26/2024
Vesting period	none	none	none	none	none	none	none	none

During 2020, the Group introduced the plan described below:

The Board of Directors decided to issue a total of 70,000 (2020) founders' warrants, i.e., 10,000 founders' warrants for each non-salaried non-executive director in office on June 17, 2020.

2020 subscription share warrants	
Date of GM establishing plan	6/26/2020
Number of authorized shares	70,000
Subscription price	€0.00
Subscription date	6/17/2020
Vesting of share subscription warrants/founders' warrants	on subscription
Exercise price	€6.14/share
Option type	American
Spot rate	€6.16
Maturity	5 years
Volatility	50.05%
EUR interest rate	-0.3107%
Dividend yield	0%
Estimated fair value per share subscription warrant/founders' share warrant	2.59

Number of options subscribed	70,000
Subscription price	0.00
<b><i>Number of options exercised</i></b>	-
Contractual expiry date	6/17/2025
Vesting period	none

#### 4.3.2 - FREE SHARES

The Company issued the following free share plans:

Allocation date	Exercise period	Total allocated	Exercised during the fiscal year	Total non-exercised and expired
			2020	
<b>Free Share Allocation</b>				
3/12/2019	03/12/2019-03/11/2020	149,200	141,800	7,400
6/26/2019	06/26/2019-06/25/2020	150,000	150,000	-
6/26/2019	06/26/2019-06/25/2020	148,400	145,300	3,100
12/10/2019	12/10/2019-12/09/2020	22,625	22,625	-
06/17/2020	06/17/2020-06/17/2021	150,000	-	-
06/17/2020	06/17/2020-06/17/2021	100,000	-	-
12/08/2020	12/08/2020- 12/08/2021	11,363	-	-
12/18/2020	12/18/2020 – 12/18/21	244,500	-	-
<b>Total Free share allocation</b>		<b>976,088</b>	<b>459,725</b>	<b>10,500</b>

Allocation on March 12, 2019, the Board of Directors allocated free shares with the following characteristics:

Allocation to employees:

- Number of shares allocated (existing or to be issued): 149,200,
- Value of the share on the allocation date (according to the market price): €4.09,
- Vesting period and employment requirement: 1 year,
- Lock-up period: 1 year.

On June 26, 2019, the Board of Directors allocated free shares with the following characteristics:

Allocation to Alexis Peyroles:

- Number of shares allocated (existing or to be issued): 150,000,
- Value of the share on the allocation date (according to the market price): €3.52,
- Vesting period and employment requirement: 1 year,
- Lock-up period: 1 year.

Allocation to employees:

- Number of shares allocated (existing or to be issued): 148,400,
- Value of the share on the allocation date (according to the market price): €3.52,
- Vesting period and employment requirement: 1 year,

- Lock-up period: 1 year.

On December 10, 2019, the Board of Directors allocated free shares with the following characteristics:

Allocation to Alexis Peyroles:

- Number of shares allocated (existing or to be issued): 22,625,
- Value of the share on the allocation date (according to the market price): €3.59,
- Vesting period and employment requirement: 1 year,
- Lock-up period: 1 year.

On June 17, 2020, the Board of Directors allocated free shares with the following characteristics:

Allocation to Nicolas Poirier:

- Number of shares allocated (existing or to be issued): 100,000,
- Value of the share on the allocation date (according to the market price): €6.16,
- Vesting period and employment requirement: 1 year,
- Lock-up period: 1 year.

Allocation to Alexis Peyroles:

- Number of shares allocated (existing or to be issued): 150,000,
- Value of the share on the allocation date (according to the market price): €6.16,
- Vesting period and employment requirement: 1 year,
- Lock-up period: 1 year.

On December 8, 2020, the Board of Directors allocated free shares with the following characteristics:

Allocation to Alexis Peyroles:

- Number of shares allocated (existing or to be issued): 11,363,
- Value of the share on the allocation date (according to the market price): €7.24,
- Vesting period and employment requirement: 1 year,
- Lock-up period: 1 year.

On December 18, 2020, the Board of Directors allocated free shares with the following characteristics:

Allocation to employees:

- Number of shares allocated (existing or to be issued): 244,500,
- Value of the share on the allocation date (according to the market price): €7.4,
- Vesting period and employment requirement: 1 year,
- Lock-up period: 1 year.

#### **4.3.3 - CORPORATE OFFICERS, EMPLOYEES AND CONSULTANTS**

The expense recognized on December 31, 2020, for benefits paid in equity instruments to corporate officers, employees and consultants stood at €1,787,000, exclusively associated with the 2020 free share allocation plans and the 2020 founders' warrant plan.

The employer's contribution in relation to free shares stood at €496,000. Thus, expenses associated with share-based payments totaled €2,283,000.

All these benefits were granted to corporate officers, employees and consultants.

Share subscription warrants/founders' warrants measured at the fair value of the options determined using the Bjerksund & Stensland model.

Free share allocations were measured using a model that considers the probability of achieving related vesting conditions.

The valuation of the conditions of the plans was measured by an external service provider.

#### 4.4 COMPANY'S BUYBACK OF ITS OWN SHARES

The Combined General Shareholders' Meeting of June 16, 2020, authorized the Board of Directors to implement, on one or more occasions, a share buyback program in accordance with the provisions of Article L. 225-209 of the French Commercial Code and pursuant to the General Regulation of the French Financial Markets Authority (AMF), in the circumstances described below:

**Share buyback objective:**

- To boost liquidity in Company shares through the intermediary of an investment services provider acting independently under a liquidity contract in accordance with the AMAFI Ethics charter recognized by the French Financial Markets Authority;
- The allocation of shares to employees or corporate officers of the Company or of French companies or groups of companies related to it in accordance with legal requirements, particularly within the context of sharing in the fruits of the Company's expansion, employee share ownership plans or Company savings plans, stock options or the free allocation of shares or in any other circumstance permitted by regulations;
- The delivery of shares in payment, or exchange, in connection with acquisitions;
- Ensuring the coverage of debt securities giving access to equity;
- The cancellation of shares by reducing the share capital, particularly for the purposes of optimizing net earnings per share, subject to the adoption of the 33rd resolution below, intended to authorize the Board of Directors to reduce the share capital;
- The implementation of any market practice that would be permitted by the French Financial Markets Authority and, more generally speaking, the completion of any transaction that complies with current regulations.

**Maximum purchase price:** €21.60 per share, not including costs and commissions, capped at €10 million overall.

**Maximum number of shares that can be purchased:** 10% of the total number of shares making up the Company's share capital, on the date of the share buyback. When the shares are acquired with the aim of boosting trading and liquidity, the number of shares taken into consideration when calculating the 10% cap provided for above, corresponds to the number of shares purchased, less the number of shares resold during the authorization period.

Summary of shares bought and sold in 2020:

2020					
	<b>1st quarter</b>	<b>2nd quarter</b>	<b>3rd quarter</b>	<b>4th quarter</b>	<b>Total</b>
Securities purchased	29,564	37,779	71,787	74,026	213,156
Price (in euros)	3.62	5.96	6.33	7.57	6.32
<b>Total amount (in K€)</b>	<b>107</b>	<b>225</b>	<b>454</b>	<b>560</b>	<b>1,347</b>
Securities Sold	29,552	55,762	65,598	70,797	221,709
Price (in euros)	3.79	6.05	6.44	7.88	6.45
<b>Total amount (in K€)</b>	<b>112</b>	<b>337</b>	<b>423</b>	<b>558</b>	<b>1,430</b>

On December 31, 2020, the Company held 32,030 OSE Immunotherapeutics shares, acquired for a total of €249,000. Sales of treasury shares generated a gain on disposal of €183,000 in 2020. Management fees for these treasury shares amounted to €31,000 (€28,000 after deduction of deferred taxes).

These amounts have been restated in equity in accordance with IAS 32. Treasury shares in shareholders' equity therefore amounted to €93,000 at December 31, 2020.

**NOTE 5: FINANCIAL LIABILITIES**

Financial liabilities are presented in the table below which distinguishes between non-current and current liabilities:

In €k	12/31/2019	Increase	Decrease	Other transactions*	12/31/2020	Interest at 12/31/2020
BPI EFFIMAB advance	3,148	-	-	142	3,290	
BPI EFFICLIN Advance	6,044	-	-	258	6,302	
P2RI Loan	0	-	-		0	
BPI EFFIDEM Advance	19	-	-	(19)		
Loan guaranteed by the French State	-	6,960	-	-	6,960	
<b>Non-current financial liabilities</b>	<b>9,211</b>	<b>6,960</b>	<b>-</b>	<b>380</b>	<b>16,552</b>	
<hr/>						
Nantes Lot 1 Lease	332			(104)	228	
Nantes Lot 2 Lease	149			(35)	114	
Paris Suffren Lease 1	932			(139)	793	
Paris Suffren Lease 2	-	1,172		(157)	1,015	
Leasing Cytometre	-	209		(41)	168	
<b>Non-current lease liabilities</b>	<b>1,413</b>	<b>1,381</b>		<b>(476)</b>	<b>2,318</b>	
<hr/>						
BPI EFFIMAB Advance	92			(92)		(50)
BPI EFFICLIN Advance	95			(95)		(163)
P2RI Loan	321		(305)	(16)	0	9
BPI EFFIDEM Advance	39		(20)	19	38	0
Loan guaranteed by the French State		11			11	(11)
Bank overdrafts	3	1	(3)		1	
<b>Current financial liabilities</b>	<b>549</b>	<b>12</b>	<b>(327)</b>	<b>(184)</b>	<b>50</b>	<b>(214)</b>
<hr/>						
Nantes Lot 1 Lease	112		(99)	104	117	(8)
Nantes Lot 2 Lease	37		(32)	35	40	(3)
Paris Suffren 1 Lease	160		(122)	139	176	(20)
Paris Suffren 2 Lease		160	(135)	157	182	(25)
Leasing Cytometre		72	(36)	41	78	(3)
<b>Current lease liabilities</b>	<b>309</b>	<b>232</b>	<b>(423)</b>	<b>476</b>	<b>594</b>	<b>(59)</b>
<hr/>						
<b>Total financial liabilities</b>	<b>11,482</b>	<b>8,585</b>	<b>(751)</b>	<b>196</b>	<b>19,513</b>	<b>(273)</b>

\*This column includes the recurring and non-recurring breakdown as well as IFRS 9, IAS 20 and IFRS 16 restatements for the year.

The table below shows the schedule of financial liabilities:

In K€	Less than 1 year	December 2022	December 2023	December 2024	December 2025 and after	Total
BPI EFFIMAB advance					3,290	<b>3,290</b>
BPI EFFICLIN Advance				699	5,603	<b>6,302</b>
P2RI Loan	0					<b>0</b>
BPI EFFIDEM Advance	38					<b>38</b>
Guarenteed loan	11				6,960	<b>6,971</b>
<b>Financial liabilities</b>	<b>50</b>	<b>0</b>	<b>0</b>	<b>699</b>	<b>15,852</b>	<b>16,601</b>
Nantes Lot 1 Lease	117	104	103	21	0	<b>345</b>
Nantes Lot 2 Lease	40	35	35	35	8	<b>154</b>
Paris Suffren Lot 1 Lease	176	137	134	132	390	<b>969</b>
Paris Suffren Lot 2 Lease	182	154	151	148	563	<b>1,198</b>
Leasing Cytomètre	78	69	68	30		<b>246</b>
<b>Lease liabilities</b>	<b>594</b>	<b>499</b>	<b>491</b>	<b>366</b>	<b>961</b>	<b>2,912</b>
<b>Total financial liabilities</b>	<b>644</b>	<b>499</b>	<b>491</b>	<b>1,065</b>	<b>16,814</b>	<b>19,513</b>

Lease liabilities (see Note 1.3)

**A P2RI (regional industrial redeployment) loan of €1,500,000 and derivative instruments transferred at the time of the merger.**

In September 2013, the Company received loans from BNP Paribas, CIC, Crédit Mutuel and from Région des Pays de la Loire, each for €375,000, i.e. a total loan of €1.5 million. The purpose of this loan is to finance development and innovative projects.

This loan was recognized at amortized cost, calculated using the effective interest rate.

The loan from the banking pool amounts to €1,125 million. It has a term of seven years, including a three-year grace period for capital repayment. The interest rate is equal to the three-month Euribor rate plus a fixed margin of 300 basis points. This loan has been repaid quarterly since October 5, 2016. Interest is payable quarterly.

This loan was fully repaid as of December 31, 2020.

The Company received the full amount of the loan from Région des Pays de la Loire, amounting to €375,000, in December 2013. The term of the loan is seven years, including a three-year grace period for repayment. The annual percentage rate stands at 4.06% payable annually.

This loan was fully repaid as of December 31, 2020.

#### **Bpifrance repayable advance of €100,000**

In September 2014, the Group also obtained an interest-free repayable advance from Bpifrance for a maximum of €100,000, as part of the OSE 172 (Formerly EFFE-DEM) project: Feasibility of immunomodulatory monoclonal antibodies in the treatment of cancer.

Bpifrance payments were staggered between the signing of the contract and the end of the project, i.e.:

- An initial payment of €80,000 once the contract was signed (received on December 23, 2014).
- A second payment of €20,000 received on December 2, 2015, settling the balance of payments to be received from this advance.

As a result of the success of this project, repayment of this support will commence as follows:

€20,000 on September 30, 2018,

€40,000 on September 30, 2019,

€40,000 on September 30, 2020, which was subject to a six-month repayment delay in the context of the COVID-19 pandemic.

The fair value of this advance was determined on the basis of a market interest rate. The difference between the advance amount at historical cost and that of the advance discounted at market rate is recognized less R&D expenses, as costs are incurred for the relevant research programs.

At December 31, 2020, the remaining balance stood at €40,000.

#### **Bpifrance repayable advance for EFFIMab project of €2,328,000 and €820,000**

On June 19, 2017, the Company received from Bpifrance the first payment of €2,328,000 as part of a repayable advance for the EFFIMab project.

This interest-bearing advance (interest rate of 1.66% under the contract) was initially for an amount up to €3,609,000 paid on achievement of three key milestones within a completion period of 72 months.

If all milestones are achieved, a notional repayment in annual installments was to be put in place from June 30, 2021, based on a notional amount of €3,609,000 at the applicable contractual discount rate of 1.66%, i.e., a fixed amount of €4,100,000, including interest of €490,595. Repayments, amounting to €4,100,000, were spread between June 30, 2021, and June 30, 2025.

Following the signature of Amendment no. 2 on December 28, 2018, this interest-bearing advance now stands at an amount of up to €3,991,000 to be paid on achievement of four key milestones within a completion period of 115 months.

If all milestones are achieved, the notional repayment in annual installments from December 31, 2024, based on a receivable notional amount of €3,991,000, now stands at a fixed amount of €4,590,000.

Repayments will be spread between December 31, 2024, and December 31, 2028.

The Company received a portion of the advance on achievement of the third key milestone, i.e., €2,328,000 in accordance with the amendment to the initial contract.

The Company received the second payment of the repayable advance, i.e., €820,000, on achievement of the fourth key milestone on April 10, 2019.

Following the signature of Amendment no. 3 in October 2020, this interest-bearing advance now stands at an amount of up to €5,264,000 to be paid on achievement of four key milestones within a completion period of 122 months.

If all milestones are achieved, the theoretical repayment is now a fixed amount of €6,198,000, which will be paid in annual installments from September 30, 2025, and which has been calculated on the basis of the theoretical €5,264,000 receivable.

Repayments will be spread between September 30, 2025, and September 30, 2030.

#### **Bpifrance repayable advance of €1,236,000 and €4,808,000**

On December 18, 2017, the Company received from Bpifrance a first payment of €1,236,000 as part of a repayable advance for the EFFI-CLIN project. This interest-bearing advance (discount rate of 0.90% according to the agreement) is for up to €8,106,000 paid on achievement of four key milestones within a completion period of 60 months.

If all milestones are achieved, a notional repayment in annual installments from June 30, 2024, based on the notional amount of €8,106,000 at the applicable contractual discount rate of 0.90%, will be a fixed amount of €9,850,000, including interest of €1,744,000.

Repayments, amounting to €9.85 million, will be spread between June 30, 2024, and March 31, 2028.

The Company received a portion of the advance, i.e., €1,236,000 at the start of the study.

On September 18, 2019, the Company received the second payment of the repayable advance, i.e., €4,808,000 on achievement of the first key milestone.

If the Company's program is successful, the first payment will be repaid between June 30, 2024, and March 31, 2028.

#### **French Government-guaranteed loan**

To address the financial consequences of the COVID-19 pandemic, on May 5, 2020, a French Government-guaranteed loan of €6,960,000 was granted, split between three banks (CIC, CM and BNP).

These loans meet the conditions of the Rectifying Finance Law for 2020, n°2020-289, of March 23, 2020, and the specifications defined in the decree dated March 23, 2020, providing the French Government guarantee to credit and financial institutions under that law.

This funding is one-year cash loan immediately made available to the borrower for the full amount on the date that the funds are transferred into their current account. Capital will be repaid and interest and ancillary costs paid in a single installment on the annual repayment date, with the option for the borrower to apply to spread the outstanding amount due on the repayment date over a further four years. Management has already decided to exercise the option and repay this loan at the end of 5 years. This loan is therefore presented as non-current in the consolidated financial statements. This is a French Government-guaranteed loan under article 6 of the aforementioned law. This French Government-Guaranteed loan constitutes a form of public aid and has been recognized at fair value on the date it was obtained and at amortized cost with an overall effective rate of 0.25% (corresponding to the guarantee commission and in the context of the extension of the loan after the 1st year, the interest rate will be determined by amendment). The fair value of the loan has been assumed to be equal to the amount of cash received net of transaction costs.

The funds received and conditions are as follows:

- Crédit Mutuel = €2,300,000 received May 6, 2020, repayable on May 6, 2025.
- BNP = €2,300,000 received on May 6, 2020, repayable on May 6, 2025.
- CIC = €2,360,000 received on May 18, 2020, repayable on May 18, 2025.

#### **NOTE 6: CURRENT DEBTS**

##### **6.1. TRADE PAYABLES**

In €K	12/31/2020	12/31/2019
Trade payables	7,389	4,284
Accrued invoices	2,897	2,634
<b>Total trade payables</b>	<b>10,286</b>	<b>6,918</b>

This item increased compared to the end of 2019 mainly due to the increase in subcontracting expenses related to OSE127, OSE172 and OSE279 research.

##### **6.2. TAX AND SOCIAL SECURITY LIABILITIES**

In €K	12/31/2020	12/31/2019
Staff costs	990	773
Social security and other social organizations	963	852
Other taxes, duties and similar payments	155	99
Current tax liability	2	20
<i>Other payables</i>	<b>2,108</b>	<b>1,723</b>
<b>Tax and social security liabilities</b>	<b>2,110</b>	<b>1,743</b>

The increase in tax and social security liabilities was in line with the increased workforce.

### 6.3. OTHER CURRENT LIABILITIES

In €K	12/31/2020	12/31/2019
Deferred income	1,087	4,811
Miscellaneous	1	2
<b>Total other debts and accruals</b>	<b>1,088</b>	<b>4,812</b>

The €3.72 million decrease in deferred income was mainly due to:

- Revenue of €3.4 million relating to the amount received in 2019 following the exercise of Servier's option under the OSE-127 license agreement was recognized at December 31, 2020.
- Revenue of €189,000 relating to the amount received in 2019 of €15 million as part of the collaboration and license agreement signed with Boehringer Ingelheim (OSE 172) was recognized at December 31, 2020. As of December 31, 2020, deferred income remains at €383,000, corresponding to the estimated costs still to be incurred by the Group in 2021.

### NOTE 7: CURRENT AND NON-CURRENT PROVISIONS

Provisions break down as follows:

In €K	12/31/2010	Increase	Decrease	12/31/2020
Provision for pension commitments (1)	377	155		531
	<b>377</b>	<b>155</b>	<b>-</b>	<b>531</b>

of which the effect of actuarial gains and losses of €3,400.

#### Provision for pension commitments

The provision for pension commitments was measured in accordance with the applicable collective agreement, i.e. the pharmaceutical industry collective agreement. The assumptions made were as follows:

- Mortality table: regulatory table TH (men)/TF (women) 00-02,
- Estimated retirement age: 65,
- Ratio of wage increases: 2%,
- Staff turnover: low turnover,
- Discount rate: 0.74%,
- Social security contribution rates: between 37% and 45% depending on the category.

On December 31, 2020, the average monthly headcount stood at 43, compared with 35 on December 31, 2019.

### NOTE 8: OPERATING INCOME

#### 8.1. Revenue FROM COLLABORATION AGREEMENTS

As of December 31, 2020, the breakdown of operating income is as follows:

	2020	2019

	<b>Revenue</b>	<b>Deffered income</b>	<b>Revenue</b>	<b>Deffered income</b>
<b>BI Agreement</b>				
Disposal of IP			12,456	
Re-invoicing of direct cost	3,690	1,079	5,448	1,336
<b>Servier agreement</b>				
Milestone	3,355		6,645	3,355
Reagent sales	2,872		626	
<b>Rafa agreement</b>				
Distribution license			77	
<b>CKD agreement</b>				
Distribution license	500		700	
<b>Total</b>	<b>10,418</b>	<b>1,079</b>	<b>25,952</b>	<b>4,692</b>

Revenue stood at €10,418,000 and comprised:

- €3,502,000 for re-invoicing of expenses as provided in the agreement signed with Boehringer Ingelheim (BI) and €189,000 of co-development fees related to the staggering of milestone payments received and deferred to include development services to be provided by OSE.
- €3,355,000 corresponding to the recognition in revenue of a portion of the amount of the option received in 2019 following the signature of the amendment signed with Servier in March 2020 and €2,872,000 related to the sale of bottles of OSE-127 including the rebilling of a part of intellectual property costs.
- €500,000 for meeting the first milestone in the contract with CKD signed in 2019.

For deferred income, see Note 6.1. Other current debts.

## 8.2. R&D EXPENSES

<b>R&amp;D expenses in €K</b>	<b>31/12/2020</b>	<b>31/12/2019</b>
Subcontractor	20,268	18,909
Fees	1,795	1,559
Small equipement	831	491
Advertising and press relation	188	110
Payroll expenses	4,554	3,830
Depreciation and provisions	245	156
Taxes	49	33
Others	159	159
<b>R&amp;D expenses</b>	<b>28,089</b>	<b>25,247</b>
CIR	- 5,120	- 3,059
Subsidy income	- 613	- 533
<b>Total R&amp;D expenses adjusted</b>	<b>22,355</b>	<b>21,655</b>

Subcontracting expenses increased compared to 2019. They mainly comprise costs for Tedopi® Phase 3, OSE-127's CMC and OSE-172 Phase 1.

The increase in fees is directly correlated with an increase in consultancy costs linked to the number and complexity of research and development projects. Intellectual property fees have also increased in line with the changing patent portfolio.

The increase in employee benefits expense is mainly due to the increase in the number of employees.

The increase in provisions is mainly due to the new Cytometer lease restated in accordance with IFRS 16 (see note 1.3).

After deduction of the research tax credit, the total amount of R&D expenses increased by €738,000, in particular due to the increase in headcount.

### 8.3. OVERHEAD EXPENSES

Overhead expenses in €K	31/12/2020	31/12/2021
Fees	1,827	1,353
Small equipment	31	30
Advertising and press relation	64	31
Payroll expenses	1,800	1,571
Depreciation and provisions	484	326
Taxes	82	43
Board fees	222	151
Others	275	393
<b>Total overhead expenses</b>	<b>4,783</b>	<b>3,898</b>

The fees consist of various expenses (legal, accounting, financial communication, listing, etc.) increased compared to 2019. This increase is due to significant efforts by the company in communications with investors/shareholders.

The increase in the provisions item is mainly due to the new Suffren Lot 2 lease restated in accordance with IFRS 16 (see note 1.3).

The increase in employee benefits expense is mainly due to the increase in the number of employees.

The sharp decline in travel, receptions and seminars is mainly due to the reduction in travel in the context of COVID-19.

### 8.4 EXPENSES RELATED TO SHARE-BASED PAYMENTS

The benefits associated with the allocation of financial instruments in 2020 break down as follows:

In €K	12/31/2020	12/31/2019
Expenses related to share-based payments	2,283	1,868

Expenses of €2,283,000 included €1,787,000 in expenses relating to corporate officers, employees or consultants (see Note 4.3) and €496,000 in employer's contribution to free shares.

### 8.5. EMPLOYEE BENEFITS EXPENSE

R&D expenses of €4,554,000 and overheads of €1,800,000 recognized as employee benefits expense break down as follows:

In €K	12/31/2020	12/31/2019
Salary and wage benefits	6,202	5,148
Directors' fees	222	151

Pension commitments	151	253
	<b>6,575</b>	<b>5,552</b>
Expenses related to employee share-based payments	2,102	1,789
	<b>2,102</b>	<b>1,789</b>

On December 31, 2020, the average monthly headcount stood at 43, compared with 35 on December 31, 2019.

#### NOTE 9: NET FINANCIAL INCOME

In K€	31/12/2020	31/12/2019
Foreign exchange gain	18	67
Revenue on cash equivalents	12	70
Other financial income	0	2
Change in fair value of marketable securities	0	82
<b>Total financial income</b>	<b>31</b>	<b>221</b>
Foreign exchange loss	14	22
Interest expense	214	148
Research Tax Credit prefinancing interest		
Interest on lease liabilities	59	33
Provision for impairment of marketable securities	-	11
<b>Total financial expenses</b>	<b>288</b>	<b>213</b>
<b>Total Financial income</b>	<b>(257)</b>	<b>8</b>

The decrease in net financial income was mainly due to:

An increase in interest expenses to €214,000, mainly due to interest on the EFFIMAB and EFFICLIN repayable advances.

An increase in lease liabilities to €59,000, mainly as a result signing 2 new leases.

#### NOTE 10: CORPORATE TAX

##### 10.1. DEFERRED TAX ASSETS

The Company recognized a deferred tax asset for OPI (Swiss subsidiary) valued at €1.18 million calculated on the basis of a 13.99% tax rate (Swiss rates under ordinary law applied since January 1, 2020).

At December 31, 2020, deferred tax assets stood at €165,000.

##### 10.2. NET DEFERRED TAX LIABILITIES

Given its level of development, the Company only recognizes deferred tax assets in the amount of its tax liabilities recognized as deferred tax liabilities, payment of which may be avoided by the Company, even in the absence of any profit forecast. As of December 31, 2020, the amount of tax loss carryforwards amounts to €57.49 million.

In 2016, the Company recognized a deferred tax liability for the FR104 and OSE-127 molecules, valued at €52.6 million. Consequently, the Company recognized its deferred tax assets at the level of its deferred tax liabilities. As at December 31, 2018, the net deferred tax liability amounted to €2,010,000.

Since January 1, 2019, under the 2019 finance act modifying the tax regime for income from the sale or licensing of patents, the Company applied a deferred tax rate of 10% when calculating deferred tax liabilities and assets generated in France.

As of December 31, 2019, pending administrative clarifications, the tax loss carryforwards were not considered to be chargeable to the profits eligible for the preferential regime.

Given these factors, an impairment of €3,370,000 was applied to these deferred tax assets.

In light of the administrative clarifications of April 22, 2020, profits eligible for the preferential regime may be offset against tax loss carryforwards as of 12/31/2019. As a result, deferred tax assets on tax loss carryforwards were recognized in the amount of deferred tax liabilities within the limits of the restrictions imposed by the tax authorities. Deferred tax assets on tax loss carryforwards not recognized at the reporting date amounted to €2,738,000.

As a result, as of December 31, 2020, the net deferred tax liability amounted to €2,080,000.

### **10.3. INCOME TAX EXPENSE**

At December 31, 2020, the Group generated income (net of tax) of €2,692,000, which breaks down as follows:

Net deferred tax income for €2,744,000 (of which €123,000 recognized in equity) mainly corresponding to:

A decrease in deferred tax liabilities of €2,986,000 between December 31, 2019, and December 31, 2020 (including €632,000 relating to deferred tax assets on tax loss carryforwards at December 31, 2020).

A decrease in deferred tax assets of €118,000 between December 31, 2019, and December 31, 2020, related to the OPI patents following a change in the tax rate under Swiss common law from January 1, 2020 (from 24.16% to 13.99%).

Tax expense payable of €52,000 (including €50,000 in withholding tax).

The tax proof breaks down as follows:

Consolidated result (IFRS)	31/12/2020
Net income before tax	(19,247)
Tax rate	10%
Theoretical tax	1,925
Permanet differences	428
Swiss tax rate	(118)
Other tax or tax credit	(52)
Deffered tax on recognized deficit	(3,370)
Deffered tax on non-recognized deficit	(2,738)
Other	(122)
Income tax	2,692
Income tax accounted	(2,692)
<i>Net effective tax rate</i>	<i>13,99%</i>

### **NOTE 11: COMMITMENTS**

#### **11.1. RESEARCH-RELATED OBLIGATIONS**

On January 25, 2018, the Company signed a contract with ACCELOVANCE, and committed to a budget re-estimated during 2018 of €10.1 million.

To continue the trial, this budget was re-estimated at a maximum of €13.5 million.

#### **11.2. Commitments RECEIVED UNDER LICENSING AND DISTRIBUTION CONTRACTS WHERE APPLICABLE**

Under licensing and distribution agreements, BOEHRINGER INGELHEIM, SERVIER, RAFA and CKD, agreed to pay the Company:  
 One-off payments when certain development milestones and revenue are reached;  
 Royalties on product sales.

#### **11.3. COMMITMENTS IN VIEW OF SUBLICENSING CONTRACTS WITH SELEXIS**

Under commercial licensing agreements with Selexis, OSE Immunotherapeutics agreed to pay Selexis:  
 Fixed payments based on the completion of certain milestones, as compensation for the license granted by Selexis;  
 Royalties or milestones (optional depending on the level of sales) when products are marketed.

#### **11.4. COMMITMENTS IN VIEW OF SUBLICENSING CONTRACTS WITH INSERM**

Two operating agreements were signed with the Nantes Institute of Health and Medical Research (Inserm):

- In October 2011 for the MD707 project, including filing a co-ownership patent; and
- In March 2013 for the FR104 project, including filing a co-ownership patent.

These agreements grant worldwide operating rights on the patent licenses for each of the projects. For FR104, if OSE Immunotherapeutics signs an agreement with a sub-licensee, the agreement provides for the payment of royalties calculated on the revenues from sublicensing agreements.

#### **11.5. Other off-STATEMENT OF FINANCIAL POSITION COMMITMENTS**

As part of the initial transaction for the acquisition of Memopi® (including Tedopi®) assets from the pharmaceutical company Takeda, the Company agreed to pay an earn-out when its product was registered, then no more than single-digit royalties on future sales.

##### *Collateral pledged*

Interest-bearing bank account pledged to Crédit Mutuel as collateral, amounting to €10,000

Interest-bearing bank account pledged to CIC as collateral, amounting to €146,000

Interest-bearing bank account pledged to CIC as collateral, amounting to €161,000

##### *Guarantees given*

€18,000 lease payment guarantee to CIC

##### *Guarantees received*

The Company received a guarantee from Bpifrance covering 70% of the original amount of its loans from BNP, Crédit Mutuel and CIC, for €375,000 each. The outstanding principal at June 30, 2020, amounted to €70,000.

The Company does not have any other off-statement of financial position commitments.

#### **NOTE 12: EARNINGS PER SHARE**

Earnings per share are calculated by dividing consolidated net income by the weighted average number of shares outstanding in the fiscal year.

1. Result per share	31/12/2020	31/12/2019
2.		
3. Basic earnings in K€		
4.		
5. Net Result in K€	(16 555)	(4 652)
6.		
7. Weighted average number of shares outstanding	15 556 046	14 892 496
8.		
9. Basic earnings per share (€/share)	(1.06)	(0.31)

10.		
11. Diluted earnings		
12.		
<b>13. Net Result in K€</b>	<b>(16,555)</b>	<b>(4,652)</b>
14.		
15. Weighted average number of shares outstanding	15 556 046	14 892 496
16.		
17. Adjustment for dilutive effect of share subscription warrants, founders' share warrants and free share allocation	949,845	854,207
18.		
<b>19. Diluted earnings per share (€/share)</b>	<b>(1,06)</b>	<b>(0,31)</b>

The weighted average number of shares at December 31, 2020, takes capital increases occurring during the fiscal year into consideration.

The allocations of share warrants, founders' warrants and free shares have no dilutive effect on earnings per share.

#### **NOTE 13: FINANCIAL RISK MANAGEMENT**

The Group's main financial instruments are in cash. These instruments are managed for the purpose of funding the Company's activities. The Group's policy is not to subscribe for financial instruments for speculative purposes. The Group does not use any financial derivatives.

The main risks to which the Company is exposed are liquidity risk, foreign exchange risk and interest rate and credit risk.

##### **13.1. LIQUIDITY RISK**

The Company carried out a specific review of its liquidity risk; it considered that its available cash at the date [of the Universal Registration Document] as well as future cash flows will enable it to finance its clinical trials.

##### **13.2. FOREIGN EXCHANGE RISK**

The Company's exposure to foreign exchange risk is solely due to trading relations with customers and suppliers outside the euro area (currencies in USD, GBP).

At this stage of its development, the Company has not made any hedging arrangements to protect its business against foreign exchange rate fluctuations. The Company cannot, however, discount the fact that a significant increase in its business would increase its exposure to foreign exchange risk.

The Company then envisages implementing a suitable policy to hedge such risks.

##### **13.3. CREDIT RISK**

Credit risk is from cash and deposits with banks and financial institutions, as well as exposures to client credit, particularly outstanding receivables and agreed transactions.

Credit risk associated with cash and current financial instruments was immaterial considering the quality of the co-contracting financial institutions.

##### **13.4. INTEREST RATE RISK**

The Company's exposure to interest rate risk mainly concerns the variable-rate P2RI loan which is hedged by a fixed-rate CAP. The CAP ended in April 2019.

#### NOTE 14: RELATED PARTIES

##### 14.1. COMPENSATION OF MANAGEMENT AND MEMBERS OF THE BOARD OF DIRECTORS

No post-employment benefits were granted to members of the Board of Directors.

Compensation paid to management and members of the Board of Directors breaks down as follows:

In K€	31/12/2020	31/12/2019
Salaries and other short-term advantages*	1,170	809
Directors' fees	222	142
Share base payment**	1,350	689
Fees	11	11
<b>Total</b>	<b>2,753</b>	<b>1,651</b>

\* Excluding social charges

\*\* Relating to the allocation of free shares and share subscription and founders' warrants

Methods used to measure the benefit of share-based payments are shown in Note 4.3.

#### NOTE 15: EVENTS AFTER THE REPORTING PERIOD

- Release of €1.3 million after reaching milestone 5 of the EFFIMab program
- Following the completion of Phase 1 trials of OSE-127 and the achievement of BPI France's requirements, the Company received a repayable advance of €1.3 million in January 2021.
- Signature of a loan agreement with the EIB for €25m

In February 2021, the Company signed a loan agreement with the EIB for €25 million, which will be available in three tranches according to the criteria defined in the contract. The first tranche of €10 million not subject to conditions should be paid in May.

This loan will carry a fixed interest rate of 5% per annum and paid annually over a five-year maturity (each drawdown is treated separately in terms of maturity). The repayment of each tranche will therefore be made at the end of a period of five years after the date of disbursement of said tranche.

The loan agreement also contains an agreement to issue share subscription warrants to EIB for the first two tranches of the financing, in particular the issue of 850,000 share subscription warrants with respect to the drawdown of the first tranche. An additional 550,000 share subscription warrants could be issued if OSE Immunotherapeutics draws down the second tranche of €10 million.

## 18.2 Interim financial information

The reader is referred to the half-year financial report (RFS) including the financial statements as of June 30, 2020, published on September 17, 2020, and incorporated by reference into this Universal Registration Document.

## 18.3 Auditing of historical annual financial information

### 18.3.1 Auditing of historical annual financial information

The financial information in this document has been the subject of an independent audit carried out by the statutory auditors, in accordance with Directive 2014/56/EU of the European Parliament and of the Council and Regulation (EU) No 537/2014 of European Parliament and the Council.

### **18.3.2 Other information audited by statutory auditors**

None

### **18.3.3 Other information non-audited by statutory auditors**

None

## **18.4 Pro forma financial information**

None

## **18.5 Dividend policy**

### **18.5.1 Dividend payment policy**

Given the development stage of the Company, there are no plans to initiate a short-term dividend payment policy.

### **18.5.2 Dividends paid in the last three fiscal years**

N/A.

## **18.6 Legal and arbitration proceedings**

On the registration date of this Universal Registration Document, there were no governmental, legal or arbitration proceedings, including those of which the Company is aware, which are pending or threatened, that may have, or have had in the last 12 months, materially impacted the Company's financial position, business or results and/or its subsidiaries.

## **18.7 Significant change in financial position**

There has been no material change in the Group's financial position since the publication of the audited financial statements for the fiscal year ended on December 31, 2020.

## 19 Additional information

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### 19.1 Stated capital

#### 19.1.1 Issued capital

As of the date of this Universal Registration Document, the share capital stood at €3,596,607.60.

It was divided into 17,983,038 shares with a nominal value of €0.20 each.

As of January 1, 2020, there were 15,005,724 Company shares outstanding.

Please also refer to Chapter 18 of this Universal Registration Document

#### 19.1.2 Non-equity shares

There were no non-equity shares.

Please refer to Section 15.2.

#### 19.1.3 Treasury shares

On December 31, 2020, the Company owned 32,030 OSE Immunotherapeutics shares, whose market value was €249,000 . Sales of treasury shares generated a net loss on disposal of €183,000 in 2020.

The Company announced on January 26, 2021 that it was increasing the cash balance of its liquidity contract by an additional contribution of €150,000.

#### 19.1.4 Potential capital

As of the date of this Universal Registration Document, the Company had:

- Issued **65,000 founders' warrants**:

-25,000 could be subscribed from October 1, 2019 – if all these founders' warrants were exercised, this would give entitlement to **25,000** new shares.

If all these founders' warrants were exercised, this would give entitlement to **25,000** new shares.

- Issued and allocated 52,000 **2017 share subscription warrants** – if all these share subscription warrants were exercised, this would give entitlement to **42,000** new shares, given the lapse of 10,000 2017 share subscription warrants.

- Issued and allocated 42,850 **2018 share subscription warrants** to Gérard Tobelem (to replace the 25,000 2016 share subscription warrants) – if all these share subscription warrants were exercised, this would give entitlement to **42,850** new shares;

- Issued and allocated 25,900 **2018 share subscription warrants** to Dominique Costantini (to replace the 12,162 2016 founders' warrants) – if all these founders' warrants were exercised, this would give entitlement to **25,900** new shares;

- Issued and allocated 60,000 **2019 founders' warrants** to each of the non-salaried, non-executive directors in post at June 26, 2019 – if all these founders' warrants were exercised, this would give entitlement to **60,000** new shares;

- Issued and allocated 70,000 **2020 founders' warrants** to each of the non-salaried, non-executive directors in post at June 17, 2020 – if all these founders' warrants were exercised, this would give entitlement to **70,000** new shares;
- Issued and allocated 150,000 free shares to Alexis Peyroles – if all these free shares vested, they would give entitlement to **150,000** new shares.
- Issued and allocated 100,000 free shares to Nicolas Poirier – if all these free shares vested, they would give entitlement to **100,000** new shares.
- Issued and allocated 250,000 free shares to management and non-corporate officer employees of OSE Immunotherapeutics – if all these free shares vested, they would give entitlement to **244,500** new shares; given that 5,500 free shares were not allocated;
- Issued and allocated 11,363 free shares to Alexis Peyroles – if all these free shares vested, they would give entitlement to **11,363** new shares.

Details of the various dilutive instruments outstanding are given in paragraph 15.2.1.1 of this Universal Registration Document.

	<b>Number of shares created</b>	<b>Percentage interest</b>	<b>Dilution</b>
<b>Existing securities</b>	17,983,038	1.00%	-
If only the 2015 founders' warrants are exercised	25,000	1.00%	0.14%
If only the 2017 share subscription warrants are exercised	42,000	1.00%	0.23%
If only the 2018 share subscription warrants are exercised	42,850	1.00%	0.24%
If only the 2018 founders' warrants are exercised	25,900	1.00%	0.14%
If only the 2019 founders' warrants are exercised	60,000	1.00%	0.33%
If only the 2020 founders' warrants are exercised	70,000	1.00%	0.39%
If only 150,000 free shares actually vest (end of the vesting period)*	150,000	0.99%	0.83%
If only 100,000 free shares actually vest (end of the vesting period)*	100,000	0.99%	0.55%
If only 250,000 free shares actually vest (end of the vesting period)*	244,500	0.99%	1.34%
If only 11,363 free shares actually vest (end of the vesting period)*	11,363	1.00%	0.06%
If all dilutive instruments are exercised	<b>18,754,651</b>	0.96%	4.11%

On the date of this Universal Registration Document, the total number of shares likely to be created by the exercise, and as the case may be, the vesting of instruments allocated and outstanding, giving access to the Company's equity, stood at 771,613 new shares, thus generating a dilution of 4.11% based on existing share capital to date.

In addition, the Company could, in the future, allocate or issue new instruments giving access to equity.

The Company was also authorized by the General Shareholders' Meeting on June 17, 2020, to carry out capital increases by private placement of up to 20% of the capital. In this respect, the Company carried out a capital increase with cancellation of preferential subscription rights through a private placement with 25 qualified French and international investors, a large majority of which were new shareholders, and by the accelerated construction of an order book, for €18.6 million. Thanks to this fundraising, the Company strengthened its financial visibility until the first quarter of 2022. The total amount of this capital increase corresponded to the issuance of 2,517,589 new ordinary shares at a subscription price of €7.40 per new common share (issue premium included), i.e. a dilution rate of 16.3% of the share capital before the transaction on an undiluted basis and 14.0% after the transaction.

The exercise of instruments giving access to outstanding capital, any new allocation or issue of such instruments, or any capital increase by private investment, in particular, by the Board of Directors using the authorizations referred to below, would result in a significant dilution for shareholders.

The table below shows the different financial authorizations in progress which were granted by the Company's General Shareholders' Meetings on June 13, 2018, June 26, 2019, and June 16, 2020:

Purpose of the resolution	Resolution	Duration and expiry of the authorization	Methods	Setting the price of the shares issued	Maximum nominal amount in euros	Use
Capital increase, through the issue – with preferential subscription rights – of shares and/or transferable securities giving access to the Company's equity and/or the issue of transferable securities giving entitlement to the allocation of debt securities	16th	26 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	The price of one share issued will be at least equal to the nominal value of the share on the issue date	1,500,000*	
Capital increase through the issue – without preferential subscription rights – of shares and/or transferable securities giving access to the Company's equity and/or the issue of transferable securities giving entitlement to the allocation of debt securities through an offering, as referred to in Article L. 411-2 II of the French Financial and Monetary Code, in particular, to qualified investors or a restricted circle of investors	17th	26 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	The price of one share will be at least equal to the average price weighted by volume based on the last three (3) trading sessions prior to the issue price being set, which may be reduced by a maximum discount of five (5)%	1,500,000*	
Capital increase, through the issue of shares and/or debt securities and/or transferable securities giving access to equity or giving entitlement to a debt security, without preferential subscription rights, with no indication of beneficiaries and by public offering	18th	26 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	The price of one share will be at least equal to the average price weighted by volume based on the last three (3) trading sessions prior to the issue price being set, which may be reduced by a maximum discount of five (5)%	10% of the capital 1,500,000*	
Capital increase through the issue of common shares and/or any other transferable securities giving access to equity and/or giving entitlement to the allocation of debt securities – without preferential subscription rights – to	19th	18 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	The common share issue price will be at least equal to the average weighted price based on the last three trading sessions prior to the issue price being set, which may be reduced by a	1,500,000*	

categories of persons with specific characteristics				maximum discount of 20% or increased by a surcharge at the full discretion of the Board of Directors depending on the category of person		
ISSUE of financial instruments comprising and/or giving entitlement to (upon exercise of subscription warrants) debt securities giving access to Company equity, to which equity warrants are attached – without preferential subscription rights – to a single category of person in accordance with Article L. 225-138 of the French Commercial Code	20th	18 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	The issue price of financial instruments comprising debt securities giving access to Company equity, to which share subscription warrants are attached, will be determined on the basis of their nominal value, which may be reduced by a discount of no more than 10%.  The issue price of the common shares, resulting from the exercise of rights attached to these debt securities or share subscription warrants, will be at least equal to the lowest daily price, weighted by volume, based on the last ten trading sessions prior to the issue price being set, which may be reduced by a discount of no more than 10%	1,500,000*	
Increase in the number of securities to be issued in the event of a capital increase, with or without preferential subscription rights for shareholders, in the event of over-subscription, of up to 15% of the initial issue	22nd	26 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	Same price as that used for the initial issue and within thirty days of closure of the subscription period	*	
Capital increase through the incorporation of premiums, reserves, profits or other items	23rd	26 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	N/A	1,500,000	
ISSUE of common shares and/or transferable securities giving access to Company equity, as payment in kind comprising equity securities or transferable securities giving access to equity	24th	26 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	None	*	
ISSUANCE of common shares and/or transferable securities giving access to Company equity, in the event of a public exchange offering initiated by the Company	25th	14 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	None	1,500,000*	
Allocation of free performance shares to be issued to the Group's salaried members of staff and corporate officers, or some of them, without preferential subscription rights	28th	38 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	N/A		
Allocation of existing or future free shares to the Group's salaried members of staff and corporate officers, or to some of them	29th	38 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	N/A		

ISSUE of founders' warrants under the terms provided for in Article 163 bis G of the French General Tax Code without preferential subscription rights for shareholders, to a single category of person	30th	18 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	The price of a share will be at least equal to the average closing price based on the last twenty (20) trading sessions prior to the allocation date without, if the capital increase was carried out through the issue of securities giving entitlement to equivalent rights within the last six months prior to allocation, the price being lower than the issue price of said securities	Overall cap of 500.0000 securities	
ISSUE of equity warrants to a single category of person**	31st	18 months from the General Shareholders' Meeting of June 16, 2020	Delegation of power to the Board of Directors	The issue price of a share subscription warrant will be set by the Board of Directors on the basis of a valuation report prepared by an independent expert in accordance with the requirements of Article 262-1 of the AMF general regulation  The subscription price of shares issued as a result of share subscription warrants being exercised will be no less than the average closing price based on the last twenty (20) trading sessions prior to the date on which the share subscription warrants were allocated		
Capital increase, through the issue – with preferential subscription rights – of shares and/or transferable securities giving access to the Company's equity and/or the issue of transferable securities giving entitlement to the allocation of debt securities	12th	26 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	The price of one share issued will be at least equal to the nominal value of the share on the issue date	1,500,000*	
Capital increase through the issue – without preferential subscription rights – of shares and/or transferable securities giving access to the Company's equity and/or the issue of transferable securities giving entitlement to the allocation of debt securities through an offering, as referred to in Article L. 411-2 II of the French Financial and Monetary Code, in particular, to qualified investors or a restricted circle of investors	13th	26 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	The price of one share will be at least equal to the average price weighted by volume based on the last three (3) trading sessions prior to the issue price being set, which may be reduced by a maximum discount of five (5)%	1,500,000*	
Capital increase, through the issue of shares and/or debt securities and/or transferable securities giving access to equity or giving entitlement to a debt security, without preferential subscription rights, with no indication of beneficiaries and by public offering	14	26 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	The price of one share will be at least equal to the average price weighted by volume based on the last three (3) trading sessions prior to the issue price being set, which may be reduced by a maximum discount of five (5)%	10% of the capital 1,500,000*	
Capital increase through the issue of common shares and/or any other transferable securities giving	15th	18 months from the General Shareholders'	Delegation of power to the Board of Directors	The common share issue price will be at least equal to the average weighted price	1,500,000*	

access to equity and/or giving entitlement to the allocation of debt securities – without preferential subscription rights – to categories of persons with specific characteristics		Meeting of June 26, 2019		based on the last three trading sessions prior to the issue price being set, which may be reduced by a maximum discount of 20% or increased by a surcharge at the full discretion of the Board of Directors depending on the category of person		
ISSUE of financial instruments comprising and/or giving entitlement to (upon exercise of subscription warrants) debt securities giving access to Company equity, to which equity warrants are attached – without preferential subscription rights – to a single category of person in accordance with Article L. 225-138 of the French Commercial Code	16th	18 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	The issue price of financial instruments comprising debt securities giving access to Company equity, to which share subscription warrants are attached, will be determined on the basis of their nominal value, which may be reduced by a discount of no more than 10%.  The issue price of the common shares, resulting from the exercise of rights attached to these debt securities or share subscription warrants, will be at least equal to the lowest daily price, weighted by volume, based on the last ten trading sessions prior to the issue price being set, which may be reduced by a discount of no more than 10%	1,500,000*	
Increase in the number of securities to be issued in the event of a capital increase, with or without preferential subscription rights for shareholders, in the event of over-subscription, of up to 15% of the initial issue	18th	26 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	Same price as that used for the initial issue and within thirty days of closure of the subscription period	*	
Capital increase through the incorporation of premiums, reserves, profits or other items	19th	26 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	N/A	1,500,000	
ISSUE of common shares and/or transferable securities giving access to Company equity, as payment in kind comprising equity securities or transferable securities giving access to equity	20th	26 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	None	*	
ISSUANCE of common shares and/or transferable securities giving access to Company equity, in the event of a public exchange offering initiated by the Company	21st	14 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	None	1,500,000*	
Allocation of existing or future free shares to the Group's salaried members of staff and corporate officers, or to some of them	24th	38 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	N/A		
ISSUE of founders' warrants under the terms provided for in Article 163 bis G of the French General Tax Code without	25th	18 months from the General Shareholders'	Delegation of power to the Board of Directors	The price of a share will be at least equal to the average closing price based on the last twenty (20) trading		

preferential subscription rights for shareholders, to a single category of person		Meeting of June 26, 2019		sessions prior to the allocation date without, if the capital increase was carried out through the issue of securities giving entitlement to equivalent rights within the last six months prior to allocation, the price being lower than the issue price of said securities	Overall cap of 500.0000 securities	
ISSUE of equity warrants to a single category of person**	26th	18 months from the General Shareholders' Meeting of June 26, 2019	Delegation of power to the Board of Directors	The issue price of a share subscription warrant will be set by the Board of Directors on the basis of a valuation report prepared by an independent expert in accordance with the requirements of Article 262-1 of the AMF general regulation  The subscription price of shares issued as a result of share subscription warrants being exercised will be no less than the average closing price based on the last twenty (20) trading sessions prior to the date on which the share subscription warrants were allocated		
Allocation of existing or future free shares to the Group's salaried members of staff and corporate officers, or to some of them	26	38 months from the General Shareholders' Meeting of June 13, 2018	Delegation of power to the Board of Directors	N/A	Board of Directors meeting on 06/26/2019	
ISSUE of founders' warrants under the terms provided for in Article 163 bis G of the French General Tax Code without preferential subscription rights for shareholders, to a single category of person	27	18 months from the General Shareholders' Meeting of June 13, 2018	Delegation of power to the Board of Directors	The price of a share will be at least equal to the average closing price based on the last twenty (20) trading sessions prior to the allocation date without, if the capital increase was carried out through the issue of securities giving entitlement to equivalent rights within the last six months prior to allocation, the price being lower than the issue price of said securities	Board of Directors meeting on 06/26/2019	
ISSUE of equity warrants to a single category of person**	28	18 months from the General Shareholders' Meeting of June 13, 2018	Delegation of power to the Board of Directors	The issue price of a share subscription warrant will be set by the Board of Directors on the basis of a valuation report prepared by an independent expert in accordance with the requirements of Article 262-1 of the AMF general regulation  The subscription price of shares issued as a result of share subscription warrants being exercised will be no less than the average closing	Overall cap of 500.0000 securities	

				price based on the last twenty (20) trading sessions prior to the date on which the share subscription warrants were allocated		
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\* The overall maximum nominal amount of capital increases that may be carried out under these resolutions is capped at €1,500,000.

\*\* The right to subscribe for equity warrants was allocated to the category of persons defined as follows: members of the Board of Directors who are not employees or executive corporate officers subject to the Company's tax arrangements for employees, as well as the Company's external consultants, i.e. natural or legal persons outside the Company who, due to their expertise, help the Company to develop in particularly specialized technical and state-of-the-art fields of a scientific, medical or operational nature.

**19.1.5 Information on requirements governing any acquisition right and/or any obligation attached to authorized, but not issued, capital or on any company aiming to increase the capital**

N/A.

**19.1.6 Information on the share capital of any member of the Group that is subject to an option or conditional or unconditional agreement to place it under option**

N/A.

### 19.1.7 Table showing the history of the Company's share capital

Dates	Nature of the transaction	Nominal (in €)	Additional paid-in capital (in €)	Price per share (in €)	Adjusted price per share	Number of shares created/canceled	Total number of shares	Capital after the transaction (in €)
Creation								
April 27, 2012	10 for 1 split	1	0	1		1,000	1,000	1,000
April 27, 2012	Increase	1		1		25,500	26,500	26,500
April 27, 2012	Increase	1	0	1		500,000	526,000	526,000
April 10, 2014	5 for 1 split	0.20	0	0.20			2,632,500	526,500
April 10, 2014	Increase	0.20	9.80	10		5,000,000	7,632,500	1,526,500
June 30, 2014	Increase	0.20	7.80	8		355,947	7,988,447	1,597,689.40
July 29, 2014	Increase	0.20	7.80	8		37,500	8,025,947	1,605,189.40
March 30, 2015	Increase	0.20	10.60	10.80		1,955,000	9,980,947	1,996,189.40
June 24, 2015	Increase	0.20	7.80	8		31,250	10,012,197	2,002,439.40
September 9, 2015	Increase	0.20	7.80	8		36,744	10,048,941	2,009,788.20
May 31, 2016	Increase	0.20	-	-	-	4,107,187	14,156,128	2,831,225.60
May 31, 2016	Increase	0.20	7.80	8		88,256	14,244,384	2,848,876.80
June 17, 2016	Increase	0.20	5.60	5.80		6,369	14,250,753	2,850,150.60
December 6, 2016	Increase	0.20	5.60	5.80		39,217	14,289,970	2,857,994
March 28, 2017	Increase	0.20	-	-		85,000	14,374,970	2,874,994
December 13, 2017	Increase	0.20	-	-		113,851	14,488,821	2,897,764.20
June 13, 2018	Increase	0.20	-	-		173,040	14,661,861	2,932,372.20
July 18, 2018	Increase	0.20	-	-		40,151	14,702,012	2,940,402.40
December 5, 2018	Increase	0.20	0.80	1		115,000	14,817,012	2,963,402.40
June 26, 2019	Increase	0.20				150,000	14,967,012	2,993,402.40
December 10, 2019	Increase	0.20				38,712	15,005,724	3,001,144.80
March 26, 2020	Increase	0.20	-	-		141,800	15,147,524	3,029,504.80
June 27, 2020	Increase	0.20	-	-		150,000	15,297,524	3,059,504.80
June 27, 2020	Increase	0.20	-	-		145,300	15,442,824	3,088,564.80
November 17, 2020	Increase	0.20	7.20	7.40		2,517,589	17,960,413	3,592,082.60
December 18, 2020	Increase	0.20	-	-		22,625	17,983,038	3,596,607.60

## 19.2 Company's constitution and bylaws as of the date of this Universal Registration Document

### 19.2.1 Company's purpose (Article 2)

The Company is registered with the Nantes Trade and Companies Register under number 479 457 715.

The Company's purpose, in France and abroad:

- The design, research and development of healthcare products from creation to obtaining marketing authorization, and all related operations including marketing;

- The acquisition, filing, obtaining, sale or licensing of all patents, brands, licenses and use processes;
- The acquisition of interests in any companies or undertakings already established or to be established, in France or abroad, whether or not they have a similar purpose to that of the Company;
- The provision of services, consultancy in research and development, marketing or commercial consultancy, consultancy on market access (pricing and reimbursement), structural audits in the field of healthcare, pharmaceuticals, cosmetics, nutrition and veterinary;
- And, more generally, all industrial, commercial, financial, civil, intangible property or real estate transactions directly or indirectly related to one of the above purposes or to any similar or related purpose that could be useful to the achievement and development of the Company's business;
- It may carry out any transactions that are compatible with, related to and contribute to achieving this purpose.

## **19.2.2 Rights attached to shares (Articles 11 to 18)**

### **Article 11 – Rights and obligations attached to shares**

#### **I - Common rights attached to common shares**

Each common share confers the right to company profits and assets in proportion to the portion of capital that it represents.

Shareholders are only liable for losses up to their contributions.

The rights and obligations attached to common shares follow said shares, regardless of any change of ownership.

Ownership of common shares automatically entails full compliance with the bylaws and decisions taken by General Shareholders' Meetings.

Each common share confers the right to participate, under the terms set by legislation and the bylaws, in General Shareholders' Meetings and vote on resolutions.

Whenever it is necessary to own more than one share in order to exercise any given right, or even in the event of an exchange, grouping or allocation of shares, or as a result of a capital increase or reduction, a merger or any other transaction, owners of isolated shares or numbers of shares below the required number may only exercise said right on condition that they personally carry out the grouping and, where appropriate, the purchase or sale of the common shares necessary.

#### **II - Rights attached to A Shares**

A Shares and the rights of their owners are governed by the French Commercial Code, in particular, by Articles L. 228-11 et seq.

A Shares are subject to all the provisions of the bylaws and decisions taken by general meetings of owners of common shares.

A Shares do not confer distribution rights in the event of any distribution or, where applicable, allocation of assets, decided on for each common share.

A Shares do not have preferential subscription rights for any capital increase or transaction with entitlement to common shares; on the other hand, the conversion ratio will be adjusted to preserve the rights of holders of A Shares, in accordance with legal and regulatory requirements, as shown in Article 12 of these bylaws. With regards to ownership of Company assets, A Shares confer the right to liquidating dividends in proportion to the amount of capital that they represent.

A Shares do not confer voting rights at ordinary and extraordinary meetings of common shareholders, given that they have voting rights at special meetings of A Shareholders. Holders of A Shares shall meet in a special meeting for any proposed modification of the rights attached to the A shares. In addition, in accordance with Article L. 228-17 of the French Commercial Code, any plans for the merger or spin-off of the Company under which A Shares may be exchanged for shares conferring equivalent special rights, will be subject to the approval of any related special meeting.

Decisions taken by special meetings are only valid if the shareholders present or represented by proxy hold, upon first convocation, at least one third, and on second convocation, one fifth, of the preference shares with voting rights. In the event of modification or depreciation of capital, the rights of A Shareholders are adjusted to preserve their rights in accordance with Article L. 228-99 of the French Commercial Code. Given that the other rights attached to A Shares are temporary, these rights are specified in Article 12 of these bylaws.

#### **Article 12 – A Shares**

Subject to fulfilling the conditions set out below, A Shares, on their conversion date, will automatically be converted by the Company into common shares.

The Company may inform holders of A Shares that the shares are being converted, by whatever means, before the effective conversion date.

Two years after the A Shares are allocated by the Board of Directors, they will be converted into common shares using a conversion ratio which is dependent on at least one criterion based on changes in the market price of the common share compared with an initial threshold which cannot be lower than the market price of the common share as recognized on the date on which the A Shares were allocated and one criterion relating to the Group's performance.

Subject to adjustment in accordance with legal and regulatory requirements, the conversion ratio will be 100 common shares per A Share where the target objective is met in full, for the criterion based on changes in the market price, with a proportional and linear reduction in the event of failure to meet the criterion in full and, for the performance-based criterion, a reduction in line with the degree of fulfilment of the criterion if it has not been met in full.

Where the total number of common shares due to be received by the holder by applying the conversion ratio to the number of A Shares held is not a whole number, the number of shares received by said holder will be rounded down to the next whole number.

Notwithstanding the above, the conversion may take place prior to the two-year deadline from the date of allocation of the A Shares by the Board of Directors, if the beneficiary becomes disabled (category two or three disability provided for in Article L. 341-4 of the French Social Security Code), at the beneficiary's request, at any time after said disability is recognized.

The Board of Directors, or by delegation of authority under the terms set out by legal requirements, the Chairman of the Board of Directors, shall recognize the conversion of A Shares into common shares where the conversion is carried out under the conditions set out above.

At intervals which it shall itself determine, the Board of Directors shall acknowledge, where applicable, the number of common shares resulting from the conversion of A Shares in the fiscal year in question and shall make the necessary changes to the bylaws, in particular, with regard to the breakdown of shares by category. This option may be delegated to the Chief Executive Officer in accordance with legal requirements.

Common shares arising from the conversion of A Shares will be identical in all respects to outstanding common shares.

#### **Article 13 – Type of shares**

Shares are either registered or bearer shares, at the shareholder's choice. They can only be bearer shares once they are fully paid-up.

Fully paid-up A Shares are registered shares.

The Company is authorized to identify the holders of bearer securities by simple request to the organization in charge of clearing bearer securities, the name or corporate name, nationality, year of birth or year of incorporation, address of the holders of securities as well as the quantity of securities held by each of them.

#### **Article 14 – Payment for shares**

In the event of a capital increase, at least one quarter of the nominal value of shares issued for cash and, where necessary, the full issue premium, is paid up at the time of subscription.

The balance may be paid in one or more instalments at the Board of Director's request, within five years of the date on which the transaction becomes final in the case of a capital increase.

Shareholders are notified of calls for funds by individual recorded delivery letters, at least fifteen days prior to the date set for each payment.

Shareholders who fail to make the payments owing for the shares by the due date shall, automatically, and without any formal notification, be liable to pay the Company late payment interest calculated on a daily basis, from the due date, at the legal rate applicable to commercial transactions, plus three points.

In order to secure the payment of these sums, the Company is entitled to apply the sanctions provided for by Articles L. 228-27 et seq. of the French Commercial Code.

#### **Article 15 – Transfer of shares**

Shares are freely transferable as soon as they are issued, in accordance with the procedures laid down by law.

They are registered in a share account and transferred between accounts on the basis of instructions signed by the transferor or their qualified representative.

#### **Article 16 – Disclosure thresholds**

Pursuant to Article L. 233-7 of the French Commercial Code, any individual or legal entity, acting alone or in concert, within the meaning of Article L. 233-10 of the French Commercial Code, who comes to hold or ceases to hold a number of shares representing a fraction equal to 5%, 10%, 15%, 20%, 25%, 30%, 33.33%, 50%, 66.66%, 90% or 95% of the share capital or voting rights, is required to disclose to the Company no later than the close of trading on the fourth trading day following the date on which the aforementioned shareholding threshold is crossed, the number of shares and voting rights held. The individual required to disclose the above information shall specify the number of securities held giving future access to the share capital and related voting rights.

A shareholder who has not properly made the required disclosures as referred to above shall be stripped of the voting rights attached to the shares in the conditions pursuant to the French Commercial Code.

#### **Article 17 – Indivisibility of shares – Bare ownership – Usufruct**

(i) The shares are indivisible in respect of the Company.

Joint owners of undivided shares are represented at General Shareholders' Meetings by one owner or by a single proxy. In the event of a disagreement, the proxy is appointed by the court at the request of the joint owner acting first.

(ii) The beneficial owner has the voting right at Ordinary General Shareholders' Meetings and the bare owner at Extraordinary General Shareholders' Meetings. Shareholders may, however, agree to any distribution of voting rights at General Shareholders' Meetings. The Company is notified of the agreement by registered letter, and is obliged to apply this agreement for any meeting that may be held after one month has lapsed since the letter was sent.

#### **Article 18 – Double voting rights**

Each common share and each A Share confers entitlement to one vote. Double voting rights of those conferred by other common shares in terms of the portion of capital that they represent are given to any fully paid-up common shares that can be proven to have been registered for at least two years in the name of the same shareholder.

Should obtaining double voting rights result in the shareholding threshold being crossed, under the requirements of Article 16 of the bylaws, the shareholder in receipt of the double voting rights would be obliged to comply with the provisions of said article.

This double voting right is also conferred on ordinary registered shares, as soon as they are issued, in the event of a capital increase through the incorporation of reserves, profits or issue premiums, allocated free of charge to shareholders who hold old common shares which confer this right.

Common shares transferred as a result of inheritance, the liquidation of community property between spouses or *inter vivos* gifts to a spouse or close relative do not result in the loss of the right acquired and do not interrupt the qualifying periods provided for above.

It is likewise, in the event of transfer of common shares following the merger or spin-off of a corporate shareholder.

In addition, the merger or spin-off of the Company does not affect the double voting rights that may be exercised within one or more beneficiary companies if permitted by their bylaws.

**19.2.1 Company bylaws, charters or regulations that may have the effect of delaying, postponing or preventing a change of control.**

N/A.

## 20 Important contracts

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In the two years prior to the publication of this Universal Registration Document, the Company did not enter into any material contract (it being recalled that the Boehringer Ingelheim contract to develop BI 765063 (OSE-172) was signed on April 4, 2018).

As of the date of this Universal Registration Document, the Group as a whole is bound by the following contracts, conferring a material obligation or right for the entire group:

- OSE Pharma retained the confidential contractual obligations entered into by its subsidiary, OPI, in respect of Takeda, with a milestone payment upon registration of Tedopi® in the United States and in Europe, then additional payments (fees or royalties) corresponding to a percentage of sales of Tedopi® by OSE Pharma, this being no greater than a single-digit percentage.
  
- OSE Pharma signed a licensing contract with OPI in Switzerland in July 2012 for Tedopi® (OSE-2101). This first contract gives OSE Pharma the commercial rights to market the product in Europe as well as responsibility for international development in Europe and the United States. OSE Pharma will set up an international development team and will seek to obtain the green light from the two Registration Agencies (EMA and FDA) in both Europe and the United States.

## **21 Publicly available documents**

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So long as this Universal Registration Document is valid, the following documents (or copies of them) may be physically viewed at the Company's registered office at 22, Boulevard Benoni Goullin – 44200 Nantes, France:

- The Company's instrument of incorporation and bylaws;
- The 2018 Registration Document;
- any reports, letters and other documents, historical financial information, assessments and statements produced by an expert at the Company's request, some of which are included or referred to in this Universal Registration Document;
- The Company's historical financial information for each of the three fiscal years preceding the publication of this Universal Registration Document.

The regulated information within the meaning of the General Regulation of the AMF is available on the Company's website ([www.ose-immuno.com](http://www.ose-immuno.com)) and the websites of the AMF ([www.amf-france.org](http://www.amf-france.org)) and Euronext ([www.euronext.com](http://www.euronext.com)).

## 22 Glossary

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**Adjunctive:** an antigen mixed for example with a mineral oil (adjunctive), generates an inflammatory reaction at the point of injection and an activation of innate immunity (cells presenting antigens) leading to recognition of those antigens, then co-stimulation signals on the surface of antigen-presenting cells that will be necessary for the activation of T lymphocytes.

**Antibodies:** these are proteins produced by cells, plasmocytes, resulting from the activation of B lymphocytes (B lymphocyte cells at the origin of antibodies). Antibodies are specifically directed against the tumor antigens. They bind onto these latter to form an immune complex. The existence of this complex triggers several defense mechanisms including the recruitment of innate immunocompetent cells such as macrophages or NK cells.

**Checkpoint Inhibitor:** specific antibodies of certain cellular signaling channels that intervene in immuno-oncology treatments.

**Cytokines:** molecules that play a messenger role allowing communication between cells.

These are the regulating principles of the immune response.

**Dendritic cells:** these are “sentinel” cells present in tissues and migrating in lymphoid tissues. They have the capacity to present tumor antigens to T lymphocytes to activate them. They also secrete substances called cytokines, messengers that stimulate the overall immune response.

**Epitope:** this fragment of tumor antigen called “antigenic determinant” is the often very small molecular structure that binds to cell receptors and triggers an immune response.

**HLA:** the human Major Histocompatibility Complex (MHC) is also called HLA (Human Leukocyte Antigens). HLA plays a role in the acceptance or rejection of a transplant. The presentation of the antigen (in reality a small peptide called epitope or antigenic determinant) is provided by the HLA system. Two classes exist: class I and class II.

**HLA-A2** (also called HLA-A\*02 or A\*02): HLA serotype (belonging to the class I MHC, is measured by a positive or negative serology test). This receptor is involved in immunosurveillance and in T cell response. It is expressed in approximately 45% of the general population.

**Major Histocompatibility Complex (MHC):** MHC molecules are on the surface of antigen-presenting cells and ensure the antigen is presented to the T lymphocytes in order to activate them. There are class I and class II MHC molecules. In humans, we speak of HLA antigens. This group of genes is expressed on the surface of cells and has been analyzed internationally for organ transplants. The class I genes are the A, B, C genes; the class II genes are the DP, DQ and DR genes.

MHC I molecules are present on all nucleated cells of the organism and present the antigen to cytotoxic T lymphocytes.

The MHC II molecules are found on the surface of antigen-presenting cells (APC) as dendritic cells, activated B lymphocytes, macrophages, in order to educate the lymphocytes in the non-recognition of self-peptides and the recognition of “foreign” peptides of the non-self.

These two systems take part in immune responses and are the key to cellular immunity and communication between cells providing for the protection of the organism.

**Monoclonal antibodies:** antibodies that possess the same chemical structure and therefore a unique specificity for an antigen. Produced by recombinant protein technology in bioreactors, they are used as therapeutic agents in many areas of medicine, in particular in cancerology, immunology and inflammation.

**Myeloid cells:** these are white blood cells that play a major role in the initiation and control of inflammation. Suppressive myeloid cells accumulate in some forms of cancer, where they prevent the T cells from destroying the tumor.

**NK Lymphocytes:** these innate immunity cells can recognize and kill tumor cells without having been activated. Their mechanism of recognition is non-specific for tumor antigens. In the absence of unique receptors for a particular antigenic target, the NK cells cannot distinguish the self from the non-self.

**Regulatory T Lymphocytes (Treg):** these cells control the occurrence and the intensity of immune responses made by the T lymphocytes. They are naturally present and their absence leads to autoimmune diseases. Inversely, their accumulation reduces autoimmunity and prevents the rejection of transplants.

**T Lymphocytes:** these cells provide the specific cellular response. A distinction is made between T-CD8 lymphocytes, activated in cytotoxic lymphocytes that will directly attack the tumor cells and, on the other hand, T-CD4 cells, helper T cells or auxiliaries, that mainly provide the functions of stimulation/regulation of the immune response. Initially naive (that is “non-informed”) these cells are educated by the dendritic cells that teach them to specifically recognize tumor antigens.

**TCR:** this is a specific immunoreceptor; the T lymphocytes express this TCR receptor (T-Cell Receptor) on their surface. It only recognizes the epitopes presented by the major histocompatibility system (or HLA system).

**Tumor antigens or tumor-associated antigens:** these are macromolecules, proteins and protein fragments specific to the tumor. They betray its presence. When they are recognized by the immune system, they produce a response specifically directed against the tumor cells. Sometimes shared with other healthy tissues, they are not recognized since they are considered as “self-antigens”.

**Tumor escape:** the capacity of tumor cells TO escape the surveillance of the immune system and create metastases in other parts of the body.

**LIST OF ABBREVIATIONS**

ALK	Anaplastic Lymphoma Kinase: genetic abnormality with abnormal activation of the ALK protein, i.e. 4 to 5% of non-small cell lung cancers for which targeted therapies are available
APC	Antigen-Presenting Cells: dendritic, macrophage cells, etc. presenting antigens
APC	Antigen Presenting Cells: or APC see above.
ASCI	Antigen-Specific Cancer Immunotherapeutic: a vaccine targeting a tumor antigen, an antigenic proteinaceous macromolecule
ASCO	American Society Of Clinical Oncology: annual cancer conference in the United States
BRCA1	Breast Cancer Gene 1: mutations of this gene with an increased risk of cancer
CD4 T	CD4 T Lymphocytes: helper or auxiliary T cells are "amplifier cells" of the immune response. They carry a CD4 marker on their surface.
CD8 T	Cytotoxic T Lymphocytes (CD8 T or killer T cells) destroy the infected or "foreign" cells, and are able to destroy target cells that present specific antigens through the MHC class I. They carry a CD8 marker on their surface.
CEA	Carcino Embryogenic Antigen: tumor antigen very frequently expressed on the surface of tumor cells
CMC	Chemistry Manufacturing Control: part of a drug's pharmaceutical dossier
CMO	Contract Manufacturing Organization: organization for production of industrial lots
CRO	Contract Research Organization: organization subcontracting trials
CTLA-4	Cytotoxic T Lymphocyte-Associated Protein 4: checkpoint blocking T responses
EBV	Epstein Barr Virus: an oncogenic virus at the origin of some cancers
ECOG	Eastern Cooperative Oncology Group Performance Status: index of patient's condition
EGFR	Epidermal Growth Factor Receptor: mutations of the EGFR gene in some cancers, overexpression of the EGFR protein, therapies targeted on that target, the frequency of EGFR mutations is 5 to 20%
ELISPOT	Enzyme-Linked Immunosorbent Spot assay: measures specific responses of T lymphocytes
EMA	European Medicines Agency: European drug agency
EP-2101	Former code of OSE2101:
ER	Estrogen receptor: a marker in breast cancer influencing the therapeutic options
ErbB	Family of epidermal growth factors EGFR and HER/neu belong to this family of receptors, involved in many cancers.
EU	European Union
FDA	Food And Drug Administration: American drug agency
FIGO	International Federation of Gynecology and Obstetrics
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GLP, GMP, GCP	Good Laboratory Practices, Good Manufacturing Practices, Good Clinical Practices
GMP	Good Manufacturing Practice
HER-2/neu	Human Epidermal Receptor-2/Neurological: Tumor antigen

HLA	Human Leukocytes Antigens: molecules on the surface of cells that allow identification by the immune system. These proteins are called "Major Histocompatibility Complex" (MHC) molecules.
ICH	International Conference on Harmonization (of Technical Requirements for Registration of Pharmaceuticals for Human Use) International Pharmaceutical Standards
IFN	Interferon: a cytokine produced by the cells of the immune system,
IL	Interleukin cytokine produced by cells to communicate between themselves
IND – United States	Investigational New Drug Application: complete documentation of a pharmaceutical dossier in the United States
IMPD – Europe	Investigational Medicinal Product Dossier: complete documentation of a pharmaceutical dossier in Europe
Ligand	A molecule able to bind itself to a specific protein
MAGE 2/ MAGE 3	Melanoma Antigen type 2/type 3: tumor antigens expressed in many cancers
MHC	Major Histocompatibility Complex
MHC class I	Major Histocompatibility Complex or HLA system: the MHC class I molecules enable presentation of the peptide (or antigenic determinant = epitope) to the T CD8-lymphocytes - the most important are the HLA-A, HLA-B and HLA-C molecules.
MHC class II	The MHC class II molecules enable the presentation of the antigenic peptide to the T CD4 lymphocytes. The most important are the HLA-DP, HLA-DQ and HLA-DR molecules.
MUC	Tumor antigen associated with many cancers
NK	Natural Killer: these natural killer cells are immunity cells.
NSCLC	Non-Small Cell Lung Carcinoma: non-small cell lung cancer or non-small cell bronchial carcinoma NSCLC, the most common form of lung cancer
ORR	Overall Response Rate: tumor response rate
OSE-2101	Product code of the multiepitopes targeting 5 tumor antigens – Tedopi® trademark, from the optimized multiepitope technology - Memopi® trademark
p53	A Nuclear Regulatory Protein Oncogene: The gene coding for the p53 protein is disabled in half of human cancers. This protein is a tumor antigen.
PARP	Poly ADP Ribose Polymerase enzyme, targeted cancer therapies targeting that enzyme
PCT	Patent Cooperation Treaty: treaty for cooperation on patents (PCT) at the international level
PD-L1	PD-1 Ligand 1: checkpoints blocking T responses
PDCD1	Programmed Cell Death 1: checkpoints blocking T responses
PR	Progesterone Receptors: a breast cancer marker influencing therapeutic options
QP	Qualified Person: person qualified for pharmaceutical responsibility in Europe
RCC	Renal Cell Carcinoma: kidney cancer
RECIST	Response Evaluation Criteria In Solid Tumor: RECIST criteria are used to evaluate and measure the tumor response.
TCR	T-Cell Receptor: the TCR receptor, expressed on the surface of T cells, recognizes a peptide presented in a molecule of the Major Histocompatibility Complex (MHC)
TIL	Tumor Infiltrating Lymphocytes: intra-tumoral lymphocytic infiltrate
TKI	Tyrosine Kinase Inhibitors: therapies targeted on certain mutations or molecular alterations of the cancerous cell (for example, erlotinib and gefitinib)

TNBC	Triple Negative Breast Cancer: triple negative breast cancer, tumor cells negative for three prognostic markers (estrogen receptors (ER), progesterone receptors (PR), overexpression of the HER2 protein)
VEGF	Vascular Endothelial Growth Factor plays a role in tumor growth. Bevacizumab is the first monoclonal antibody directed against the VEGF and marketed for treatment against some cancers in 2004.

## **Appendix A – Board of Directors’ Management Report**

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**OSE IMMUNOTHERAPEUTICS**

Limited company (*société anonyme*) with a Board of Directors  
With share capital of €3,596,607.60  
Registered office: 22 Boulevard Benoni Goullin 44200 Nantes  
479 457 715 Nantes Trade and Companies Register

**BOARD OF DIRECTORS' MANAGEMENT REPORT PRESENTED TO THE COMBINED GENERAL****SHAREHOLDERS' MEETING OF JUNE 24, 2021****Fiscal year ended December 31, 2020**

Dear Shareholders,

In accordance with legal and regulatory provisions, we have convened this Combined General Shareholders' Meeting (Ordinary and Extraordinary), in order to report to you on the Company's position and activity as well as the results achieved during the fiscal year ended December 31, 2020.

The Statutory Auditors will provide you, in their report on the separate financial statements, with all information concerning the regularity and fairness of the financial statements presented to you.

We will give you all additional clarifications and information concerning the material and documentation provided for by the regulations in force and which were made available to you within the legal deadlines.

In accordance with the provisions of Article L. 225-100 of the French Commercial Code, please note that the various information provided in this report constitute our objective and thorough analysis of the business development, results and financial position of the Company for the fiscal year ended on December 31, 2020.

**1. ACTIVITY OF THE COMPANY DURING FISCAL YEAR 2020****1.1 Position and development of the Company's business over the fiscal year****1.1.1 *Capital structure at December 31, 2020***

See Section 16.1 of the Universal Registration Document.

**1.1.2 *Development of the Company's business***

During 2020, the Company continued to develop.

**JANUARY 2020** The Japanese Patent Office issued a new family of patents relating to Tedopi®, a combination of neoepitopes, covering the product's method for inducing an early T-lymphocyte memory response when using the product to treat cancer in HLA-A2 positive patients. This patent protects the product until 2035.

**FEBRUARY 2020** A collaboration agreement was signed with MAbSilico, an innovative company based in Tours (France) specializing in the use of artificial intelligence algorithms to discover and characterize therapeutic antibodies.

**MARCH 2020** Signature of an amendment to the two-step worldwide licensing option agreement on the exclusive rights of OSE-127/S95011, Interleukin-7 receptor antagonist, signed with Servier in December 2016. This amendment modifies the arrangements for the potential exercise of the licensing option agreement's second step. OSE Immunotherapeutics will thus receive a milestone payment of €5 million from Servier on enrollment of the first patient in Phase 2a clinical study scheduled to start

in Sjögren's Syndrome and an additional payment of €15 million on exercise of the option at the end of the two scheduled Phase 2 studies, with priority being given to the study in Sjögren's Syndrome. The initial agreement provided for a total payment of €20 million at the end of Phase 2 in ulcerative colitis.

<b>APRIL 2020</b>	Announcement of positive result of stage 1 of the Phase 3 clinical trial of Tedopi®, Atalante 1, in non-small cell lung cancer: Primary endpoint of stage 1 achieved with a survival rate at 12 months in patients treated with Tedopi®. In the context of the COVID-19 epidemic, decision taken to voluntarily and definitively discontinue screening and the enrolling new patients in step 2 initially planned in the trial and which will therefore not be conducted. The Company will continue additional analyses of the step 1 data and initiate discussions with the regulatory authorities to determine the best path to take for development of the product, in view of the high therapeutic need of the population of patients suffering from advanced lung cancer following failure of treatment by checkpoint inhibitor.
<b>MAY 2020</b>	<p>Announcement of a COVID-19 prophylactic vaccine program that leverages the Company's expertise in the selection and optimization of peptides, and its patented Memopi® technology to explore a T-lymphocyte response with immune memory in COVID-19.</p> <p>Announcement of the presentation of preclinical data on CLEC-1 (among CLR receptors - C-type lectin receptors), an immune myeloid checkpoint and new therapeutic target of interest in immuno-oncology, in an oral presentation at the Annual Virtual Meeting (II) of the American Association of Cancer Research (AACR) [June 22 - 24, 2020].</p> <p>Signature of a €7 million non-dilutive loan agreement in the form of French Government-Guaranteed loan set up in the context of the COVID-19 pandemic, with a group of French banks.</p>
<b>JUNE 2020</b>	<p>Identification and characterization of a new myeloid checkpoint target, CLEC-1 (a C-type lectin CLR receptor), and of the first monoclonal antibody antagonists of CLEC-1 identified as an innovative step in cancer immunotherapy, presented at the Annual Virtual Meeting (II) of the American Association of Cancer Research (AACR) [June 22 - 24, 2020].</p> <p>The latest advances made on the BiCKI® platform for anti-PD-1 bispecifics fused to cytokines or costimulatory molecules, and a preclinical update on BiCKI®-IL-7, a bifunctional anti-PD1/IL-7 fusion protein (1), were presented at the Annual Virtual Meeting (II) of the American Association of Cancer Research (AACR) [June 22 - 24, 2020].</p>
<b>JULY 2020</b>	Funding of €200,000 from Nantes Métropole for the development of a prophylactic vaccine against the pandemic SARS-CoV-2 virus. This grant was awarded as part of the Metropolitan Fund to support health innovations related to the COVID-19 health crisis.
<b>AUGUST 2020</b>	Online publication on BioRxiv of positive data from a preclinical study and an <i>ex vivo</i> study in humans on CoVepiT, a prophylactic vaccine program against COVID-19. These data support CoVepiT's potential as a novel and differentiated vaccine against COVID-19, using technology known to induce memory T lymphocytes against multiple SARS-CoV-2 virus targets. The results show that CoVepiT provides tissue-resident memory sentinel T cell response with long-term protective immunity in barrier tissues such as the respiratory tract and the lung, associated with long-term protective immunity. The clinical trial is planned for the end of 2020/beginning of 2021.
<b>SEPTEMBER 2020</b>	<p>Presentation of the Company at the HC Wainwright Annual Global Investment Conference held virtually (September 14 - 16, 2020).</p> <p>Oral presentation at the virtual meeting of the European Society for Medical Oncology (ESMO) of the positive results of step 1 of the Phase 3 Tedopi® trial in patients with non-small cell lung cancer (NSCLC) after failure of an immune checkpoint inhibitor treatment. These results show a clearly improved overall survival time with Tedopi® compared to the standard treatment, a significant increase in survival after progression, the maintenance of a good ECOG score* reflecting the change in the general health of the patient, and the confirmation of a better tolerability profile for Tedopi®.</p>

Overall, the benefit/risk ratio is favorable to Tedopi® and better than that of standard treatment in these patients previously treated with checkpoint inhibitors.

*\*The ECOG score is a performance scale used to assess the overall state of health of the patient. It is subdivided into 5 grades from 0 to 5, ranging from fully active (0) to completely disabled and then to death (5).*

#### OCTOBER 2020

The European Patent Office (EPO) granted FR104, a first-in-class selective CD28 antagonist, a European patent protecting the innovative administration of FR104 until 2036 in the prevention and treatment of T-lymphocyte-mediated autoimmune diseases, inflammatory diseases, transplantation and graft-versus-host disease (GVHD)

Publication in "Journal of Clinical Investigation (JCI) data from preclinical and translational studies showing, in vivo models in rodents and ex vivo in humans, the efficacy and mechanism of action of BI 765063 (OSE-172), the first selective antagonist of the "Don't Eat Me" signal mediated by SIRP $\alpha$ . For the first time, the OSE R&D team has identified the "Don't Find Me" signal, a complementary mechanism mediated by SIRP $\alpha$  whereby tumor cells evade immune detection by preventing T lymphocytes from entering the heart of the tumor.

Presentation of preclinical efficacy data on OSE-230, an innovative monoclonal antibody agonist therapy, at the FOCIS 2020 annual meeting ("Federation of Clinical Immunology Societies") [28 - 31 October]. OSE-230 is an agonist antibody against ChemR23, also known as chemerin chemokine-like receptor 1 (CMKLR1), a G-protein coupled receptor (GPCR) expressed on myeloid immune cells known to modulate inflammation.

#### NOVEMBER 2020

Announces successful completion of its human ex vivo study with CoVepiT, a prophylactic vaccine program based on optimized epitopes selected to induce a lasting sentinel T lymphocyte immune response against SARS-CoV-2, the virus that causes COVID-19. In parallel, OSE Immunotherapeutics gave an overview on the development of this multi-target vaccine at the "World Immunotherapy Congress", or Festival of Biologics, held virtually November 2-9, 2020. This is the first presentation on a second-generation memory T cell COVID-19 vaccine at a scientific congress.

OSE Immunotherapeutics presentations at the SITC annual conference and other international immuno-oncology meetings: presentations on myeloid cells and the "Don't Eat Me" signal, an emerging and innovative research pathway in immuno-oncology.

On November 18, 2020, the Company announced the successful completion of its €18.6 million capital increase, launched on November 16, by means of a private placement. It was carried out with cancellation of preferential subscription rights through a private placement with 25 qualified French and international investors, a large majority of which were new shareholders, and by the accelerated construction of an order book, for €18.6 million.

#### DECEMBER 2020

The French National Medicines Safety Agency (Agence Nationale de Sécurité du Médicament) and the Committee for the Protection of People gave their authorization to start a Phase 1/2 clinical trial evaluating FR104, a CD-18 antagonist monoclonal antibody, in patients who have received a kidney transplant. This study will be conducted as part of a collaboration agreement between OSE Immunotherapeutics and the Centre Hospitalier de Nantes, the study sponsor.

The Company obtained funding of €5.2 million under the PSPC-COVID call for projects, operated on behalf of the French government by Bpifrance as part of the Future Investments Program (PIA) and led by the Secrétariat général pour l'investissement (SGPI), to support, under certain criteria, the CoVepiT development program, its second-generation multi-target vaccine against COVID-19, which will begin clinical trials in the 1st quarter of 2021.

On December 21, the Company announced recruitment of the first patient in the Phase 2 clinical trial evaluating OSE-127/S95011/S95011, an IL-7 receptor antagonist, in patients with moderate to severe active ulcerative colitis. This clinical trial is being sponsored by OSE Immunotherapeutics.

**1.1.3      Issue of share warrants (BSA), founders' warrants (BSPCE) and free shares**

See Section 19.1.4 of the Universal Registration Document.

**1.2      Progress made and difficulties encountered**

**T CELL VACCINES**

- **TEDOPI®, POSITIVE RESULTS OF STEP 1 OF THE PHASE 3 CLINICAL TRIAL OF TEDOPI® IN NON-SMALL CELL CANCER (NSCLC) AFTER TREATMENT FAILURE WITH A CHECKPOINT INHIBITOR.**

The international Phase 3 clinical trial of Tedopi®, Atalante 1, was designed to evaluate the benefits of the product in HLA-A<sup>2</sup> positive patients in second- or third-line therapy versus second- or third-line chemotherapy (docetaxel or pemetrexed) in invasive stage IIIB or metastatic stage IV non-small cell lung cancer after failure of treatment with anti-PD-1 and anti-PD-L1 checkpoint inhibitors. The main assessment endpoint is overall survival.

**IN APRIL 2020, OSE IMMUNOTHERAPEUTICS ANNOUNCED THE** positive result of step 1 of the Atalante 1 clinical trial with achievement of its primary endpoint: a 12-month survival rate in patients treated with Tedopi®.

At the same time, given the context of the COVID-19 epidemic, the Company decided to voluntarily and definitively discontinue the screening and the enrollment of new patients in step 2 initially planned in the trial which therefore will not be conducted.

These positive results from step 1 were presented in more detail at the ESMO (European Society for Medical Oncology) virtual meeting. They show a clearly improved overall survival time with Tedopi® compared to the standard treatment, a significant increase in survival after progression, the maintenance of a good ECOG score (performance scale to assess the patient's state of health) and the confirmation of a better tolerability profile of Tedopi®. Overall, the benefit/risk ratio is favorable to Tedopi® and better than that of standard treatment in these patients previously treated with checkpoint inhibitors.

The Company is continuing additional analyses of the step 1 data and will initiate discussions with the regulatory authorities to determine the best path to take for development of the product, in view of the high therapeutic need of the population of patients suffering from advanced lung cancer following failure of treatment by checkpoint inhibitor.

- **TEDOPI®, IN PHASE 2 CLINICAL TRIALS IN PANCREATIC CANCER: TEMPORARY SUSPENSION OF PATIENT ENROLLMENT DUE TO THE COVID-19 PANDEMIC AND AMENDMENT TO THE TRIAL PROTOCOL.**

- The Phase 2 clinical trial, TEDOPaM, is being led by the oncology cooperative group GERCOR in HLA-A2 positive patients with locally advanced pancreatic cancer.

Due to the COVID-19 pandemic, the screening and enrollment of new patients in TEDOPaM had been temporarily suspended in March 2020. After a review of the data collected before the end of March 2020 according to the initial protocol (Tedopi® alone or in combination with Opdivo® versus chemotherapy with FOLFIRI), the Independent Data Monitoring Committee (IDMC) of the trial recommended stopping the assessment the treatment arm of Tedopi® in combination with Opdivo® and introducing a treatment arm of Tedopi® + chemotherapy (FOLFIRI). GERCOR has modified the treatment regimen accordingly and the first new enrollments are expected during the second quarter of 2021 (based on the COVID-19 impact) with an amended protocol comparing Tedopi® in combination with Folfiri versus Folfiri as maintenance therapy after induction therapy with Folfirinox. The main endpoint of the trial remains the one-year survival rate.

\*\* *FOLFIRINOX: a chemotherapy regimen combining folinic acid, fluorouracil, irinotecan and oxaliplatin*

\* *FOLFIRI: a chemotherapy regimen combining folinic acid, fluorouracil and irinotecan*

**- COVEPI: POSITIVE PRECLINICAL AND EX VIVO RESULTS FOR THIS PROPHYLACTIC COVID-19 VACCINE PROGRAM - IN CLINICAL PHASE IN APRIL 2021**

In May 2020, OSE Immunotherapeutics committed to the fight against COVID-19 and announced the launch of a research program on a vaccine called CoVepiT. The vaccine incorporates peptide fragments (epitopes) selected and optimized using artificial intelligence algorithms to increase immune response and induce strong memory T cell responses. CoVepiT is generated using OSE's proprietary Memopi® technology which has been validated for both safety and efficacy through the step-1 of Phase 3 clinical phase of neopeptope vaccine Tedopi® in patients with non-small lung cancer.

The human *ex vivo* clinical study, named CoVepiT 1, was conducted in 120 convalescent COVID-19 subjects versus unexposed subjects. It aimed at assessing the memory T cell immune response at a distance from a resolving infection with SARS-CoV-2 adults. The main objective of the study was achieved: the identification of T memory immuno-dominant epitopes after infection with COVID-19 and incorporation in the vaccine composition.

As of August, positive results in preclinical and *ex vivo* in humans were published online at BioRxiv:

- Data support the potential as a novel and differentiated COVID-19 vaccine designed against multiple SARS-CoV-2 targets with technology known to induce memory T lymphocytes.
- Studies show that CoVepiT provides tissue-resident memory (Trm) sentinel T cell response with long-term protective immunity in barrier tissues such as the respiratory tract and the lung.
- The emergence of new mutated coronavirus variants strengthens the multi-epitope approach against 11 viral proteins to generate a T lymphocyte response.

These results from both preclinical and human *ex vivo* studies as well as the expected emergence of new SARS-CoV-2 variants build a strong basis for supporting the development of CoVepiT as a novel and differentiated COVID-19 vaccine designed against multiple coronavirus targets with vaccinal technology known to induce long-lasting memory T lymphocytes.

On April 1, 2021, OSE Immunotherapeutics announced the authorization of the Federal Agency for Medicines and Health Products (FAMHP) and the Belgian Ethics Committee to start a Phase 1 clinical trial that will assess tolerability, reactogenicity and immunogenicity of the vaccine in healthy adult volunteers.

The CoVepiT development program is supported by €5.2 million of financing obtained as part of the PSPC-COVID call for projects, operated on behalf of the French State by Bpifrance as part of the Future Investments Program (PIA), managed by the General Secretariat for Investment (SGPI). It is subject to achieving certain criteria.

**IN IMMUNO-ONCOLOGY: CLINICAL AND PRECLINICAL ADVANCES**

**- BI 765063 (OSE-172), IN PHASE 1 CLINICAL TRIALS IN ADVANCED SOLID TUMORS**

BI 765063, a checkpoint inhibitor targeting the SIRPa receptor on the SIPRa/CD47 axis, is being developed as part of a partnership with Boehringer Ingelheim, which acquired the worldwide rights in April 2018 for the development, registration and marketing of the product. At the same time, the Company obtained €9.2 million in financing from Bpifrance as part of a collaborative project (EFFI-CLIN) to support the development of BI 765063 which includes product manufacturing, translational studies and a clinical trial program through Phase 2.

In March 2019, the Company obtained the Belgian and French regulatory approvals for the launch of Phase 1 aimed at evaluating BI 765063 in patients with advanced solid tumors. This first-in-human Phase 1 trial is a dose finding study of BI 765063 administered as a single agent and in combination with Boehringer Ingelheim's monoclonal antibody PD-1 antagonist BI 754091, a T-lymphocyte checkpoint inhibitor. The trial aims to characterize safety, pharmacokinetics, pharmacodynamics and preliminary efficacy of the immunotherapy in patients with advanced solid tumors. This trial is currently underway.

In June 2020, an OSE Immunotherapeutics publication in the Journal of Clinical Investigation (JCI) confirmed the new mechanism of BI 765063: for the first time, the OSE R&D team has identified the "Don't Find Me" signal, a complementary mechanism mediated by SIRPa whereby cancer cells evade immune detection by preventing T lymphocytes from entering the heart of the tumor. The new anti-SIRPa strategy reverses this major resistance mechanism called "T lymphocyte exclusion" by releasing the brakes on T lymphocyte chemotaxis and migration into the tumor core.

- **CLEC-1, IDENTIFICATION OF MONOCLONAL ANTIBODY ANTAGONISTS OF CLEC-1 AS INHIBITORS OF A NEW CHECKPOINT INHIBITOR OF IMMUNE MYELOID CELLS IN IMMUNO-ONCOLOGY.**

The OSE Immunotherapeutics teams have characterized a new CLEC-1 myeloid checkpoint target (among CLR receptors - C-type lectin receptors), and have identified monoclonal antibody antagonists that block this new signal “Don't Eat Me”. They increase both the phagocytosis of tumor cells by macrophages and the uptake of antigens by dendritic cells. These data were presented to the 2020 meeting of the American Association for Cancer Research (AACR).

The identification of CLEC-1 and its antagonists constitute an exciting innovative step in cancer immunotherapy.

- **BICKI®, PRECLINICAL ADVANCES**

New data presented to the American Association for Cancer Research showed that the platform of bispecific anti-PD-1 checkpoint inhibitors, BiCKI®, and the innovative bispecific anti-PD-1 therapy with a cytokine IL-7, BiCKI®-IL-7, represent a potential new tool in the fight against the resistance mechanisms to anti-PD(L)-1 treatments and are intended for a population of patients in immune escape from checkpoint inhibitor treatments.

- **OSE-279, A HUMANIZED ANTI-PD-1 MONOCLONAL ANTIBODY**

This anti-PD-1 is intended to enter Phase 1/2 clinical trials in a niche indication in immuno-oncology. This will enable the Company to own a patented anti-PD-1 that it may subsequently develop in combination with other products in its portfolio.

## IN THE FIELD OF AUTOIMMUNITY AND INFLAMMATION

- **FR104, START OF A PHASE 1/2 CLINICAL TRIAL IN KIDNEY TRANSPLANTATION**

FR104 is an immunomodulator consisting of an optimized monoclonal antibody fragment targeting the CD28 receptor, a key component of the destruction function of effector T lymphocytes which are deleterious in autoimmune diseases and transplantation.

The results of the Phase 1 clinical trial of FR104 showed good clinical and biological tolerance of the product. Its immunosuppressive activity in humans has demonstrated that the product has the potential to show clinical activity in the treatment of transplantation and immune-mediated diseases.

In December 2020, the French National Medicines Safety Agency (Agence Nationale de Sécurité du Médicament) and the Committee for the Protection of People gave their authorization to start a Phase 1/2 clinical trial evaluating FR104, administered for the first time in patients who have received a kidney transplant. This study is being conducted under a collaboration agreement between OSE Immunotherapeutics and the Centre Hospitalier Universitaire de Nantes, which is the sponsor.

This Phase 1/2 clinical trial aims to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of FR104 in patients who have received a kidney transplant.

- **OSE-127/S95011, START OF A PHASE 2 CLINICAL TRIAL FOR ULCERATIVE COLITIS**

OSE-127/S95011, an immunomodulatory monoclonal antibody targeting the CD127 receptor, the alpha chain of the Interleukin 7 receptor, is being developed under a two-step licensing option agreement granted to Servier for its development and marketing in autoimmune diseases.

The Phase 1 clinical trial of OSE-127/S95011 was completed at the end of 2019 with positive results showing a good safety and tolerability profile of the product. All pharmacokinetic and pharmacodynamic parameters were consistent and demonstrated dose-proportionality throughout the dose escalation to 10 mg/kg. These data made it possible to determine the administration schedule for the two independent Phase 2 clinical trials: one in ulcerative colitis sponsored by OSE, in progress since December 2020, and the other planned in Sjögren's Syndrome sponsored by Servier, which is scheduled to start in at the end of the 2nd quarter or beginning of the 3rd quarter 2021.

The phase 2 study in ulcerative colitis began in December 2020 with the inclusion of a first patient. This randomized, double-blind, placebo-controlled trial aims to assess the efficacy and safety of OSE-127/S95011 in patients suffering from moderate to severe active ulcerative colitis after failure, loss of response or intolerance to previous treatment(s).

- **OSE-230, FIRST PRESENTATION OF DATA CHARACTERIZING A NEW THERAPY THAT TRIGGERS THE RESOLUTION OF INFLAMMATION**

OSE-230 is an agonist antibody against ChemR23, also known as chemerin chemokine-like receptor 1 (CMKLR1), a G-protein coupled receptor (GPCR) expressed on myeloid immune cells known to modulate inflammation.

Most anti-inflammatory agents act using a mechanism that blocks pro-inflammation pathways. In contrast, OSE Immunotherapeutics is developing OSE-230 as a first-in-class therapeutic agent with the potential to resolve chronic inflammation by driving affected tissues to complete the inflammation program and restore tissue integrity.

Preclinical efficacy data for OSE-230 were presented at the annual FOCIS (Federation of Clinical Immunology Societies) meeting on October 29, 2020. The data show that OSE-230 is the first monoclonal antibody triggering the activation of specialized receptors of resolution to restore tissue homeostasis, integrity and functions. The product has a strong therapeutic potential in various chronic pathologies.

### **1.3 FORESEEABLE changes and future outlook**

#### **T CELL VACCINES**

- **TEDOPI®**

**Tedopi®** is currently being evaluated in a Phase 3 trial, called Atalante 1, in advanced NSCLC for HLA-A2 positive patients after failure from previous treatment with PD-1/PD-L1 checkpoint inhibitors.

In June 2019, at the end of the clinical data (including safety data) review, the Independent Data Monitoring Committee (IDMC) recommended that the Atalante 1 trial should be continued without any modifications.

On April 1, 2020, the Company announced the positive outcome of Step 1 of the Tedopi® Phase 3 clinical trial. Analysis of the data showed that the primary endpoint for this milestone was achieved with a 12-month survival rate in patients treated with Tedopi® and a 10% absolute difference in this survival rate compared to chemotherapy.

These results confirm the therapeutic benefit of Tedopi® in a patient group for which there is no confirmed treatment to date and which is awaiting new therapeutic options. The Company will initiate discussions with the regulatory authorities to analyze these positive clinical results and determine the best options to pursue the development of Tedopi® and maximize the positive benefit/risk ratio data obtained. At the same time, given that the positive Step 1 results significantly strengthened the value of Tedopi®, the Company is continuing to explore any potential partnering opportunities for the product.

Due to the global COVID-19 epidemic, the Company, in conjunction with the Independent Data Monitoring Committee (IDMC) and the Trial Steering Committee, analyzed the potential impact of this epidemic on the Atalante 1 trial. The clinical trials data could be strongly impacted by the worldwide COVID-19 pandemic and by the increased risk for patients with advanced lung cancer, as COVID-19 can cause serious pulmonary complications in this immunocompromised patient population. Moreover, for patient safety, several scientific and medical societies currently recommend the voluntary suspension of new patient recruiting in clinical trials in oncology.

Consequently, following the recommendation from both IDMC and Atalante 1 Steering Committee, OSE Immunotherapeutics voluntarily decided to terminate patient screening and accrual in the Step 2 initially planned and now canceled.

A Phase 2 clinical trial began in 2019, in collaboration with the GERCOR, the digestive cancer cooperative group. This is a maintenance trial using Tedopi® in combination with FOLFIRI versus FOLFIRI\* chemotherapy in locally advanced or metastatic pancreatic cancer. GERCOR is the sponsor of this Phase 2 maintenance trial using Tedopi® in patients with stable disease after four months of standard chemotherapy with FOLFIRINOX\*\*

Due to the COVID-19 pandemic, the screening and enrollment of new patients in TEDOPaM had been temporarily suspended in March 2020. After a review of the data collected before the end of March 2020 according to the initial protocol (Tedopi® alone or in combination with Opdivo® versus chemotherapy with FOLFIRI), the Independent Data Monitoring Committee (IDMC) of the trial recommended stopping the assessment of the treatment arm of Tedopi® in combination with Opdivo® and introducing a treatment arm of Tedopi® + chemotherapy (FOLFIRI). GERCOR has modified the treatment regimen accordingly and the first new enrollments are expected during the second quarter of 2021 (based on the COVID-19 impact) with an amended protocol comparing Tedopi® in combination with Folfiri versus Folfiri as maintenance therapy after induction therapy with Folfirinox. The main endpoint of the trial remains the one-year survival rate.

\* *FOLFIRI: a chemotherapy regimen combining folinic acid, fluorouracil and irinotecan*

\*\* *FOLFIRINOX: a chemotherapy regimen combining folinic acid, fluorouracil, irinotecan and oxaliplatin*

In March 2021, the National Medicines Safety Agency (ANSM) and the Committee for the Protection of People (CPP) gave their approval to start a new Phase 2 clinical trial evaluating Tedopi® in patients with ovarian cancer relapse (TEDOVA trial) sponsored by the ARCAGY-GINECO cooperative group. Tedopi® will be evaluated as a single agent and in combination with Keytruda® (pembrolizumab), a Merck checkpoint inhibitor, as maintenance therapy after chemotherapy in patients with ovarian cancer.

The TEDOVA trial will include three treatment arms and will evaluate Tedopi® as a monotherapy maintenance treatment or in combination with the anti-PD-1 Keytruda® versus the reference treatment in patients with ovarian cancer in a situation of platinum-sensitive relapse, and whose disease is controlled following chemotherapy with platinum.

Tedopi® could also be evaluated, in monotherapy or in combination with a checkpoint inhibitor, in a number of cancers of interest in which:

- There is a high therapeutic need,
- The role of HLA-A2 in immunosurveillance failures is established,
- The five tumor antigens are expressed at an advanced stage,

These include, for example, lung cancer (Tedopi® in combination), ovarian cancer and rarer tumors.

#### - COVEPIIT

Following the results of preclinical and *ex vivo* studies in humans, the development of CoVepiT, a vaccine against COVID-19 based on a vaccine technology that induces a sustained memory T lymphocyte response against multiple coronavirus targets, is continuing.

Following the authorization of the Federal Agency for Medicines and Health Products (FAMHP) and the Belgian Ethics Committee in April 2021, OSE Immunotherapeutics will launch a Phase 1 clinical trial with CoVepiT to evaluate its tolerability, reactogenicity and immunogenicity in healthy adult volunteers.

The CoVepiT development program is supported by €5.2 million of financing obtained as part of the PSPC-COVID call for projects, operated on behalf of the French State by Bpifrance as part of the Future Investments Program (PIA). It is led within a consortium led by OSE Immunotherapeutics, in partnership with the teams of Prof. Eric Tartour, Head of the biological immunology department at the European Hospital Georges-Pompidou-APHP and Professor at University of Paris, in charge of immune-monitoring, and with the teams of Prof. Odile Launay, Professor of infectious and tropical diseases at University of Paris and coordinator of the Cochin-Pasteur Clinical Investigation Center at the Cochin-AP-HP hospital, for the inclusion of patients in the study. It is subject to achieving certain criteria.

#### IN IMMUNO-ONCOLOGY: CLINICAL AND PRECLINICAL ADVANCES

##### - BI 765063 (OSE-172)

A new generation checkpoint inhibitor targeting suppressive myeloid cells via the SIRP $\alpha$  receptor: in April 2018, Boehringer Ingelheim acquired the global rights to the development, registration and marketing of BI 765063 (OSE-172) (a monoclonal antibody targeting SIRP $\alpha$ , expressed by the myeloid cell family), strengthening its constant commitment to research and innovation in immuno-oncology. According to the terms of the agreement, OSE Immunotherapeutics

received €15 million on contract signature, €10 million after regulatory authorization to launch Phase 1 and another €5 million in milestone payments when the first patient was included in the Phase 1 study. In total, OSE Immunotherapeutics could potentially receive over €1.1 billion according to predefined development, marketing and sales steps, plus royalties on net global sales of the product.

After obtaining regulatory authorizations in Belgium and France in March 2019 for the launch of Phase 1 aimed at evaluating BI 765063 in patients with advanced solid tumors, the first patient was treated in the trial in June 2019. Since then, the trial has been ongoing.

In June 2020, an OSE Immunotherapeutics publication in the Journal of Clinical Investigation (JCI) confirmed the new mechanism of BI 765063: for the first time, the OSE R&D team has identified the “Don’t Find Me” signal, a complementary mechanism mediated by SIRP $\alpha$  whereby cancer cells evade immune detection by preventing T lymphocytes from entering the heart of the tumor. The new anti-SIRP $\alpha$  strategy reverses this major resistance mechanism called “T lymphocyte exclusion” by releasing the brakes on T lymphocyte chemotaxis and migration into the tumor core.

The Company will continue the preclinical development of its other preclinical immuno-oncology products: CLEC-1, a new myeloid immune checkpoint that regulates the antitumor response, BiCKI®, the platform of anti-PD-1 bispecific checkpoint inhibitors and OSE-279, an anti-PD-1 similar to those on the market, such as Opdivo®. The entry of OSE-279 into Phase 1/2 clinical trials for a niche indication in immuno-oncology is planned for 2021. This would allow the Company to own a patented anti-PD-1 that it could subsequently develop in combination with other products in its portfolio.

#### IN THE FIELD OF AUTOIMMUNE DISEASES AND TRANSPLANTATION: TWO CLINICAL TRIALS STARTED AT THE END OF 2020 AND A NEW PRODUCT IN PRECLINICAL TRIALS

##### - **FR104**

With good clinical and biological tolerability and immunosuppressive activity in humans has demonstrated in Phase 1, FR104 has the potential to show clinical activity in the treatment of transplantation and immune-mediated diseases.

Since December 2020, FR104 is currently undergoing a Phase 1/2 clinical trial in patients who have received a kidney transplant. This Phase 1/2 clinical trial aims to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and efficacy of FR104 in patients who have received a kidney transplant. It is being carried out under a clinical collaboration agreement between OSE Immunotherapeutics and the Centre Hospitalier Universitaire de Nantes, which is the sponsor.

At the same time, OSE Immunotherapeutics is preparing a new Phase 2 clinical trial of FR104 in a niche indication for autoimmune diseases, a priori the Graves disease.

##### - **OSE-127/S95011**

OSE-127/S95011 is subject to a two-step licensing option granted to Servier for its development and marketing in autoimmune diseases. This licensing option will allow the product to be developed until the completion of a Phase 2 clinical trial. After positive Phase 1 clinical results of OSE-127/S95011 and the exercise of option 1 in February 2019, a Phase 2 clinical study has been underway in ulcerative colitis since December 2020, sponsored by OSE Immunotherapeutics and another Phase 2 trial for Sjögren's Syndrome sponsored by Servier should start at the end of the 2<sup>nd</sup> quarter/beginning of the 3<sup>rd</sup> quarter 2021. The enrollment of the first patient in the Phase 2 clinical trial in Sjögren's Syndrome will trigger a milestone payment of €5 million to OSE.

Option 2 is expected to be exercised upon completion of these two Phase 2 studies, with priority being given to the study in Sjögren's syndrome. Further development beyond Phase 2, if Phase 2 of this licensing option is validated, will be carried out by Servier.

Product development will also continue until the Phase 2 clinical trial as part of the EFFIMab consortium (with public and private partners and with OSE Immunotherapeutics as leader). Continued development after this Phase 2 will be ensured by Servier under the licensing option concluded in December 2016.

- **OSE-230**

The Company will continue the preclinical development of OSE-230, a ChemR23 agonist antibody, in chronic inflammation. This first-in-class therapeutic agent has the potential to activate the physiological pathways of chronic inflammation and restore the integrity of the pathological tissue.

The Company continues to seek new collaboration or license agreements that could be initiated at various stages of product development, with industry players involved in the field of activation and regulation immunology and in therapeutic combinations of high clinical interest.

### **SIGNIFICANT EVENTS SINCE THE END OF THE FISCAL YEAR**

#### **JANUARY 2021**

Received €1.3 million of financing from Bpifrance for the development of OSE-127/S95011 as part of Bpifrance's support for industrial strategic innovation projects (ISI) for the EFFIMab collaborative project, dedicated to assessing OSE 127/S95011, an interleukin-7 (IL-7R) antagonist, developed in partnership with Servier. This new €1.3 million of financing was triggered by the completion of several key milestones for OSE-127/S95011, including the strengthening of preclinical and translational data for ulcerative colitis (UC), at the end of the Phase 1 clinical trial, the first regulatory authorization for a Phase 2 clinical trial for UC and specific steps in the manufacture of the product.

#### **FEBRUARY 2021**

A new collaboration agreement with MAbSilico, an innovative TechBio company based in Tours, France and specializing in the use of artificial intelligence algorithms to discover and characterize therapeutic antibodies. The extension of their collaboration involves ten new antibody programs.

OSE Immunotherapeutics has signed a €25 million financing with the European Investment Bank to expand the clinical development of its leading immunotherapy programs. This financing will consist of three tranches divided into two tranches of €10 million and one of €5 million.

#### **MARCH 2021**

OSE IMMUNOTHERAPEUTICS announces that new preclinical data on CLEC-1 (a C-type lectin receptors), a novel myeloid checkpoint target blocking the "Don't Eat Me" signal, BiCKI®-IL-7, a bifunctional targeting PD-1 and IL-7 and OSE-230 an innovative monoclonal agonist treatment that triggers the resolution of inflammation, have been selected for presentation as an e-poster(1) at the AACR (American Association of Cancer Research) virtual annual meeting from April 10 to 15, 2021.

OSE Immunotherapeutics and the French cooperative group ARCAGY-GINECO have announced that the National Agency for the Safety of Medicines (ANSM) and the Committee for the Protection of People (CPP) gave their authorization to start a new Phase 2 clinical trial evaluating Tedopi® in patients with ovarian cancer relapse (TEDOVA trial). Tedopi® will be evaluated as a single agent and in combination with Keytruda® (pembrolizumab), a Merck checkpoint inhibitor, as maintenance therapy after chemotherapy in patients with ovarian cancer.

#### **APRIL 2021**

On April 1, 2021, OSE Immunotherapeutics received authorization from the Federal Agency for Medicines and Health Products (FAMHP) and the Belgian Ethics Committee to start a Phase 1 clinical trial with CoVepiT. This study will assess the safety, reactogenicity and immunogenicity of the vaccine in healthy adult volunteers.

#### **1.4 Research and development activities**

The Company conducts Research & Development projects in T-cell-based vaccines (Tedopi®, CoVepiT), immuno-oncology (BI 765063 (OSE-172), BiCKI® platform, CLEC-1, OSE-279), and in autoimmunity (FR104, OSE-127/S95011) and inflammation (OSE-230), on its own or in partnership.

In fiscal year 2020, R&D expenses amounted to €22.4 million and research tax credits recognized in respect of 2020 were €5.1 million.

#### **Tedopi®**

- The international Phase 3 clinical trial of Tedopi® (Atalante 1) is underway in patients with non-small cell lung cancer (NSCLC) after failure from previous treatment with PD-1/PD-L1 checkpoint inhibitors.

The trial was planned in two steps: a first step including approximately 100 patients overall with a planned analysis of data on the percentage of patients achieving 12 months' survival. At the end of this first step, and depending on the results obtained, the Company had to decide on the best development strategy for Tedopi® in lung cancer after failure of checkpoint inhibitor therapy.

On April 1, 2020, the Company announced positive results for Step 1 of the study. Analysis of the data showed that the primary endpoint for this milestone was achieved with a 12-month survival rate in patients treated with Tedopi® and a 10% absolute difference in this survival rate compared to chemotherapy.

These results confirm the therapeutic value of Tedopi® in a population of patients for whom there is currently no validated treatment, pending new therapeutic options. The Company will initiate discussions with the regulatory authorities to analyze these positive clinical results and determine the best options to pursue the development of Tedopi® and maximize the positive benefit/risk ratio data obtained. At the same time, given that the positive step 1 results significantly strengthened the value of Tedopi®, the Company is continuing to explore any potential partnering opportunities for the product.

- A Phase 2 clinical trial of Tedopi® is underway in pancreatic cancer, sponsored by the cooperative group GERCOR.

Due to the COVID-19 pandemic, the screening and enrollment of new patients in TEDOPaM had been temporarily suspended in March 2020. After a review of the data collected before the end of March 2020 according to the initial protocol (Tedopi® alone or in combination with Opdivo® versus chemotherapy with FOLFIRI), the Independent Data Monitoring Committee (IDMC) of the trial recommended stopping the assessment the treatment arm of Tedopi® in combination with Opdivo® and introducing a treatment arm of Tedopi® + chemotherapy (FOLFIRI). GERCOR has modified the treatment regimen accordingly and the first new enrollments are expected during the second quarter of 2021 (based on the COVID-19 impact) with an amended protocol comparing Tedopi® in combination with FOLFIRI versus FOLFIRI as maintenance therapy after induction therapy with FOLFIRINOX. The main endpoint of the trial remains the one-year survival rate.

*\*\* FOLFIRINOX: a chemotherapy regimen combining folinic acid, fluorouracil, irinotecan and oxaliplatin*

*\* FOLFIRI: a chemotherapy regimen combining folinic acid, fluorouracil and irinotecan*

- In March 2021, the National Medicines Safety Agency (ANSM) and the Committee for the Protection of People (CPP) gave their authorization to start a new Phase 2 clinical trial evaluating Tedopi® in patients with ovarian cancer relapse (TEDOVA trial) sponsored by the ARCAGY-GINECO cooperative group. Tedopi® will be evaluated as a single agent and in combination with Keytruda® (pembrolizumab), a Merck checkpoint inhibitor, as maintenance therapy after chemotherapy in patients with ovarian cancer.

The TEDOVA trial will include three treatment arms and will evaluate Tedopi® as a monotherapy maintenance treatment or in combination with the anti-PD-1 Keytruda® versus the reference treatment in patients with ovarian cancer in a situation of platinum-sensitive relapse, and whose disease is controlled following chemotherapy with platinum.

- OSE Immunotherapeutics announces that new preclinical data on CLEC-1 (a C-type lectin receptors), a novel myeloid checkpoint target blocking the "Don't Eat Me" signal, BiCKI®-IL-7, a bifunctional targeting PD-1 and IL-7 and OSE-230 an innovative monoclonal agonist treatment that triggers the resolution of inflammation, have been selected for presentation as an e-poster(1) at the AACR (American Association of Cancer Research) virtual annual meeting from April 10 to 15, 2021.

- OSE Immunotherapeutics and the French cooperative group ARCAGY-GINECO have announced that the National Agency for the Safety of Medicines (ANSM) and the Committee for the Protection of People (CPP) gave their

authorization to start a new Phase 2 clinical trial evaluating Tedopi® in patients with ovarian cancer relapse (TDOVA trial). Tedopi® will be evaluated as a single agent and in combination with Keytruda® (pembrolizumab), a Merck checkpoint inhibitor, as maintenance therapy after chemotherapy in patients with ovarian cancer.

The TDOVA trial will include three treatment arms and will evaluate Tedopi® as a monotherapy maintenance treatment or in combination with the anti-PD-1 Keytruda® versus the reference treatment in patients with ovarian cancer in a situation of platinum-sensitive relapse, and whose disease is controlled following chemotherapy with platinum.

#### **CoVepiT**

- CoVepiT was developed from epitopes to fight infections caused by SARS-CoV-2, the virus responsible for COVID-19. The CoVepiT program is based on a clinically validated technology (Memopi®) that induces the response of memory T lymphocytes in barrier tissues against multiple SARS-CoV-2 targets. This T-response ensures long-term protective immunity. In addition, this vaccine is designed to anticipate ongoing recurrent virus mutation and evolution, that should reinforce its long-term protective potential.
- CoVepiT 1 was a human *ex vivo* clinical study, conducted in 120 convalescent COVID-19 subjects versus unexposed subjects, which enabled OSE to identify T memory immuno-dominant epitopes after infection with COVID-19, selected for their strong immunogenicity potential.
- New SARS-CoV-2 mutated variants spread rapidly across Europe, some of them bearing mutations in some key targets of the virus in particular the Spike protein and Nucleoprotein. On the basis of new analyses on nearly 226,000 different virus sequences isolated on a global scale, the OSE bioinformatics team confirmed no mutations had occurred in the very stable region of the viral genome of the 11 targets selected by OSE, which reinforces the multiplicative approach against these virus proteins to generate a T lymphocyte response. The CoVepiT vaccine therefore covers both initial and new SARS-CoV-2 strains and variants.
- All of these results, and the probable emergence of new SARS-CoV-2 variants, constitute a solid rationale for continuing the development of CoVepiT. Following the authorization of the Federal Agency for Medicines and Health Products (FAMHP) and the Belgian Ethics Committee (April 1<sup>st</sup>, 2021), OSE Immunotherapeutics will launch a Phase 1 clinical trial with CoVepiT to evaluate the tolerability, reactogenicity and immunogenicity in healthy adult volunteers.

#### **BI 765063 (OSE-172)**

- BI 765063 is being developed under a license and collaboration agreement with Boehringer Ingelheim, which acquired the exclusive rights to the product in April 2018.
- BI 765063 is undergoing a Phase 1 clinical trial in advanced solid tumors, used as monotherapy or in combination with a monoclonal antibody and an antagonist of PD-1 and Boehringer Ingelheim, BI 754091 (first patient treated in June 2019).
- The screening and enrollment of new patients were impacted by the COVID-19 situation during the second quarter of 2020 but resumed thereafter and since then the clinical study has continued.
- In June 2020, an OSE Immunotherapeutics publication in the Journal of Clinical Investigation (JCI) confirmed the new mechanism of BI 765063: for the first time, the OSE R&D team has identified the “Don’t Find Me” signal, a complementary mechanism mediated by SIRPα whereby cancer cells evade immune detection by preventing T lymphocytes from entering the heart of the tumor. The new anti-SIRPα strategy reverses this major resistance mechanism called “T lymphocyte exclusion” by releasing the brakes on T lymphocyte chemotaxis and migration into the tumor core.

#### **BiCKI®**

- BiCKI® is a bispecific fusion protein platform built around a key backbone component anti-PD-1 (OSE-279). This is a new reference treatment in oncology merged with innovative immunotherapy targets. The BiCKI® platform aims

to inhibit key immune checkpoint inhibitors while simultaneously delivering cytokines capable of modulating regulatory T cells, and/or increasing the responses of exhausted T cells within the tumor. It can also incorporate other therapeutic methods to modify the tumor microenvironment by delivering, for example, costimulation signals to restore the activity of antitumor T lymphocytes or restore phagocytic functions and macrophage polarization.

- Based on an anti-PD-1 bifunctional antibody platform technology, BiCKI® is designed to expand the type of patients responding to immunotherapies. This is the second generation of PD-(L)1 inhibitors used to increase antitumor efficacy in hard-to-treat cancers by addressing untapped immune escape mechanisms. The first cytokine selected to be paired with the anti-PD-1 in the bispecific antibody is Interleukin-7 (IL-7), which has been shown to improve immune functions and cancer immunotherapy efficacy. Preclinical results have shown that the bifunctional anti-PD-1/IL-7 from OSE immuno therapeutics modifies the immune balance in favor of the effector T cells by stimulating the functions of these cells and by disarming the regulatory T cells.

#### **OSE-279**

- OSE-279 is a humanized anti-PD monoclonal antibody. It should enter Phase 1/2 clinical trial in 2021 for a niche indication in immuno-oncology. This would allow the Company to own a patented anti-PD-1 that it could subsequently develop in combination with other products in its portfolio.

#### **CLEC-1**

- The OSE Immunotherapeutics teams have characterized a new CLEC-1 myeloid checkpoint target (among CLR receptors - C-type lectin receptors), and have identified monoclonal antibody antagonists that block this new signal "Don't Eat Me". They increase both the phagocytosis of tumor cells by macrophages and the uptake of antigens by dendritic cells. These data were presented to the 2020 meeting of the American Association for Cancer Research (AACR).
- The identification of CLEC-1 and its antagonists constitute an exciting innovative step in cancer immunotherapy.

#### **OSE-127/S95011**

- This product is developed in collaboration with Servier under a collaboration and license agreement signed in December 2016.
- This study was a first-in-human dose escalation, randomized, double-blind, placebo-controlled Phase 1 clinical trial, aimed to evaluate the safety and tolerability of single- and multiple-ascending intravenous and subcutaneous doses of OSE-127/S95011 in 63 healthy volunteers. Secondary endpoints included measures of pharmacokinetics, pharmacodynamics and immunogenicity to help assess and understand how the drug is absorbed and metabolized.

In December 2019, the positive results of the study showed a good safety and tolerability profile of the product. All pharmacokinetic and pharmacodynamic parameters were consistent and demonstrated dose proportionality throughout the dose escalation to 10 mg/kg. These data made it possible to determine the dosing and administration schedule used in each of the two parallel Phase 2 clinical trials:

- In ulcerative colitis: Phase 2 clinical trial sponsored by OSE Immunotherapeutics with the enrollment of the first patient in December 2020.

This randomized, double-blind, placebo-controlled Phase 2 clinical trial aims to assess the efficacy and tolerability of OSE-127/S95011 in patients suffering from moderate to severe active ulcerative colitis after failure, loss of response or intolerance to previous treatment(s).

The patient population (with moderate to severe ulcerative colitis, failure or intolerance to immunosuppressants, anti-TNF $\alpha$ , anti-integrins, ustekinumab and/or corticosteroids) was selected because of these patients' need for new treatment options to avoid disease-related complications for as long as possible and in which the safety profile of OSE-127/S95011 can be reliably assessed.

- In Sjögren's Syndrome: Phase 2 clinical trial sponsored by Servier, scheduled to start at the end of the 2nd

quarter/beginning of the 3rd quarter 2021.

#### **FR104**

- The Company regained the worldwide rights to FR104, its CD18 first-in-class antagonist, from Janssen Biotech Inc., with effect from December 31, 2018. The positive results of Phase 1 clinical proof-of-concept study of FR104, combined with the preclinical tolerability profile and the efficacy data for a large number of preclinical models of inflammatory and autoimmune diseases support the continuation of the product's clinical development.
- In December 2020, the French National Medicines Safety Agency (Agence Nationale de Sécurité du Médicament) and the Committee for the Protection of People gave their authorization to start a Phase 1/2 clinical trial evaluating FR104, administered for the first time in patients who have received a kidney transplant. This study is carried out under a collaboration agreement between OSE Immunotherapeutics and the Center Hospitalier Universitaire de Nantes, which is the sponsor.
- This Phase 1/2 clinical study aims to evaluate the safety, tolerance, pharmacokinetics, pharmacodynamics and efficacy of FR104 in patients who have received a renal transplant.
- At the same time, OSE Immunotherapeutics is preparing a new Phase 2 clinical trial of FR104 in a niche indication for autoimmune diseases, Graves disease.

#### **OSE-230**

- OSE-230 is an agonist antibody against ChemR23, also known as chemerin chemokine-like receptor 1 (CMKLR1), a G-protein coupled receptor (GPCR) expressed on myeloid immune cells known to modulate inflammation.
- Most anti-inflammatory agents act using a mechanism that blocks pro-inflammation pathways. In contrast, OSE Immunotherapeutics is developing OSE-230 as a first-in-class therapeutic agent with the potential to resolve chronic inflammation by driving affected tissues to complete the inflammation program and restore tissue integrity.
- Preclinical efficacy data for OSE-230 were presented at the annual FOCIS (Federation of Clinical Immunology Societies) meeting on October 29, 2020. The data show that OSE-230 is the first monoclonal antibody triggering the activation of specialized receptors of resolution to restore tissue homeostasis, integrity and functions. The product has a strong therapeutic potential in various chronic pathologies.

Based on OSE's diverse scientific and technological platforms (neoepitopes, agonist or antagonist monoclonal antibodies), the Company is pursuing advancement of new innovative research programs.

#### **1.5 Main risks and uncertainties to which the Company is exposed**

See Section 3 of the Universal Registration Document.

#### **1.6 Use of financial instruments by the Company**

The Company used financial instruments during the past fiscal year (see Note 3 to the financial statements, Section 18.1.6 of the Universal Registration Document).

#### **1.7 Transactions with related parties**

See Section 17.1.2 of the Universal Registration Document.

## **2. FINANCIAL STATEMENTS FOR THE FISCAL YEAR ENDING DECEMBER 31, 2020**

### **Presentation of the Company's statutory financial statements**

Please note that the presentation rules regarding and the valuation methods used to prepare the statutory financial statements for the fiscal year ended comply with the regulations in force.

General accounting policies have been applied in accordance with the prudence principle, in line with the following basic assumptions:

- Going concern;
- Consistency of accounting rules from one fiscal year to another;
- Independence of fiscal years.

and in accordance with the general rules for preparing and presenting the separate financial statements as described in the opinion of the French National Accounting Council (Article R. 123-180 of the Commercial Code and Art. 531-1 § 1 of the French General Tax Code).

For more information on the accounting rules and methods, please see the notes to the statutory financial statements.

#### ***2.1.1 Statement of financial position***

The Company's overall statement of financial position at December 31, 2020, was €135,515,000 versus €128,403,000 the previous fiscal year.

Assets include €50,814,000 in equity interests, €42,734,000 in intangible assets, €947,000 in property, plant and equipment, €1,074,000 in trade receivables and €8,092,000 in other receivables, €29,358,000 in cash and cash equivalents and marketable securities and €2,496,000 in prepaid expenses.

Apart from share capital of €3,597,000, liabilities include €132,170,000 in share premiums (€13,261,000) in retained earnings, €1,060,000 in provisions for risks and expenses, €9,232,000 in conditional advances, €6,978,000 in borrowings from credit institutions, €10,278,000 in trade payables, €1,902,000 in other tax and social security liabilities and €704,000 in deferred income.

#### ***2.1.2 Income statement***

In 2020, the Company generated revenue of €9,743,000, mainly comprised of the upfront payment from Servier, and recognized as expenses are incurred, the sale of products to Servier to conduct their Phase 2 clinical trial and the re-invoicing to Boehringer Ingelheim of development costs incurred by OSE for BI 765063 (OSE-172).

In 2019, the Company generated revenue of €10,602,000, mainly comprised of the upfront payment from Servier, recognized as expenses were incurred, and of the re-invoicing to Boehringer Ingelheim of development costs borne by OSE for BI 765063 (OSE-172).

In 2020, other operating income amounted to €1,301,000 and mainly corresponds to subsidies received during the fiscal year.

In 2019, other operating income stood at €16,653,000, corresponding mainly to milestone payments received from Boehringer Ingelheim, to the upfront payment received following the signing of a license agreement with CKD and subsidies received over the fiscal year.

2020 operating expenses totaled €33,469,000 versus €30,639,000 in 2019.

Operating expenses by type – in €k	2020	2019	Change	Change %
Purchases and external expenses	25,949	23,629	2,320	10%
Taxes and similar payments	131	129	2	2%
Employee benefits expense	6,710	5,687	1,023	18%
Allocation to depreciation, amortization and provisions	427	1,013	-586	-58%
Other expenses	251	181	70	39%
<b>Total</b>	<b>33,469</b>	<b>30,639</b>	<b>2,829</b>	<b>9%</b>

The “external expenses” item in 2020 broke down as follows:

- €20,268,000 for subcontracting: conducting the Phase 3 clinical trial of Tedopi®, conducting and validating GMP batches for OSE-127/S95011 and BI 765063 (OSE-172), Phase 1 clinical trials for OSE-127/S95011 and BI 765063 (OSE-172), consulting international clinical experts on the pivotal Phase 3 trial with Tedopi®, for OSE-127/S95011 and BI 765063 (OSE-172);
- €3,630,000 in fees: fees relating to the Company’s status as a listed company and legal transactions, fees particularly for industrial property;
- €2,051,000: cost of premises, insurance premiums, travel expenses, consumables and others.

Employee benefits expense in 2020 totaled €6,710,000 versus €5,687,000 in 2019.

Average headcount was 45 in 2020 versus 36 in 2019.

Operating income for fiscal year 2020 was -€22,425,000.

With a net financial loss of €264,000, extraordinary income of €220,000 and tax income of €5,120,000 (research tax credit), the net loss for fiscal year 2020 was €17,398,000.

## **2.2 Presentation of the Company's consolidated financial statements**

The consolidated financial statements of OSE Immunotherapeutics and its subsidiaries (the Group), are presented in euros and are drawn up in accordance with IFRS standards (International Financial Reporting Standard) as adopted by the European Union.

### ***2.2.1 Consolidated statement of financial position***

The Company’s consolidated statement of financial position at December 31, 2020, was €96,973,000 versus €88,933,000 the previous fiscal year.

### ***2.2.2 Consolidated income statement***

The Group recognized €10,418,000 in revenue in 2020 versus €25,952,000 in revenue generated in 2019.

Operating expenses by function in €K	2020 (consolidated)	2019 (consolidated)
R&D expenses	22,355	21,655
Overhead expenses	4,783	3,898
Expenses related to share-based payments	2,283	1,868
Total	29,421	27,421

R&D expenses in 2020 mainly comprised:

- €22,063,000 in subcontracting and fees, before recording the research tax credit of €5,120,000 and subsidies received in the amount of €613,000
- €4,554,000 in employee benefits expense allocated to research and development
- €1,472,000: seminars, insurance premium, storage costs and others.

Overhead expenses in 2020 mainly comprised:

- €1,827,000 in fees: accounting, legal, consultancy, stock-market listing and advertising costs;
- €1,800,000 in employee benefits expense allocated to operations management, finance, communication and Company Secretary;
- €222,000 in Directors' fees
- €934,000: cost of premises, insurance premiums, travel expenses, and others.

Operating income for fiscal year 2020 was -€18,989,000.

Net income for fiscal year 2020 was -€16,555,000.

### **2.3 Indebtedness (statutory financial statements and consolidated financial statements)**

#### **Statutory financial statements**

Other receivables amount to €8,092,000, of which €6,224,000 in tax receivables, €1,192,000 in current account advances granted to its subsidiary OPI, €450,000 in accrued revenue (subsidies and miscellaneous), and €99,000 in assets receivable.

The cash available to OSE Immunotherapeutics stood at €29,358,000 at December 31, 2020, of which €10,267,000 in cash and cash equivalents and €19,091,000 in term deposits and other short-term investments.

The total amount of the Company's operating liabilities is €12,180,000 (comprising €10,278,000 in trade payables and €1,902,000 in tax and social security liabilities).

The amount of loans with financial institutions is €6,978,000 (French Government-Guaranteed loan) and the amount of repayable advances is €9,232,000.

#### **Consolidated financial statements**

Other receivables amount to €9,390,000 and correspond to tax receivables, prepaid income and accrued income (prepaid expenses).

Funds available to the Group stood at €29,368,000 in net cash at December 31, 2020.

The total amount of the Company's operating liabilities is €12,394,000 (comprising €10,286,000 in trade payables and €2,108,000 in tax and social security liabilities).

The amount of loans with financial institutions is €6,971,000 (French Government-Guaranteed loan) and the amount of repayable advances is €9,629,000.

Other liabilities amount to €1,088,000 and correspond to deferred income.

## 2.4 Expenses mentioned in Article 39-4 of the French General Tax Code

In accordance with Article 223 quarter of the French General Tax Code, please note that for the fiscal year ending on December 31, 2020, there were no expenditure or costs of the type qualifying as "extravagant expenditure" under point 4 of Article 39 of the General Tax Code, or excessive amortization as referred to in the same point 4.

## 2.5 Information on payment terms for suppliers and customers

Invoices received and not paid on the reporting date							
Maturities	1 to 30 days	31 to 60 days	61 to 90 days	91 days and over	Total	Invoices not yet due	Total #401
Number of invoices	276	86	15	6	383	235	618
Amount incl. VAT in €K	2 777	2 377	115	465	5 734	1 648	7 382
% of amount incl. VAT of purchases during the fiscal year	9%	8%	0%	1%	18%	5%	24%

Invoices received and not paid on the reporting date which are past due							
Maturities	1 to 30 days	31 to 60 days	61 to 90 days	91 days and over	Total	Invoices not yet due	Total #411
Number of invoices	4	-	-	-	4	-	4
Amount incl. VAT in €K	191	-	-	-	191	-	191
% of revenue incl. VAT during the fiscal year	2%	0%	0%	0%	2%	0%	2%

We hereby inform you that the Company's financial statements as submitted show trade payables in the amount of €10,278,000 at December 31, 2020.

In accordance with the provisions of Articles L. 441-6-1 and D. 441-4 of the French Commercial Code, please find below the following information relating to the breakdown of the balance of trade payables at the close of the last two fiscal years by due date:

Balance of trade payables and receivables at December 31, 2020, by due date (in €k):

Balance of trade payables and receivables at December 31, 2019, by due date (in €k):

## 2.6 The Company's results over the last five fiscal years

In accordance with the provisions of Article R. 225-102 of the Commercial Code, the Company's results over the last five fiscal years can be found in Note 1.

## 2.7 Proposed appropriation of net income for the fiscal year

The separate financial statements the fiscal year ended on December 31, 2020, show a loss of €17,398,439, which we propose to appropriate to retained earnings, which, as a result, will move from -€13,261,403 to -€30,659,742.

In order to comply with the provisions of Article 243 bis of the General Tax Code, please note that no dividends have been

Invoices received and not paid on the reporting date							
Maturities	1 to 30 days	31 to 60 days	61 to 90 days	91 days and over	Total	Invoices not yet due	Total #401
Number of invoices	276	86	15	6	383	235	618
Amount incl. VAT in €K	2 777	2 377	115	465	5 734	1 648	7 382
% of amount incl. VAT of purchases during the fiscal year	9%	8%	0%	1%	18%	5%	24%

Invoices received and not paid on the reporting date which are past due							
Maturities	1 to 30 days	31 to 60 days	61 to 90 days	91 days and over	Total	Invoices not yet due	Total #411
Number of invoices	4	-	-	-	4	-	4
Amount incl. VAT in €K	191	-	-	-	191	-	191
% of revenue incl. VAT during the fiscal year	2%	0%	0%	0%	2%	0%	2%

distributed over the last three fiscal years.

Invoices received and not paid on the reporting date							
Maturities	1 to 30 days	31 to 60 days	61 to 90 days	91 days and over	Total	Invoices not yet due	Total #401
Number of invoices	73	15	-	15	103	124	227
Amount incl. VAT in €K	2,147	146	-	511	2,805	1,471	4,276
% of amount incl. VAT of purchases during the fiscal year	8.3%	0.6%	0.0%	2.0%	10.9%	5.7%	16.6%
Invoices received and not paid on the reporting date which are past due							
Maturities	1 to 30 days	31 to 60 days	61 to 90 days	91 days and over	Total	Invoices not yet due	Total #411
Number of invoices	-	1	4	2	7	5	12
Amount incl. VAT in €K	-	29	14	20	62	181	243
% of revenue incl. VAT during the fiscal year	0.0%	0.1%	0.0%	0.1%	0.2%	0.5%	0.7%

### **3. SUBSIDIARIES AND EQUITY INTERESTS – INVESTMENT SECURITIES**

#### **3.1 Subsidiary activities**

The activity of our subsidiary OPI is limited to managing the industrial property of our OSE-2101 technology. The activity of our subsidiary OSE Immunotherapeutics Inc. remains limited at the current time. Over the medium term, it will be used to support international scientific or pharmaceutical collaborations.

#### **3.2 Equity holdings or takeovers**

N/A.

#### **3.3 Controlled company**

Since March 25, 2014, the Company holds all capital and voting rights in OPI and OSE Immunotherapeutics Inc., established in the State of Delaware in 2017, and is managed by Alexis Peyroles as Chief Executive Officer.

### **EMPLOYEE SHAREHOLDING**

In accordance with the provisions of Article L. 225-102 of the French Commercial Code, please note that there were thirty-two employee shareholders in the Company on the last day of the fiscal year, i.e., December 31, 2020, the most important of which (in terms of share ownership on the basis of 17,983,038 shares) were as follows:

- Dominique Costantini, whose employment contract dates from July 1, 2014, as Director of Development, who holds 1,947,330 shares, representing 10.83% of share capital at December 31, 2020.
- Alexis Peyroles, Chief Executive Officer, whose employment contract dates from July 1, 2014, as Chief Operations Officer, who holds 503,499 shares (directly) and 265,000 shares (via his company, Aperana Consulting), representing 4.27% of share capital at December 31, 2020.
- Maryvonne Hiance, whose employment contract dates from May 31, 2016, as Director of Public Relations, who holds 236,666 shares (directly) and 187,418 shares (via her company, Hiance MD2A), representing 2.36% of share capital at December 31, 2020.
- Nicolas Poirier, whose employment contract dates from May 31, 2016, as Chief Scientific Officer, who holds 92,802 shares, representing 0.52% of share capital at December 31, 2020.

On December 5, 2018, the Board of Directors approved in principle the issue and allocation of 150,000 free shares to employees who are not corporate officers of the Company and gave all powers to the CEO to issue and allocate said shares. As such, on March 12, 2019, the Chief Executive Officer decided to issue and allocate 149,200 free shares to employees who are not corporate officers of the Company (leading to the acquisition of 141,800 free shares recognized by the Board of Directors on March 26, 2020).

On June 26, 2019, the Board of Directors approved in principle the issue and allocation of 150,000 free shares to employees who are not corporate officers of the Company and gave all powers to the CEO to issue and allocate said shares. As such, on June 26, 2019, the Chief Executive Officer decided to issue and allocate 148,400 free shares to employees who are not corporate officers of the Company (leading to the acquisition of 145,300 free shares by the Chief Executive Officer on June 27, 2020).

On June 17, 2020, the Board of Directors approved in principle the issue and allocation of 250,000 free shares to employees who are not corporate officers of the Company and gave all powers to the Chief Executive Officer to issue and allocate said shares. Thus, on June 18, 2020, the Chief Executive Officer decided to issue and allocate 244,500 free shares to employees who are not corporate officers of the Company.

However, the Company does not have any employee shareholder whose shares are subject to collective management as per the above-mentioned article (i.e., as part of an employee savings scheme or company mutual fund).

**4. INFORMATION ON THE FINANCIAL RISKS RELATING TO THE EFFECTS OF CLIMATE CHANGE**

Given the nature of its business, the Group is not significantly exposed to environmental risks and has not identified any financial risks relating to the effects of climate change. The risks of climate change are limited due to the fact that the Company is not involved in any industrial activity, marketing or research and development.

**5. CONTROL MECHANISM**

Article 18 of the bylaws gives double voting rights to all fully paid-up shares that have been registered in the name of the same shareholder for at least two years.

APART these double voting rights, there are no other special rights attached to the shares.

There are also no control mechanisms in employee shareholding arrangements or agreements between shareholders of which the Company is aware and which could lead to restrictions on share transfers.

**6. GENERAL INFORMATION ON THE COMPANY AND ITS SHARE CAPITAL**

**6.1 Identity of the Company**

(i) Name

The name of the Company is OSE Immunotherapeutics.

(ii) Registered office

The registered office of the Company is: 22 boulevard Benoni Goullin, 44200 Nantes.

(iii) Legal form

OSE Immunotherapeutics is a limited company (*société anonyme*) with a Board of Directors, whose shares have been listed in compartment C of Euronext Paris under ISIN code FR0012127173 since March 30, 2015.

(iv) Capital

The share capital of OSE Immunotherapeutics currently stands at three million five hundred and ninety-six thousand six hundred and seven euros and sixty cents (3,596,607.60). It is made up of seventeen million nine hundred and eighty-three thousand and thirty-eight (17,983,038) shares with twenty (20) euro cents par value, all of the same class.

(v) Company's buyback of its own shares

The Combined General Shareholders' Meeting of June 16, 2019, authorized the Board of Directors to implement a share buyback program in the conditions described in Section 18.1.6 (Note 4.4 to the consolidated financial statements) of this Universal Registration Document.

In this respect, the Company carried out the following transactions in fiscal year 2020:

Number of shares purchased	188,680 shares
Average purchase price	€6.11
Number of shares sold	197,233 titles
Average sale price	€6,266
Total trading expenses	N/A
Number of shares used in 2020	8,553 shares
Number of shares registered in the name of the Company at fiscal year end and percentage of share capital	32,030 shares (i.e. 0.18%)
Value measured at average purchase price	€195,703
Total nominal value	€6,406

All of these purchases were made under the liquidity agreement with Invest Securities covering the Company's shares. As at the date of the Board of Directors meeting of March 26, 2021, the number of Treasury shares held by the Company stood at 25,543 shares, representing 0.14% of share capital.

(vi) Term

The Company was incorporated for a term of 99 years from the date of its registration with the Trade and Companies Register.

(vii) Incorporation details

The Company is registered with the Nantes Trade and Companies Register under number 479,457,715.

(viii) APE code

The APE code of OSE Immunotherapeutics is as follows: 7211Z.

(ix) Consultation of legal documentation

At the registered office of OSE Immunotherapeutics, at the register of the Nantes Commercial Court and on the Company's website: <http://ose-immuno.com/>

(x) Company's purpose

The purpose of OSE Immunotherapeutics in France and abroad is:

- The design, research and development of healthcare products from creation to obtaining marketing authorization, and all related operations including marketing;
- The acquisition, filing, obtaining, sale or licensing of all patents, brands, licenses and use processes;
- The acquisition of interests in any companies or undertakings already established or to be established, in France or abroad, whether or not they have a similar purpose to that of the Company;
- The provision of services, consultancy in research and development, marketing or commercial consultancy, consultancy on market access (pricing and reimbursement), structural audits in the field of healthcare, pharmaceuticals, cosmetics, nutrition and veterinary;
- And, more generally, all industrial, commercial, financial, civil, intangible property or real estate transactions directly or indirectly related to one of the above purposes or to any similar or related purpose that could be useful to the achievement and development of the Company's business;
- It may carry out any transactions that are compatible with, related to and contribute to achieving this purpose.

(xi) Fiscal year

The fiscal year of OSE Immunotherapeutics begins on January 1 and ends on December 31 of each year.

(xii) General Shareholders' Meetings

See Section 19.2.2 of the Universal Registration Document and Articles 29–35 of the Company's bylaws.

(xiii) Shareholding disclosure thresholds

The Company's bylaws provide that the crossing of thresholds will be subject to the following disclosures:

### **ARTICLE 16 – DISCLOSURE THRESHOLDS**

Pursuant to Article L. 233-7 of the French Commercial Code, any individual or legal entity, acting alone or in concert, within the meaning of Article L. 233-10 of the French Commercial Code, who comes to hold or ceases to hold a number of shares representing a fraction equal to 5%, 10%, 15%, 20%, 25%, 30%, 33.33%, 50%, 66.66%, 90% or 95% of the share capital or voting rights, is required to disclose to the Company no later than the close of trading on the fourth trading day following the date on which the aforementioned shareholding threshold is crossed, the number of shares and voting rights held. The individual required to disclose the above information shall specify the number of securities held giving future access to the share capital and related voting rights.

A shareholder who has not properly made the required disclosures as referred to above shall be stripped of the voting rights attached to the shares in the conditions pursuant to the French Commercial Code.

(xiv) Identification of bearer securities

### **ARTICLE 1 – TYPE OF SHARES**

Shares are either registered or bearer shares, at the shareholder's choice. They can only be bearer shares once they are fully paid up.

The Company is authorized to identify the holders of bearer securities by simple request to the organization in charge of clearing bearer securities, the name or corporate name, nationality, year of birth or year of incorporation, address of the holders of securities as well as the quantity of securities held by each of them.

(xv) Distribution of profits

### **ARTICLE 39 - APPROPRIATION AND DISTRIBUTION OF EARNINGS**

The difference between income and expenses for the fiscal year constitutes the profit or loss for the fiscal year.

At least 20% of profit, less any prior losses, are appropriated to the statutory reserve. This appropriation is no longer mandatory once the reserve equals one-tenth of the share capital. It becomes mandatory again if, for any reason, the reserve falls below this one-tenth percentage.

The profit available for distribution is made up of the profit for the fiscal year less any prior losses and the appropriation referred to above, and plus any retained earnings.

This profit is available to shareholders who, on the proposal of the Board of Directors, can decide to carry it forward in full or in part, to allocate it to general or special reserve funds, or to distribute it to shareholders as dividends. The dividend can be in the form of Company shares.

The General Shareholders' Meeting may also decide to distribute amounts deducted from reserves, in which case, the resolution must expressly indicate the reserve items from which the deductions are made. However, dividends must be taken as a priority from the distributable profit for the fiscal year.

Losses carried forward by resolution of the General Shareholders' Meeting are registered in a special account on the liabilities side of the statement of financial position, to be charged to the profits of subsequent years until extinction, or posted as a deduction of reserves.

## **ARTICLE 40 – PAYMENT OF DIVIDENDS**

Dividends are paid annually at the times and places determined by the General Shareholders' Meeting or the Board of Directors within a maximum period of nine months from fiscal year end. An extension of this deadline may be granted by court order.

If shareholders wish to receive their dividend in the form of shares, they must make a request to this effect within a deadline set by the General Shareholders' Meeting no more than three months after the date of the meeting. This deadline may be suspended for a period not exceeding three months by decision of the Board of Directors in the event of a capital increase.

## **6.2 Company activity**

OSE Immunotherapeutics is a biotechnology company specializing in immune response activation and regulation with agonist and antagonist biotherapies developed in immuno-oncology and in autoimmune diseases.

- (i) Intellectual property

See Section 5.5 of the Universal Registration Document.

- (ii) Important contracts

See Section 20 of the Universal Registration Document.

## **7. CONTROL PROCEDURES INTERNAL AND RISK MANAGEMENT RELATING TO THE PREPARATION AND PROCESSING OF ACCOUNTING AND FINANCIAL INFORMATION**

This presentation of the internal control and risk management procedures implemented by the Company is based on the reference framework implementation guide published by the AMF and applicable to financial market mid-cap and small-cap stocks.

In view of the Company's headcount (51 people at December 31, 2020), OSE Immunotherapeutics considers that the internal control procedures are not relevant overall in order to assess its reliability. Nevertheless, OSE Immunotherapeutics has implemented measures proportionate to its specific organizational structure, and plans to develop assignments focused on these elements, and to improve them gradually as its operational and financial position progresses. These items are presented below.

## OBJECTIVES OF INTERNAL CONTROL

OSE Immunotherapeutics has implemented an internal control organization, in order to guarantee optimization of control within the Company, taking particular care to ensure that there are no material elements capable of jeopardizing the reliability of the statutory and consolidated financial statements presented to shareholders.

The aim of this organization is to ensure:

- Compliance with applicable legislation and regulations,
- Safeguarding and protection of assets,
- Reliability of financial information,
- Prevention and control of risks, and implementation of process optimization.

This internal control mechanism contributes to prevention and control of risks from the Company's activity, including those linked to risks of error and fraud. Like any control system, it cannot, however, provide an absolute guarantee that these risks will be completely eliminated.

## ORGANIZATION OF INTERNAL CONTROL

Internal control is also based on a specific organizational structure.

Therefore, in order to liaise with every level of OSE Immunotherapeutics, internal control is based on three internal control lines, and is based on the recommendations formulated by the external auditors, as presented below:

### *1st control line: compliance with procedures*

Each Company employee contributes to the efficiency and smooth operation of the internal control mechanism, by complying with the procedures in place in their field of activity. The existence and application of the procedures, supervised by the Financial Director, is thus the first level of control.

### *2nd control line: support services and tools*

This level of control is provided by specific control, monitoring and steering functions and tools, providing key decision support to the Board of Directors.

- **Budgetary control carried out** by the Chief Financial Officer. This provides quarterly monitoring of the budgetary commitments made by the Company and its subsidiaries OPI and OSE Immunotherapeutics Inc. and is given to the Board of Directors every quarter. This reporting also contains non-financial and prospective information to optimize steering of its subsidiary.
- **An outsourced accounting department**, guaranteeing financial information reliability, and liaising with the Finance Department. The Company's tax statements are prepared by an outsourced chartered accountant and verified by the Chief Financial Officer of OSE Immunotherapeutics. These statements are in addition regularly reviewed by external consultants.
- **The legal status of OSE Pharma International (OPI)**, a Swiss law-subsidiary, enables OSE Immunotherapeutics to carry out controls based on the information and management by its single director.
- **The legal status of OSE Immunotherapeutics, Inc.**, a US law-subsidiary, enables OSE Immunotherapeutics to carry out control based on the information and management by its CEO who is also Chief Executive Officer of the French parent Company.
- **Centralized cash reporting to monitor legal operations** (contract, legal secretariat, dispute management, internal restructuring and external growth operations), making occasional use of advice from external consultants.
- **Consolidation** is carried out by an outsourced accountancy firm and reviewed by the Chief Financial Officer, in order to guarantee consistency of consolidation restatements, and ensure they comply with the Company's rules and procedures. Reporting data are reconciled with the prepared consolidated financial statements and published semi-annually.

### *3rd control line: compliance and optimization audits*

Due to the Company's size, it does not have an internal audit department.

However, following creation of an Audit Committee at the meeting of the Board of Directors on March 27, 2015, this Committee also has the mission to monitor issues relating to the preparation and control of accounting and financial information. It is responsible for continuous assessment of the existence and efficiency of the Company's financial control and risk control procedures, in particular concerning internal control (see Section 1.1.2.1 of the Universal Registration Document).

### *External recommendations: legal audits*

In addition to the control lines presented above, as part of their work, the Statutory Auditors assess the internal control procedures, and may issue recommendations, which are taken into account to improve reliability and timeliness when preparing financial information, as well as in risk management.

## **IMPLEMENTATION OF INTERNAL CONTROL**

### **Main actions in the 2020 fiscal year**

OSE Immunotherapeutics implemented a number of procedures in 2016, which were renewed in the subsequent fiscal years.

These procedures are as follows:

- Control of document standards
- Personnel training
- Organization of the Pharmacovigilance system
- Management of product quality claims
- Selection of GLP, GMP, GCP suppliers
- Management of discrepancies, preventive and corrective actions
- Management of internal and external audits / inspections
- Management of products for clinical trial
- Management of clinical trials
- Batch recall
- Filing and archiving
- Administrative and financial management
- Human resources management
- Management of inventions and inventors
- *Pre-study site visit*
- *Site initiation visit*
- *Monitoring visits*
- *Close out visit*
- Management of privileged information
- Medical review
- *Change control*
- Personal data protection

### **2021-2022 areas of work**

The areas of work for the 2021-2022 fiscal year will concern in particular the continuous improvement of the main procedures that have been put in place, as well as implementation of procedures directly associated with clinical trials.

## **MAIN CHANGES**

As a continuation of the efforts devoted by the Company during fiscal year 2020, the Company will continue its work on internal control to achieve its internal governance goals. Accordingly, the Company plans to double its efforts to implement

its policy to improve internal control mechanisms during fiscal year 2021. Therefore, the Company will strive to put into practice the risk management system and to focus on tracking the identified action plans by preparing a more detailed mapping of the risks encountered. The Company will also continue to update its internal control mechanism by taking into account the changes in its internal organization and its activity, as well as real time changes to its risk management process.

**8. SERVICES OTHER THAN THE CERTIFICATION OF THE FINANCIAL STATEMENTS PROVIDED BY THE STATUTORY AUDITORS**

- None

**9. POWERS TO CARRY OUT FORMALITIES**

We propose that you confer full powers on the bearer of copies or extracts of these minutes in order to perform all legal formalities.

The Board of Directors  
Chairman

**Appendix to the management REPORT: Summary of transactions by management and persons mentioned in Article L. 621-18-2 of the French Monetary and Financial Code**

In accordance with Article 223-26 of the AMF General Regulation and Article L. 621-18-2 of the French Monetary and Financial Code, pursuant to Article 19 of Regulation (EU) no. 596/2014 of the European Parliament and the Council of April 16, 2014, on market abuses, the Company states that it has not received any notification of any transaction involving the Company's shares carried out during the fiscal year 2020 by persons exercising managerial responsibilities and those closely related to them.

## Appendix B - The Company's results over the last five years

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Nature of the indications	2020 fiscal year	2019 fiscal year	2018 fiscal year	2017 fiscal year	2016 fiscal year
<b>I. Capital at fiscal year end</b>					
Stated capital	€3,596,607.60	€3,001,144.80	€2,963,402.40	€2,897,764.20	€2,857,994
Number of existing common shares	17,983,038	15,005,724	14,817,012	14,488,821	14,289,970
Number of bonds convertible into shares	0	0	0	0	0
Number of existing common shares	17,983,038	15,005,724	14,817,012	14,488,821	14,289,970
<b>II. Transactions and profit/(loss) for the fiscal year</b>					
Revenue excluding tax	€9,742,877	€10,601,683	€9,600,963	€6,824,627	€1,974,522
Profit (loss) before tax, depreciation, amortization and provisions	-€22,024,907	-€1,960,524	€1,170,394	-€13,965,647	-€2,701,210
Income tax (tax credit)	-€5,070,367	-€2,988,795	-€4,485,807	-€2,939,842	-€2,645,482
Profit (loss) after tax, depreciation, amortization and provisions	-€17,398,439	€125,113	€5,501,174	-€11,150,716	-€159,876
Amount of profit distributed	- €	- €	- €	- €	- €
<b>III Operating earnings per share</b>					
Profit (loss) after tax, but before depreciation, amortization and provisions	-€0.94	€0.20	€0.07	-€0.76	-€0.19
Profit (loss) after tax, depreciation, amortization and provisions	-€0.97	€0.01	€0.38	-€0.96	-€0.01
Dividend paid per share	- €	- €	- €	- €	- €
<b>IV Personnel</b>					
Number of employees	45	35	29	25	22
Payroll	€4,359,307	€3,745,399	€3,011,508	€2,121,280	€1,976,218
Amounts paid in respect of social benefits	2,247,621.28	€1,817,092	€1,354,951	€982,557	€1,030,954

## Appendix C - Corporate governance report

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In accordance with Article L. 225-37 of the French Commercial Code, the corporate governance report for fiscal year 2020 comprises information concerning the Board's composition, and the application of the principle of gender balance on the Board, the conditions for preparation and organization of the work of the Board of Directors, as well as information concerning the corporate officers. This report also specifies that the Company voluntarily applies a corporate governance code, indicates the specific arrangements concerning participation of shareholders in the General Shareholder's Meeting and presents the principles and rules adopted by the Board of Directors to determine the compensation and benefits in kind granted to the corporate officers. Finally, it mentions disclosure of the information pursuant to Article L. 225-100-3 of the French Commercial Code.

This report was reviewed by the Audit Committee at its meeting on March 22, 2021, in the presence of representatives of the OSE Immunotherapeutics' Statutory Auditors, and was then approved by the Board of Directors at its meeting on March 26, 2021, in the presence of representatives of the OSE Immunotherapeutics' Statutory Auditors.

This report is presented as part of the Ordinary and Extraordinary General Shareholders' Meeting of OSE Immunotherapeutics to be held on June 24, 2021.

### 1. Supervisory and management bodies

Since the IPO of the Company, the Board of Directors has decided that the role of Chairman of the Board of Directors should be separate from that of Chief Executive Officer. The Board of Directors is chaired by Dominique Costantini. The Chief Executive Officer of the Company is Alexis Peyrolles.

#### 1.1. Board of Directors

##### 1.1.1. Composition of the Board of Directors

These provisions are pursuant to Article 1 of the Board of Directors Internal Rules.

No one over the age of 70 may be appointed director if their appointment meant that more than one-third of the members of the Board of Directors would be over 70.

If this proportion is exceeded, the oldest director is deemed to have resigned automatically at the end of the Ordinary General Shareholders' Meeting called to approve the financial statements of the fiscal year during which this threshold was crossed.

The Board discussed the desired balance in its composition and in that of its Committees, in particular concerning balanced gender representation, representation of nationalities and the diversity of skills, and the provisions capable of providing guarantees to shareholders and the market that its missions are accomplished with the necessary independence and objectivity.

The Company's directors originate from different backgrounds and have a variety of experience and skills thereby reflecting the goals of the Board of Directors. The Company complies with Law No. 2011-103 of January 27, 2011, which stipulates that the Board must include at least 40% of each gender.

The details of the corporate offices held by members of the Board of Directors in office on the date of this Universal Registration Document are given in the following table:

<b>First name – Last name or corporate name of the member</b>	<b>Other current offices held in other companies</b>	<b>Other offices and positions held in other companies during the last five years and not exercised on the date of this Universal Registration Document.</b>
Dominique Costantini	- Director of Theranexus SAS - Director of Smart Immune	- Director of Abivax - Director of Theradiag SA - Director of Carthera SAS - Director of Sensorion
Maryvonne Hiance	- Vice Chairman of France Biotech - Vice Chairman of the Atlanpole Biotherapies cluster - Chairman of HealthTech For Care - Chairman of Olgram - Director of Pherecydes Pharma	- Chairman of France Biotech - Director of APAVE - Chairman of the Strategic Advisory Board of Olmix, Bréhan - Strategic Adviser for Goliver, Nantes
Sophie Brouard	- 1st Class Director of Research, CNRS	- Director of the Centaure Foundation - Director of the French Society of Immunology (SFI) - Vice Chairman of Life Sciences and Health for the Pays de la Loire region
Jean-Patrick Demonsang	- Chairman of Demonsang Consulting SAS - Chairman of the Supervisory Board of G1J Ile-de-France	- Chairman of Parexi SAS - Chief Executive Officer of Genode Partners SAS
Brigitte Dréno	- None - Consulting Firms: BMS, Fabre Oncology	- Deputy Vice-President for Scientific and Technical Culture at the University of Nantes
Didier Hoch	- President of the Supervisory Board of Pherecydes Pharma - Director of the University of the Underground Charity Foundation - Strategic Advisor for Goliver Therapeutics	- Independent Director of DBV Technology, Gentichel, Germitech - Member of the Strategic Board - Consultative Committee of Myastérix, Curavac Director of the Fondation pour Université Grenoble Alpes
Alexis Peyroles	- Chairman of Aperana Consulting - CEO of OSE Immunotherapeutics Inc.	- None
Nicolas Poirier	- Member of the Scientific Board of MabDesign and MabSillico	- None
Gérard Tobelem	- Director of Dendrogenix	- Director of SupBiotech - Director of the Louis Dreyfus business foundation - Chairman of Théradiag SA

- Presentation of each member of the Board of Directors

The nine current members of the Board of Directors, whose current composition is detailed in Section 14.1 of this Universal Registration Document, combine international expertise in development of drugs, marketing, industry and finance, as well as experience with listed biotechnology companies.

<b>DOMINIQUE COSTANTINI</b> (66 YEARS OLD, FRENCH)	<b>286 BOULEVARD RASPAIL</b> <b>75014 PARIS</b>	<b>1,978,663 shares</b>
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#### **DIRECTOR – CHAIRMAN OF THE BOARD OF DIRECTORS**

##### **Professional experience / Areas of expertise**

Since co-founding OSE in 2012, Dominique Costantini has raised private equity funds in 2014, completed the Company's IPO in 2015, acquired Effimune in 2016 to lead the Company's development programs and contributed to the partnership agreements implemented in 2016 and 2018. She is the founder and former Chief Executive Officer of BioAlliance Pharma (1997–2011), which was renamed Oxneo in 2014 and is listed on Euronext Paris. Dominique has designed, developed and secured approval for innovative cancer therapies. She raised funds from 1999 to 2005 and completed an IPO for BioAlliance Pharma on Euronext in late 2005. Three successful stock market fundraisings were then based on product development benchmarks: two innovative products were approved in Europe and the United States. She has established international industrial partnerships, signing contracts worth more than €130 million. BioAlliance Pharma is the only French biotech company to have had two products registered with the FDA. Dominique gained more than 15 years of operational management experience in the pharmaceutical industry while working at HMR (now Sanofi). She led R&D and drug marketing activities from research to market in fields including immunology, endocrinology, inflammation, infection and oncology.

Dominique Costantini is a medical doctor and immunologist (Université René Descartes Paris V).

##### **Duration of term of office**

April 27, 2012

Term of office in progress

##### **List of corporate offices and other positions held with French and foreign companies**

<b>Offices and positions held within OSE Immunotherapeutics</b>	<b>Offices and positions held outside OSE Immunotherapeutics</b>
Director and Director of Development	<ul style="list-style-type: none"> <li>- Director of Theranexus SAS</li> <li>- Director of Smart Immune</li> </ul>

#### **MARYVONNE HIANCE** (72 YEARS OLD, FRENCH)

**35, RUE EDISON**  
**44000 NANTES**

**424,084 shares**

#### **DIRECTOR, VICE-CHAIRMAN OF THE BOARD OF DIRECTORS**

##### **Professional experience / Areas of expertise**

Maryvonne Hiance, who was previously the Chairman and co-founder of Effimune, is an engineer who specializes in nuclear science. For 14 years she managed a neutron studies program at FRAMATOME (Areva). Over the past 20 years, she has led several innovative biotechnology companies including SangStat Atlantic (whose parent company, SangStat Medical Corporation, was acquired by Genzyme in 2003 for its product portfolio in immunosuppression and transplantation), DrugAbuse Sciences and TcLand. Maryvonne also founded and managed Strategic Ventures, a consulting firm for technology companies. She has been a member of the French Strategic Council for Innovation and has served as advisor to the French SMEs and Industry Ministry. Maryvonne is Vice-Chairman of France Biotech.

<b>Duration of term of office</b>	
May 31, 2016	Term of office in progress
<b>List of corporate offices and other positions held with French and foreign companies</b>	
<b>Offices and positions held within OSE Immunotherapeutics</b>	<b>Offices and positions held outside OSE Immunotherapeutics</b>
Director and Director of Public Relations	<ul style="list-style-type: none"> <li>- Vice Chairman of France Biotech</li> <li>- Vice Chairman of the Atlanpole Biotherapies cluster</li> <li>- Chairman of HealthTech For Care</li> <li>- Chairman of Olgram</li> <li>- Director of Pherecydes Pharma</li> </ul>

<b>SOPHIE BROUARD</b> (50 YEARS OLD, FRENCH)	<b>LES VAUX</b> <b>44240 SUCÉ SUR ERDRE</b>	<b>202,904 SHARES</b>
<b>DIRECTOR</b>		
<b>Professional experience / Areas of expertise</b>		
<p>Sophie Brouard is Research Director at CNRS (the French National Center for Scientific Research) in Nantes, in charge of a unit dedicated to transplantation and its mechanisms. Previously, she headed the Management Committee of the Centaure Foundation, recognized worldwide for its work on the immunological mechanisms of diabetes, in experimental models and in carrying out therapeutic trials in diabetic patients. She is the co-founder of Effimune and is the author of more than 130 scientific publications and a dozen patents.</p> <p>Sophie Brouard is an immunologist, veterinarian and transplant specialist. She completed her post-doctoral training at Harvard Medical School in Boston.</p>		
<b>Duration of term of office</b>		
May 31, 2016	Term of office in progress	
<b>List of corporate offices and other positions held with French and foreign companies</b>		
<b>Offices and positions held within OSE Immunotherapeutics</b>	<b>Offices and positions held outside OSE Immunotherapeutics</b>	
Director	1st Class Director of Research, CNRS	

<b>JEAN-PATRICK DEMONSANG</b> (68 YEARS OLD, FRENCH)	<b>149, RUE LOUIS ROUQUIER</b> <b>92300 LEVALLOIS-PERRET</b>	<b>30,000 SHARES</b>
<b>DIRECTOR</b>		
<b>Professional experience / Areas of expertise</b>		
<p>Chairman and Chief Executive Officer of Seventure Partners until 2013, Jean-Patrick Demonsang supported the activities of more than 150 companies in the information technology and life sciences sectors. A great entrepreneur, having to his credit the creation and management of several SMEs, he is also started the first club for start-ups.</p> <p>Jean-Patrick Demonsang holds an MBA from HEC and a degree in physics.</p>		
<b>Duration of term of office</b>		

April 10, 2014	Term of office in progress
<b>List of corporate offices and other positions held with French and foreign companies</b>	
<b>Offices and positions held within OSE Immunotherapeutics</b>	<b>Offices and positions held outside OSE Immunotherapeutics</b>
Director	<ul style="list-style-type: none"> <li>- Chairman of Demonsang Consulting SAS</li> <li>- Chairman of the Supervisory Board of G1J Ile-de-France</li> </ul>

<b>BRIGITTE DRÉNO (68 YEARS OLD, FRENCH)</b>	<b>10 RUE VOLTAIRE 44000 NANTES</b>	<b>0 SHARES</b>
<b>DIRECTOR</b>		
<b>Professional experience / Areas of expertise</b>		
<p>Professor Brigitte Dréno is head of the Dermatology Department at the Nantes University Hospital Center, which develops research expertise and groundbreaking treatments in skin oncology. Brigitte Dréno is also the Director of the Biotherapy Clinical Investigation Center and Director of the Unit of Cell and Gene Therapy, and as such closely oversees all immuno-oncology advances. She is Vice Dean of the Medical School. In collaboration with the academic leadership, she supports OSE Immunotherapeutics' R&amp;D initiatives on the Nantes University campus.</p>		
<b>Duration of term of office</b>		
June 14, 2017	Term of office in progress	
<b>List of corporate offices and other positions held with French and foreign companies</b>		
<b>Offices and positions held within OSE Immunotherapeutics</b>	<b>Offices and positions held outside OSE Immunotherapeutics</b>	
Director	Consulting Firms: BMS, Fabre Oncology	

<b>DIDIER HOCH (65 YEARS OLD, FRENCH)</b>	<b>1508 ROUTE DE BELLEGARDE LA SAUZÉE 42210 SAINT CYR LES VIGNES</b>	<b>7,334 SHARES</b>
<b>DIRECTOR</b>		
<b>Professional experience / Areas of expertise</b>		
<p>Didier Hoch has more than 25 years of experience in the pharmaceutical industry. From 2000 to 2010, he was Chairman of Sanofi-Pasteur-MSD, a joint venture between Sanofi and Merck dedicated to vaccines. He also held various managerial positions at Rhône Poulenc Rorer, then Aventis (Vice-President Middle East, Africa). Previously, from 2002 to 2010, Didier Hoch was Vice-President and President of the association of vaccine manufacturers "Vaccine Europe" and Chairman of the LEEM Biotechnology Committee (2006-2012).</p> <p>In 2014, Didier Hoch co-founded and managed the "Big Booster" start-up accelerator. He currently holds offices in healthcare companies including Pherecydes, Goliver Therapeutics and the University of the Underground Charity Foundation (Netherlands).</p> <p>Didier Hoch is a medical doctor.</p>		

<b>Duration of term of office</b>	
May 31, 2016	Term of office in progress
<b>List of corporate offices and other positions held with French and foreign companies</b>	
Offices and positions held within OSE Immunotherapeutics	Offices and positions held outside OSE Immunotherapeutics
Director	<ul style="list-style-type: none"> <li>- President of the Supervisory Board of Pherecydes Pharma</li> <li>- Director of the University of the Underground Charity Foundation</li> <li>- Strategic Advisor for Goliver Therapeutics</li> </ul>

<b>ALEXIS PEYROLES (48 YEARS OLD, FRENCH)</b>	<b>158, RUE DIDEROT 94300 VINCENNES</b>	<b>768,499 SHARES</b>
<b>DIRECTOR, CHIEF EXECUTIVE OFFICER</b>		
<b>Professional experience / Areas of expertise</b>		
<p>Alexis Peyroles has acquired more than 20 years of experience in financial management and control, particularly internationally. He began his career in 1996 at Sanofi-Aventis in Japan, in charge of financial control for the Asia region, then in Latvia for all the Baltic countries. He then took charge of Business Development activities for the Eastern Europe region. In 2005, Alexis joined the Guerbet group, leader in the field of contrast products (in particular for medical imaging) as Director of Management Control. In 2009, he was appointed Chief Executive Officer, Latin America, based in Brazil.</p> <p>Alexis joined OSE Pharma as Chief Financial Officer, responsible for Business Development in September 2013. From May 2016 (date of the merger between OSE Pharma and Effimune) to April 2018, Alexis was Chief Operating Officer of OSE Immunotherapeutics, responsible for Finance, Business Development and Operations.</p> <p>Alexis Peyroles is a graduate of EDHEC Business School and holds an Executive MBA from Imperial College London.</p>		
<b>Duration of term of office</b>		

May 31, 2016	Term of office in progress
<b>List of corporate offices and other positions held with French and foreign companies</b>	
Offices and positions held within OSE Immunotherapeutics	Offices and positions held outside OSE Immunotherapeutics
Director and Chief Executive Officer	<ul style="list-style-type: none"> <li>- Chairman of Aperana Consulting</li> <li>- CEO of OSE Immunotherapeutics Inc.</li> </ul>

<b>NICOLAS POIRIER (39 YEARS OLD, FRENCH)</b>	<b>4, IMPASSE DE LA ROCHÈRE 44119 GRANDCHAMPS DES FONTAINES</b>	<b>92,802 SHARES</b>
<b>DIRECTOR REPRESENTING EMPLOYEE SHAREHOLDERS</b>		
<b>Professional experience / Areas of expertise</b>		
<p>Nicolas Poirier has been chief scientific officer of OSE Immunotherapeutics since 2016. He joined the company in 2009 as project leader and then as director of scientific programs. Nicolas Poirier holds a Ph.D. in immunology and has a strong</p>		

expertise in the development of immunotherapies. His role has been to implement innovative therapeutic strategies on new targets and pathways in immunology addressing severe pathologies with high therapeutic need, thus making a robust contribution to the Company's growth. Along with his R&D team, he continues pursuing the identification of novel preclinical targets and translating them into first-class clinical-stage immunotherapies. He is the author of several high-level international publications in the area of immunotherapy.

Nicolas Poirier holds a Doctorate of Sciences in Immunology.

**Duration of term of office**

June 26, 2019

Term of office in progress

**List of corporate offices and other positions held with French and foreign companies**

<b>Offices and positions held within OSE Immunotherapeutics</b>	<b>Offices and positions held outside OSE Immunotherapeutics</b>
Director representing employee shareholders and Chief Scientific Officer	Member of the Scientific Board of MabDesign and MabSillico

**GÉRARD TOBELEM  
(73 YEARS OLD, FRENCH)**

**113, RUE MONGE  
75005 PARIS**

**31,250 SHARES**

**DIRECTOR**

**Professional experience / Areas of expertise**

Former professor of Hematology at the University of Paris 7 and Head of the Blood Diseases Department at the Lariboisière Hospital in Paris, Gérard Tobelem was Executive Chairman of the French Blood Establishment (L'Etablissement Français du Sang). He was awarded the first Diderot Innovation Prize in 2006 and has held strategic positions within the French Ministry of Higher Education and Research. He has also advised various international pharmaceutical companies on their R&D strategy.

**Duration of term of office**

Term of office in progress

**List of corporate offices and other positions held with French and foreign companies**

<b>Offices and positions held within OSE Immunotherapeutics</b>	<b>Offices and positions held outside OSE Immunotherapeutics</b>
Director	Director of Dendrogenix

- CHANGES in composition of the Board of Directors

Walter Flamenbaum resigned from his position as director on February 19, 2020. This resignation was recorded by the Board of Directors on March 26, 2020.

The terms of office of Gérard Tobelem, Brigitte Dréno and Jean-Patrick Demonsang were renewed by the Shareholders' Meeting of June 16, 2020, for a term of three years expiring at the end of the Ordinary General Shareholders' Meeting to be called to approve the financial statements for the fiscal year ended December 31, 2022.

As the term of office of Dominique Costantini expires at the end of the General Shareholders' Meeting called to approve the financial statements for the fiscal year ended on December 31, 2020, her renewal will be submitted to the General Shareholders' Meeting during the vote to be held on June 24, 2021.

- Independence

These provisions are pursuant to Articles 1 and 11 of the Board of Directors Internal Rules.

As of December 31, 2020, the Company had five independent directors: Gérard Tobelem, Jean-Patrick Demonsang, Didier Hoch, Sophie Brouard and Brigitte Dréno. Independent directors must fulfill the following criteria of the December 2008 AFEP-MEDEF code adopted as the MiddleNext corporate governance code of December 2009:

- They must not be a salaried employee or corporate officer of the Company, a salaried employee or director of its parent company or of a company that it consolidates, and must not have held such a position in the previous five years;
- They must not be a corporate officer of a company in which the Company directly or indirectly holds a directorship or in which a salaried employee appointed as such or a corporate officer of the Company (currently or who has held such a position in the course of the last five years) holds a directorship;
- They must not be a significant customer, supplier, merchant banker or commercial banker of the Company or its group, or a customer, supplier, merchant banker or commercial banker for whom the company or its group represents a significant share of its business, and this must not have been the case in the course of the last two years;
- They must not be a reference shareholder of the Company;
- They must not have a close family relationship with a corporate officer or reference shareholder;
- They must not have been an auditor of the Company during the previous six years.

The Board of Directors discusses and reviews the qualification of independent directors every year prior to publication of the annual report. Subject to justifying its position, the Board may consider as independent one of its members who does not fulfill all these criteria, and vice versa; it may also consider that one of its members who fulfills all these criteria is not independent.

In the event that the permanent representative of a legal entity director qualified as independent ceases its position, this director will be deemed to have resigned.

Each of the independent directors fulfills the above-mentioned criteria.

- Representation of women and men

To date, the Company has 44.4% of women, in compliance with the regulations applicable to listed companies since January 1, 2017.

#### 1.1.2. Functioning of the Board of Directors

These provisions are pursuant to Articles 2 and 3 of the Board of Directors Internal Rules.

- Missions of the Board of Directors

In compliance with Article 22 of the Company's Bylaws, the Board of Directors determines the Company's business strategies and ensures that they are implemented. Subject to the powers expressly granted by law to shareholders' meetings and to

the extent of the corporate purpose, it examines any issue affecting the proper functioning of the Company and through its proceedings resolves matters that concern it.

The Board of Directors determines the Company's business strategies, validates them and ensures that they are implemented. Subject to the powers expressly granted to General Shareholders' Meetings and to the extent of the corporate purpose, it examines any issue affecting the proper functioning of the Company and through its proceedings resolves matters that concern it.

In this context, the Board of Directors approves the Company's significant transactions prior to their implementation, and in particular:

Regarding control:

- Adoption of the annual and semi-annual statutory financial statements and consolidated financial statements, and preparation of the Group management report and the semi-annual financial report;
- Verification of the relevance and consistency of the accounting rules adopted to prepare the Company's consolidated and statutory financial statements;
- Review of the means implemented by the Company, the Statutory Auditors and the internal audit to ensure that the statutory and consolidated financial statements are true and fair;
- Review of the financial position, cash position and commitments of the Company, adoption of the forward planning documents and corresponding reports;
- Review and approval of the budget;
- Monitoring of the effectiveness of the internal control and risk management systems and adoption of the corresponding report;
- Authorization of the related-party agreements, and in particular the agreements concluded to the benefit of the Chairman, the Chief Executive Officer or the Chief Operating Officers, corresponding to components of compensation, indemnities or benefits due or likely to be due as a result of the termination or change of their positions or subsequently;
- Prior authorization of decisions by Executive Management described in Chapter II of these regulations below:
  - Regarding appointments and compensation;
  - Appointment and dismissal of the Statutory Auditors;
  - Determination of the methods used to carry out Executive Management of the Company;
  - Appointment and dismissal of the Chief Executive Officer and setting of his compensation;
  - Appointment and dismissal of the Chief Operating Officers following proposal by the Chief Executive Officer, setting of their compensation, where appropriate;
  - Selection and dismissal of the Chairman of the Board of Directors;
  - Co-opting of directors in the event of resignation or death;
  - Distribution of directors' fees;

- Notice of meeting for General Shareholders' Meetings, setting the agenda, preparation of the corresponding reports.

In relations with third parties, the Company is bound even for actions by the Board of Directors that do not fall within the corporate purpose unless it proves that the third party knew that the action in question exceeded this purpose or that it could not be unaware of this given the circumstances, it being stated that the mere publication of the bylaws is not sufficient to constitute this proof.

The Board of Directors may at any time perform the audits and verifications it deems appropriate. All directors must receive the information required for completing their assignments and they may obtain all documents they consider necessary from the Executive Management. The Board of Directors may give any agent of its choice any delegation of authority within the bounds of its powers under the law and these bylaws.

It may decide to create working committees tasked with studying the issues the Board or the Chairman of the Board submits to it. The Board of Directors is not qualified to vote on or authorize a bond issue; these bylaws reserve that power for the General Shareholders' Meeting.

- Information for Directors

The Board of Directors carries out the verifications and controls that it deems appropriate, at any period during the year. For this purpose, each director must receive the information necessary to accomplish their mission.

In this context, the Chief Executive Officer shall provide each director with all the documents and information that it judges necessary to carry out their control mission.

The Chief Executive Officer, the Chairman of the Board of Directors, as well as the Chairman of each of the Committees, prior to each meeting of the Board of Directors, shall provide the directors with the information and documents necessary for them to fully carry out their mission. In particular, the Chairman of each Committee shall provide the directors with the reports, assessments or consultations prepared as part of their mission.

Directors who judge that they are not in a position to deliberate in full possession of the facts have a duty to inform the Board of this situation, and to demand the necessary information. Outside the sessions of the Board of Directors, the directors receive from the Chief Executive Officer the appropriate information required at any stage in the life of the Company or Group, if warranted by the importance or urgency of the information.

They receive the press releases issued by the Company, as well as a review of press articles and financial analysis recommendations concerning the Company.

- Notices of meetings, meetings and proceedings

The Board of Directors meets as often as is required in the interests of the Company, and at least once every quarter, by notice of meeting from its Chairman or on request from the Chief Executive Officer or from at least one third of the directors if it has not met for at least two months. The meetings are held either at the registered office, or at any other place specified by the sender of the notice of meeting.

The notices of meetings are issued by any written means, in particular by letter, electronic means or by facsimile, within a period of three business days except in the case of an emergency.

The Board of Directors may invite external persons to attend the Board meetings.

- Representation

Any director can give another director power of attorney to represent them and to vote on their behalf at a specific Board session.

The Board is the sole judge of the validity of the power of attorney which may be given by any written means, in particular by simple letter, by facsimile and including by electronic power of attorney.

Each director may only represent one other director.

The provisions of the two paragraphs above are applicable to the permanent representative of a legal entity director.

- Quorum and majority

The proceedings of the Board of Directors are only valid if at least half of its members are present.

In compliance with the bylaws, decisions are taken by the majority of the directors present or represented. In the event of a tied vote, the Chairman of the session has the casting vote.

An attendance register signed by all the members participating in each Board session is kept at the registered office. However, the names of directors participating remotely in the Board meeting are simply recorded on the attendance register.

- Video conference and other means of telecommunication

The Board of Directors can opt to allow its members to participate in the proceedings (discussions and votes) by video conference (which entails a combination of sound and vision), or by a means of telecommunication such as a telephone conference call enabling them to be identified by voice transmission by each participant, and guaranteeing their effective participation in accordance with the requirements of the applicable regulations.

Videoconferencing or telephone conference calls, or other means of telecommunication must meet the technical requirements guaranteeing effective participation in the meeting of the Board of Directors, the proceedings of which are transmitted, that is, transmission of voice and picture, or at least the voices of all the participants simultaneously and continuously.

If these requirements are met, the directors participating in the meeting by video conference or telephone conference call or other means of telecommunication are deemed to be present for calculation of the quorum and majority.

A director participating in the meeting by video conference, telephone conference call or other means of telecommunication can represent another director, provided that on the day of the meeting the Chairman is in possession of a power of attorney from the director thereby represented.

Recourse to videoconferencing, telephone conference calls or other means of telecommunication is prohibited when the Board of Directors is called to approve and control the separate financial statements and the consolidated/combined financial statements, preparation of the management report and the report on management of the Group, and on appointment or dismissal of the Chairman of the Board of Directors, the Chief Executive Officer and the Chief Operating Officers.

The register of attendance at Board of Directors' sessions must indicate, if necessary, that the relevant directors are participating by video conference or by means of telecommunication.

The minutes of the Board of Directors' meeting must indicate the names of the directors participating in the meeting via video conference or by means of telecommunication.

They must also report any technical incident that may occur concerning a video conference, telephone conference call or other means of telecommunication if this incident disrupted the proceedings of the session, including the interruption and restoration of remote participation.

If malfunctioning of the video conference or telephone conference call system or the means of telecommunication is noted by the Chairman of the session, the Board of Directors is entitled to deliberate and/or to continue with only the members

that are physically present, or for whom transmission of voices and/or picture remains continuous and simultaneous, provided that the quorum requirements are met.

A director participating remotely in the Board meeting that cannot be deemed present due to a malfunction may then give power of attorney, provided it meets the requirements stipulated in Articles 1316 to 1316-4 of the French Civil Code (written document, e-mail, facsimile, etc.), to a director who is physically present, provided this power of attorney is known to the Chairman. Directors may also communicate a power of attorney in advance, stipulating that it will only take effect in the event of a malfunction preventing them from being deemed present.

- Participation of third parties and non-voting members at the sessions of the Board of Directors

#### Invitations

Depending on the items included on the agenda, the Chairman of the Board of Directors may decide, in particular following a proposal by a member of the Board of Directors, to invite any person they believe useful, whether or not a Company employee, to give a presentation or to clarify the discussions in preparation for the proceedings.

#### Statutory Auditors

The Statutory Auditors are given notice to attend all meetings of the Board of Directors during which the separate or interim financial statements are reviewed or adopted, consolidated/combined or not.

The Statutory Auditors are given notices of meetings at the same time as the members of the Board of Directors, but their notice is sent by registered letter with a request for acknowledgement of receipt.

#### Non-voting members

Non-voting members are given notice to attend all meetings of the Board of Directors. They take part in the proceedings in an advisory capacity.

In particular, their mission is to ensure the bylaws are strictly enforced. In particular, their role is to provide information, advice and supervision to the Board of Directors.

- Confidentiality obligation

If third parties who are not members of the Board of Directors are invited to a session of the Board of Directors or to the preparatory session for such a meeting, the Chairman of the Board of Directors reminds them of their confidentiality obligations concerning the information received during the meeting of the Board of Directors or in advance of such a meeting.

- Board of Directors Internal Rules

The applicable Internal Rules are the Rules as adopted by the decision of the Board of Directors on March 27, 2015, amended on June 14, 2017. The complete version of the Board of Directors Internal Rules can be consulted, following a prior written request, and the Company's registered office.

- Presentation of the main provisions

The Internal Rules of the Company contain all of the provisions relating to the methods for assigning corporate governance duties to the different Company bodies. Accordingly, it gives details of all the powers of the Board of Directors and of all the advisory committees, as well as those of the Chairman of the Board of Directors and of the Chief Executive Officer. The Rules also contain the rules concerning ethics, detailing all the principles that the Company directors must uphold, in particular relating to insider trading and market transactions.

- ASSESSMENT of the Board of Directors

Upon the initiative of the Chairman at the meeting of March 26, 2021, the members of the Board of Directors were invited to give their opinion regarding the functioning of the Board, the Audit Committee and the Appointments and Compensation Committee, and on the preparation of its work for fiscal year 2020.

This self-assessment by the members of the Board of Directors of the Board's performance was carried out on the basis of precise criteria such as the operating methods and the effective contribution of its members.

The results of this assessment were discussed in an overall and open manner by the directors, who consistently work to improve internal communication.

#### 1.1.3. Work of the Board of Directors in 2020

- Number of meetings

In 2020, the functioning of the Board was governed by the provisions of the bylaws. In addition to the obligatory Board meetings (approval of the separate and semi-annual financial statements), meetings were held as justified by the course of business.

During 2020, the Company's Board of Directors met five times:

- March 26, 2020 (review and approval of the statutory financial statements for the fiscal year ended December 31, 2019, review and adoption of the consolidated financial statements for the year ended December 31, 2019, review of the agreements in Articles L.225-38 of the French Commercial Code, acknowledgement of the acquisition of 141,800 free shares allocated to employees, review of directors' terms of office, discussion of the appropriateness of delegations, review of executive compensation and setting of the directors' fees, preparation of the Board of Directors' management report and other related reports, setting the agenda of the Combined General Shareholders' Meeting; authorization to subscribe to loans);
- June 17, 2020 (delegation to the Chief Executive Officer for the purpose of recognizing the acquisition of a maximum of 298,400 free shares; determination of the components of the fixed compensation of the Chief Operating Officer and Chief Executive Officer; allocation of 150,000 free shares to Alexis Peyrolles; allocation of 100,000 free shares to Nicolas Poirier; allocation of a maximum of 250,000 free shares to all employees of the Company who are not corporate officers and delegation of powers to the Chief Executive Officer; determination of the fixed compensation components of the Director of Development and Chairman of the Board of Directors; issue of 70,000 founders' warrants to directors);
- September 17, 2020 (review and approval of the consolidated financial statements for the first half of 2020);
- November 18, 2020 (strategic review);
- December 8, 2020 (issue of free shares following their allocation, validation of the 2020 variable objectives of the management team, and setting of the 2021 objectives, approval of the EIB financing).

The average attendance rate of the Board members was 98.15%.

- Main subjects discussed

During fiscal year 2020, the Board took a certain number of decisions relating in particular to the review of financial statements, and approval of the separate financial statements. It decided on the issue of financial instruments (free shares, share subscription warrants, founders' share warrants) and monitored the progress of Research & Development projects in

T-cell-based vaccines (Tedopi®, CoVepiT), in immuno-oncology (BI 765063 (OSE-172), BiCKI® platform, CLEC-1, OSE-279), and in autoimmunity (FR104, OSE-127/S95011) and inflammation (OSE-230), on its own or in partnership.

#### 1.1.4. Limitations placed on the powers of the Chief Executive Officer by the Board of Directors

These provisions are stipulated in Chapter II of the Board of Directors' Internal Rules.

The position of Chief Executive Officer is held by Alexis Peyroles who is invested with the most extensive powers to take action in any circumstances in the name of the Company, within the limits nevertheless of the provisions of Article 10 of the Internal Rules of the Board of Directors.

Accordingly, the Chief Executive Officer cannot adopt certain decisions or conclude certain acts, commitments or contracts if these have not been authorized in advance by the Board of Directors.

As an internal measure not binding on third parties, the Chief Executive Officer may not take the following decisions outside the limits set by the annual budget adopted and approved by the Board of Directors without the prior agreement of the Board:

Advice:

- Decisions relating to acquisition or sale in any form, in return for payment or not, rental, lease, of any real estate asset or intangible non-current assets;
- Any proposal to create subsidiaries or to acquire Companies (or a business) including any project to acquire a holding in any entity, any project to sell, liquidate or dissolve subsidiaries, to start new business activities, or to take under lease management all or part of any business;
- Taking out a loan for an amount greater than €400,000 excluding the annual budget with the exception of bank overdrafts according to the authorization of the overdraft authorized by the banks, or deposits granted by partners;
- Conclude contracts or investments relating to the Company's activity corresponding to an income or expense greater than €400,000 excluding the annual budget per fiscal year;
- Constitute sureties, grant guarantees, endorsements greater than €500,000;
- Grant loans;
- Conclude agreements with shareholders;
- Any decision relating to initiation of a dispute, conduct of legal proceedings and any decision concerning any transactional settlement of the dispute;
- Pronounce the early dissolution of a subsidiary in which the Company holds all or more than the majority of the equity securities and voting rights.
- Any project to grant licenses, to sell or acquire licenses, for any intellectual property right that the Company holds such as, for example, patents, know-how or brands not identified in the annual budget, with the exception of that pertaining to the ordinary course of business of the Company.

Similarly, as an internal measure not binding on third parties, the Chief Executive Officer cannot without the prior agreement of the Extraordinary General Shareholder's Meeting:

- Liquidate, dissolve or close down the Company, including any closure concerning all or part of the Company's activity, or any event deemed to constitute a liquidation (including its methods and conditions);
- Carry out any substantial modification in the type or nature of the Company's activity;
- Acquire significant shares or assets from another company or any other economic entity or conclude any transaction outside the normal sphere of business;
- Any decision concerning a project for merger, demerger or contribution concerning the Company;
- Any decision relating to a proposal to issue securities, to increase or reduce the share capital and any decision relating to a proposal to reorganize the share capital (share buyback, reduction in number of shares, etc.), except for share capital increases resulting from the exercise of share subscription warrants or founders' warrants;
- Any decision relating to a proposal to distribute dividends, interim dividends or reserves of any kind whatsoever;
- Any decision relating to a proposal to issue or allocate founders' warrants, share subscription warrants or any other security; setting of methods for exercise or subscription of these securities.

#### 1.1.5. Combination of employment contract and duties as corporate officers

Dominique Costantini, Chairman of the Board of Directors, has had an open-ended employment contract since July 1, 2014, as Director of Development, receiving gross annual compensation of €140,000 (for 104 working hours per month). Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets. Her employment contract was amended in April 2015 to increase her hours to 133 working hours per month, for gross annual compensation of €180,000 excluding variable compensation. Following the recommendation of the Appointments and Compensation Committee on June 22, 2015, the Board of Directors, on June 23, 2015, awarded gross variable compensation of €25,000 to Dominique Costantini for fiscal year 2014. Ms. Constantini signed an addendum to her employment contract on October 1, 2016, bringing her monthly working hours to 151.67 hours, i.e., gross annual compensation of €205,314 which increased to gross annual compensation of €275,000 on July 1, 2019, then to gross annual compensation of €302,500 on July 1, 2020. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

The Company is continuing this contract due to Dominique Costantini's unique technical roles in terms of business development and relations with health authorities. She reports to Chief Executive Officer Alexis Peyroles. The scope of her employment contract includes the implementation of strategies to define and achieve proofs of concept and explore mechanisms of action.

Dominique Costantini receives no compensation for her position of Chairman of the Board of Directors.

Alexis Peyroles, Chief Executive Officer, signed an open-ended employment contract on July 1, 2014, modified by an addendum effective July 1, 2018, as Director of Operations with a gross annual salary of €250,000, then again modified by an addendum effective July 1, 2019, for an annual gross salary of €350,000. Variable compensation equal to up to 50% of the gross annual compensation is provided for based on the achievement of certain targets, with 50% of it in the form of free shares.

The Company is continuing this contract due to Alexis Peyroles' seniority and his unique technical roles in terms of international business collaborations and implementing licensing agreements. He reports to, and acts under the authority and instructions of, the Board of Directors. The characteristics of his employment contract relate to operational management and international business collaborations.

Maryvonne Hiance, Vice Chairman of OSE Immunotherapeutics, has an operational role as Director of Public Relations within the Executive Management under a contract dated May 31, 2016. Compensation under this employment contract is calculated on the basis of €120,000 in gross annual salary. The employment contract took effect on May 31, 2016, concurrently with the completion of the merger. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets. The Company is continuing this contract due to Maryvonne Hiance's unique technical roles in terms of strategy and relations with public authorities.

#### 1.1.6. Delegations of authority and powers granted to the Board of Directors in the area of capital increases

See Section 19.1.4 of the Universal Registration Document.

#### 1.1.7. Board of Directors Committees

##### 1.1.7.1. Audit Committee

- Composition

The Audit Committee consists of Jean-Patrick Demonsang (Committee Chairman) and Didier Hoch, appointed for a two-year term at the Board of Directors' meeting on June 26, 2019.

The independent members are Jean-Patrick Demonsang and Didier Hoch. Jean-Patrick Demonsang also has specific financial, accounting and auditing skills.

- Operating procedures
  - Duties

The Audit Committee is responsible for overseeing issues relating to the preparation and audit of accounting and financial information. It is responsible for continually assessing the existence and effectiveness of the Company's financial control and risk control procedures, and has as its duties:

#### Internal control

- Ensuring that the internal control and risk management systems are effective;
- Verifying the smooth operation with assistance from the Finance Department;
- Reviewing the schedule of internal and external audits;
- Ensuring that the Statutory Auditors conduct the statutory audit of the separate financial statements and, where applicable, the consolidated financial statements;

#### Statutory financial statements and financial information

After regularly reviewing the financial position, the cash position and the commitments appearing in the Company's separate financial statements:

- Reviewing the accounting and financial documents, annual and interim financial statements;
- Overseeing the process of issuing the statutory and consolidated/combined financial statements and the process of preparing the financial information;
- Reviewing the internal control measures;
- Reviewing the material risks for the Company, particularly off-balance sheet risks and commitments;
- Validating the relevance of accounting rules and choices;
- Verifying the relevance of the financial information reported by the Company.

#### Risk management

- Reviewing any item likely to have material, financial and accounting impacts;
- Reviewing the status of major litigation;
- Reviewing off-balance sheet risks and commitments;
- Reviewing the relevance of the risk monitoring procedures;
- Reviewing any related-party agreements.

#### Statutory Auditors

- Leading the selection of the Statutory Auditors, managing their compensation and ensuring their independence;
- Ensuring the proper implementation of their assignment;
- Monitoring the statutory audit of the separate financial statements and, where applicable, the consolidated financial statements by the Statutory Auditors;
- Establishing the rules for using the Statutory Auditors for tasks other than the audit of the financial statements and ensuring the proper implementation of their assignment;
- Issuing a recommendation on the proposals for the appointment and potential reappointment of the Statutory Auditors presented to the General Shareholders' Meeting, their fees and any issues related to their independence.

- Internal Rules

The operating procedures of the Audit Committee are governed by Article 7 of the Internal Rules of the Board of Directors. These Internal Rules may be viewed at the Company's registered office upon prior written request.

- Work in 2020:

The Audit Committee met twice in 2020, to review and approve the statutory and consolidated financial statements for fiscal year 2019 (March 23, 2020) and to review and approve the consolidated financial statements for first-half 2020 (September 15, 2020).

#### 1.1.7.2. Appointments and Compensation Committee

- Composition

The Appointments and Compensation Committee consists of Gérard Tobelem (Committee Chairman) and Maryvonne Hiance, appointed for a two-year term at the Board of Directors' meeting on June 26, 2019.

The independent member is Gérard Tobelem.

- Operating procedures

- Duties

The Appointments and Compensation Committee issues recommendations to the Board of Directors on the following topics:

- Advice and assistance regarding compensation, the pension and welfare benefit plan, supplementary pensions, benefits in kind, various cash entitlements of the executive corporate officers, allocations of free or performance shares, stock subscriptions or purchase options;
- The determination of the procedures for setting the variable portion of the compensation of the executive corporate officers, and overseeing the enforcement of these procedures;
- The distribution of the directors' fees, where necessary, to the directors taking into account their attendance record and tasks accomplished on the Board of Directors;
- Any extraordinary compensation of the directors for specific assignments or duties given to them by the Board;
- Any changes to the composition of the Board of Directors or the Executive Management;
- Prevention of conflicts of interest on the Board of Directors;
- Oversight of the establishment of structures and procedures making it possible to apply proper governing practices within the Company;
- Ensuring compliance with ethical principles within the Company and in its relations with third parties;
- Discussions on the classification of independent director for each director when the director is first appointed and every year before the publication of the Universal Registration Document, and presentation of the report of its recommendations to the Board of Directors.

In addition, the Executive Management proposes to it the various stock subscriptions or purchase option plans, equity warrant plans, founders' warrant allocation plans or free share allocation plans.

- Internal Rules

The operating procedures of the Appointments and Compensation Committee is governed by Article 6 of the Board of Directors' Internal Rules. These Internal Rules may be viewed at the Company's registered office upon prior written request.

- Work in 2020:

The Appointments and Compensation Committee met twice in 2020, on June 17 for the review of management compensation and allocation of free shares to employees and founders' warrants, and on December 8 to allocate free shares and determine the objectives of the Chief Executive Officer and the Chairman of the Board of Directors.

#### 1.1.8. Statements relating to the Board of Directors

In the last five years, none of the members of the Company's Board of Directors have been:

- Convicted of fraud or subject to an incrimination or official public sanction by the statutory or regulatory authorities;
- Involved in any bankruptcies, receiverships or liquidations as a manager or corporate officer;
- Prevented from acting as a member of an administrative, management or supervisory body or from participating in the management or conduct of business of an issuer;
- Subject to any incrimination and/or official public sanction by the statutory or regulatory authorities (including designated professional organizations).

There are no family ties between directors.

#### 1.1.9. Conflicts of interest

- Describe arrangements for preventing and managing conflicts of interest

Each director strives to avoid any potential conflict between their moral and material interests and those of the companies. He or she notifies the Board of Directors in advance and in full of any actual or potential conflicts of interest between him or herself (or any other legal or natural person with whom he or she has business dealings) and the Company or any of the companies in which the Company has an investment or any of the companies with which the Company is planning on entering into an agreement of any type in which he or she may be directly or indirectly involved.

Directors must notify the Board of Directors of any conflict of interest that arises after taking office as soon as they become aware of it. They must not take part in any discussions and decision-making related to the issues in question and, where appropriate, must resign.

If a member of the Board of Directors has a doubt as to the existence of a conflict of interest or potential conflict of interest, he/she must immediately notify the Chairman of the Board of Directors who must independently decide whether there are grounds for notifying the Board of Directors.

If the Board member referred to in the previous paragraph is also the Chairman of the Board of Directors, he/she should notify the Board of Directors.

An absence of information amounts to the acknowledgement that no conflict of interests exists.

Where the agreement in question is not an agreement entered into under normal conditions, the relevant Board member shall not take part in the vote on entering into the agreement in question nor in the discussion prior to this vote.

Moreover, the Chairman of the Board of Directors, members of the Board of Directors, Chief Executive Officer and any Chief Operating Officers will not be required to disclose to any Board members of whom they have good reason to believe has a conflict of interest within the meaning of this article, information or documents relating to the agreement or transaction giving rise to the conflict of interest, and will inform the Board of Directors of this lack of such disclosure.

- List potential conflicts of interest and state the opinion of the Board of Directors

To the Company's knowledge, as of the date of this Universal Registration Document, there are no existing or potential conflicts of interest between the duties towards the Company and the private interests and/or duties of the individuals that comprise the administrative, management and executive management bodies.

- Agreements between the members of the Board of Directors and companies of the OSE Immunotherapeutics Group.

As stated in paragraph 1.1.5, Ms. Costantini has had an open-ended employment contract since July 1, 2014, as Director of Development, receiving gross annual compensation of €302,500 excluding variable compensation, as of July 1, 2020.

As stated in paragraph 1.1.5, Alexis Peyroles, Chief Executive Officer, signed an open-ended employment contract as Director of Operations, receiving gross annual compensation of €350,000. Variable compensation equal to up to 50% of the gross annual compensation is provided for based on the achievement of certain targets, with 50% of it in the form of free shares.

Maryvonne Hiance, Vice Chairman of OSE Immunotherapeutics, has an operational role as Director of Public Relations within the Executive Management under a contract dated May 31, 2016. Compensation under this employment contract is calculated on the basis of €120,000 in gross annual salary. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

Nicolas Poirier, elected as the director representing the employee shareholders on June 26, 2019, is employed as Chief Scientific Officer under an employment contract dated May 31, 2016. Compensation in respect of this employment contract has been calculated on the basis of the gross annual sum of €180,000, increased to a gross annual sum of €200,000 on July 1, 2020. Variable compensation is also provided for.

## 1.2. Application of the Middlenext Corporate Government Code for listed companies.

Through a decision dated March 27, 2015, the Board of Directors wished to establish Internal Rules in order to specify, supplement and implement the rules for its organization and operation that apply to it under the law (and to its committees), the Company's regulations and bylaws, and the ethical rules that apply to all the directors and the corporate governance principles by which it refers (Corporate Governance Code for Small and Midcaps, MiddleNext, December 2009).

In accordance with the law of July 3, 2008, the disclosures presented herein are established by referring to the corporate governance code and additional recommendations regarding communication on the compensation of executive corporate officers of listed companies as defined by MiddleNext. The MiddleNext Code used as a reference by the Company can be consulted at [the address](https://www.middlenext.com/IMG/pdf/c1_cahier_10_middlenext_code_de_gouvernance_2016.pdf)

[https://www.middlenext.com/IMG/pdf/c1\\_cahier\\_10\\_middlenext\\_code\\_de\\_gouvernance\\_2016.pdf](https://www.middlenext.com/IMG/pdf/c1_cahier_10_middlenext_code_de_gouvernance_2016.pdf).

The Reference Code contains key areas of vigilance to ensure proper governance of French companies with reminders of the questions the Board of Directors must ask itself to promote effective governance. The Company's Board of Directors acknowledged these vigilance areas at its meeting on March 27, 2015.

The Reference Code contains recommendations relating more specifically to corporate officers and the Board of Directors. The Company complies with all recommendations in the Reference Code.

### 1.3. Compensation and benefits of any kind paid or allocated for the last fiscal year ended to management.

In accordance with Article L. 22-10-34 I and II of the French Commercial Code, the Ordinary General Shareholders' Meeting called to approve the financial statements closed on December 31, 2020, will approve:

- (a) information relating to the compensation of executive corporate officers referred to in I of Article L. 22-10-9 of the French Commercial Code (general ex post vote); and on
- (b) the fixed, variable and exceptional items making up the total compensation and benefits of any kind paid or allocated in respect of the previous fiscal year by separate resolutions for the executive corporate officers.

The General Shareholders' Meeting must explicitly approve the payment of variable or exceptional compensation items (specific ex post vote). It is specified, concerning the executive corporate officers (i.e., the Chairman of the Board of Directors and the Chief Executive Officer), that the payment of variable and exceptional compensation is subject to approval by the General Shareholders' Meeting of the components of compensation of the relevant officer. Only the resolutions relating to the compensation of Dominique Costantini and Alexis Peyroles for the fiscal year ended December 31, 2020, will be submitted to a specific ex post vote at the next General Shareholders' Meeting, as Maryvonne Hiance and Nicolas Poirier are not compensated for their corporate office but under their employment contract (in their capacity as Director of Public Relations and Chief Scientific Officer).

From fiscal year 2020, the payment of the sum allocated to the directors (formerly "Directors' fees") will be suspended, if the information relating to the compensation of the corporate officers mentioned in I of Article L. 22-10-9 of the French Commercial Code is not approved by the General Shareholders' Meeting, until a revised compensation policy submitted by the Board of Directors is approved at a future General Shareholders' Meeting.

#### 1.3.1. Compensation of executive corporate officers

The work of the Appointments and Compensation Committee is based on review meetings through the course of the year and interim preparatory meetings chaired by the Committee Chairman. The principles and criteria for setting, distributing and allocating the components of total compensation and benefits in kind of executive corporate officers of OSE Immunotherapeutics for the 2020 fiscal year were thus reviewed by the Appointments and Compensation Committee before being proposed to and approved by the Board of Directors.

The Board will present the components of compensation due or allocated to each of the executive corporate officers in respect of the fiscal year ended to the Ordinary Annual General Shareholders' Meeting for approval. This presentation is to be followed by a mandatory shareholder vote. Should the Ordinary General Shareholders' Meeting reject the proposal, following the recommendation of the Appointments and Compensation Committee, the Board shall vote on the changes to be made to the compensation due or allocated in respect of the fiscal year ended or the future compensation policy. It will immediately post a statement on the Company's website setting how it intends to act on the vote by the Ordinary General Shareholders' Meeting and submits a report at the following meeting.

The Appointments and Compensation Committee submits a proposal to the Board of Directors on the compensation of executive corporate officers consistent with the rules for setting such compensation in view of the medium-term outlook and Company's results.

The Company draws on market practices of comparable Companies in particular in order to determine the structure of this compensation. These surveys are conducted with reference to a panel of French companies with similar characteristics, selected according to the following criteria: market capitalization, industrial activity, revenue, total workforce.

It ensures that none of the components of compensation are disproportionate and analyzes compensation as a whole, taking into account all components.

In fiscal year 2020, Dominique Costantini, Maryvonne Hiance and Alexis Peyroles were the only executive corporate officers. No compensation was paid to executive corporate officers in 2020 in respect of their corporate offices.

- Components of the compensation paid in 2020 or allocated in respect of the same fiscal year to the Chairman of the Board of Directors subject to the approval of the next General Shareholders' Meeting (specific "ex post" vote).

In accordance with the provisions of Article L. 22-10-34 II of the French Commercial Code, the next Ordinary General Shareholders' Meeting will be asked to vote on a draft resolution relating to the components of compensation allocated in 2020 to the Chairman of the Board of Directors, Ms. Dominique Costantini:

Dominique Costantini has held an open-ended employment contract since July 1, 2014, for her position as Director of Development. Compensation in respect of this employment contract has been calculated on the basis of the gross annual sum of €302,500 (for 151.67 working hours per month) since July 1, 2020. This increase was agreed at the meeting of the Board of Directors on June 17, 2020, in accordance with the compensation criteria set out in Article 2 of the Board of Director's Internal Rules (comprehensiveness, balance between the different components of compensation, consistency, legibility of rules, balance, transparency), and on the basis of the benchmark for compensation of equivalent biotech management.

Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

At its meeting on December 10, 2019, the Board of Directors set the following fiscal year 2020 objectives for Dominique Costantini in respect of her contract as Director of Early Development: continue to develop the Clinical portfolio; look to the future with new Research projects to be brought to the Clinical portfolio. These objectives were met in the 2020 fiscal year. Variable compensation equivalent to three months' salary was paid in cash.

The Board of Directors meeting of June 17, 2020, granted 10,000 founders' warrants to each director, including to Dominique Costantini.

- Components of the compensation paid in 2020 or allocated in respect of the same fiscal year to the Chief Executive Officer subject to the approval of the next General Shareholders' Meeting (specific "ex post" vote).

In accordance with the provisions of Article L. 22-10-34 II of the French Commercial Code, the next Ordinary General Shareholders' Meeting will be asked to vote on a draft resolution relating to the components of compensation allocated in 2020 to the Chief Executive Officer, Mr. Alexis Peyroles:

Alexis Peyroles, Chief Executive Officer, signed an open-ended employment contract on July 1, 2014, modified by an addendum effective July 1, 2018, as Director of Operations with a gross annual salary of €250,000, then again modified by an addendum effective July 1, 2019, for an annual gross salary of €350,000. This increase was agreed at the meeting of the Board of Directors on June 26, 2019, in accordance with the compensation criteria set out in Article 2 of the Board of Director's Internal Rules (comprehensiveness, balance between the different components of compensation, consistency, legibility of rules, balance, transparency), and on the basis of the benchmark for compensation of equivalent biotech management.

Variable compensation equal to up to 50% of the gross annual compensation is provided for based on the achievement of certain targets, with 50% of it in the form of free shares.

In respect of the 2020 fiscal year, at its meeting on December 10, 2019, following the recommendation of the Appointments and Compensation Committee on that date, the Board of Directors set Alexis Peyroles' objectives as follows: continue the clinical development of the Company's portfolio, R&D engine and scientific recognition, sign a new partnership agreement in the OSE portfolio and/or obtain funding. 100% of these objectives were met in the 2020 fiscal year. They gave rise to the payment of variable compensation of €175,000, in the form of €87,500 in cash and 11,363 shares.

- Components of the compensation paid in 2020 or allocated in respect of the same fiscal year to the other corporate officers (for information purposes only).

Maryvonne Hiance and Nicolas Poirier being paid only under their respective employment contracts, the components of their compensation as well as the benefits in kind allocated to them are presented here for information purposes only:

Maryvonne Hiance, Vice Chairman of OSE Immunotherapeutics, has an operational role as Director of Public Relations within the Executive Management under a contract dated May 31, 2016. Compensation under this employment contract is calculated on the basis of €120,000 in gross annual salary. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

This compensation was confirmed at the meeting of the Board of Directors on June 26, 2019, in accordance with the compensation criteria set out in Article 2 of the Board of Director's Internal Rules (comprehensiveness, balance between the different components of compensation, consistency, legibility of rules, balance, transparency), and on the basis of the benchmark for compensation of equivalent biotech management.

The Board of Directors meeting of June 17, 2020, granted 10,000 founders' warrants to each director, including Maryvonne Hiance.

Nicolas Poirier, elected as the director representing the employee shareholders on June 26, 2019, is employed as Chief Scientific Officer under an employment contract dated May 31, 2016. Compensation in respect of this employment contract has been calculated on the basis of the gross annual sum of €180,000, increased to a gross annual sum of €200,000 on July 1, 2020. Variable compensation is also provided for. Since his appointment as the director representing the employee shareholders was based on his position as a pre-existing employee, Nicolas Poirier's employment contract is considered a standard agreement entered into under normal conditions.

The Board of Directors meeting of June 17, 2020, wished to grant to Nicolas Poirier an incentive in the form of 100,000 free shares for his leadership of the Research team (one-year vesting period)(see table 6 of section 13.1 of the 2020 Universal Registration Document).

### 1.3.2. Information on the compensation granted during the fiscal year ended on December 31, 2020, to corporate officers and submitted to the approval of the General Shareholders' Meeting in accordance with article L. 22-10-34-i of the French Commercial Code (general "ex post" vote)

This section presents, for each corporate officer of the Company, all the information mentioned in Article L. 22-10-9 I of the French Commercial Code relating to their compensation for the fiscal year 2020.

In accordance with the provisions of Article L. 22-10-34 I of the French Commercial Code, the shareholders of the Company will be asked to vote on this information in a resolution submitted to the next General Shareholders' Meeting.

- Information on the compensation granted to executive corporate officers for the fiscal year ended December 31, 2020

The total compensation and benefits in kind owed to the Chairman of the Board of Directors and the Chief Executive Officer during the past fiscal year are presented in Tables 1 and 2 using the AMF nomenclature in the 2020 Universal Registration Document, which distinguishes between fixed, variable and exceptional components of this compensation.

The relative proportion of fixed and variable compensation in the total compensation due to executive corporate officers during fiscal year 2020 is approximately as follows:

- For Mr. Alexis Peyroles, Chief Executive Officer, fixed compensation represents 77.8% and variable compensation represents 18.4% of total compensation,
- For Ms. Dominique Costantini, Chairman of the Board of Directors, fixed compensation represents 77.4% and variable compensation represents 18.1% of total compensation.

The payment of variable and exceptional components of compensation will be subject to and suspended until the General Shareholders' Meeting approves the components of compensation components of the relevant executive corporate officer. Consequently, the Company does not foresee the option of requesting the return of variable compensation.

The last General Shareholder's Meeting on June 16, 2020, in its ninth and tenth resolutions, in accordance with the law in force at the time, approved the principles and criteria for setting, distributing and allocating the fixed, variable and exceptional components of the total compensation and benefits of any kind attributable to the executive corporate officers in respect of the fiscal year ended December 31, 2019.

The Company has not deviated from the procedure for implementing the compensation policy or made any exceptions to the policy.

- Breakdown of compensation and benefits in kind for each executive corporate officer.

None

- Summary of compensation and benefits in kind of executive corporate officers

None

- Summary of employment contracts, specific retirement benefits, severance payments and non-compete clauses of executive corporate officers.

The Company has not provisioned sums for the purpose of payment of pensions, retirement and other benefits for the benefit of corporate officers and/or executive corporate officers who do not benefit elsewhere (or have not benefited) from severance or a hiring bonus within the Company.

- Information on the compensation granted to the directors for the fiscal year ended December 31, 2020

All compensation received by directors for their term of office during the past fiscal year is presented in table 3 in section 13.1. of the 2020 Universal Registration Document.

If, following a change in its current composition, the Board of Directors was no longer composed in accordance with the first paragraph of Article L. 225-18-1 of the French Commercial Code, the payment of compensation to the Directors for their participation in the work of the Board would be suspended. The payment would be reinstated when the composition of the Board of Directors is legally restored, including the arrears since the suspension.

- Equity ratios between the level of management compensation and the average and median compensation of the Company's employees and annual change in compensation, Company performance and equity ratios.

This presentation is in accordance with the terms of Article L.22-10-9 of the French Commercial Code.

It sets out the level of compensation of the Chairman of the Board of Directors and the Chief Executive Officer as a ratio of both the mean compensation of employees and the median compensation of employees (excluding corporate officers) of the Company, as well as how these ratios have changed over the previous two fiscal years.

The ratios below were calculated on the basis of fixed and variable annualized compensation paid in the relevant fiscal years as well as free shares and founders' warrants allocated in the same periods at fair value. The scope of this information is based on the workforce of OSE Immunotherapeutics.

	2016 fiscal year	2017 fiscal year	2018 fiscal year	2019 fiscal year	2020 fiscal year
<b>Chairman of the Board of Directors *</b>					
Ratio with average employee compensation	518%	485%	597%	470%	596%
Ratio with median employee compensation	700%	644%	799%	622%	861%
<b>Chief Executive Officer **</b>					
Ratio with average employee compensation	491%	1657%	1351%	1514%	2441%
Ratio with median employee compensation	664%	2199%	1809%	2004%	3525%

\* Ms. Dominique Costantini was Chief Executive Officer between 2014 and March 2018 and has been Chairman of the Board of Directors since that date. The ratios were calculated on the basis of aggregate remuneration paid to Ms. Costantini for her office and employment contract. Free share allocations were also factored in when calculating these ratios.

\*\* Mr. Alexis Peyrols was Chief Operating Officer between May 2016 and March 2018, and since then has been Chief Executive Officer. The ratios were calculated on the basis of aggregate remuneration paid to Mr. Peyrols for his office and employment contract. Free share allocations were also factored in when calculating these ratios.

Given its activity, the Company believes that no financial information is relevant to qualify its performance over the last five years.

#### 1.4. Compensation policy for corporate officers for the fiscal year 2021 (principles and criteria for setting, distributing and allocating components of compensation for executive corporate officers for the purposes of *ex-ante* voting).

In accordance with Article L. 22-10-8 of the French Commercial Code, this report sets out the compensation policy for corporate officers, which is the subject of a draft resolution submitted to the approval of the General Shareholders' Meeting held to approve on the financial statements for the fiscal year 2020.

If the General Shareholders' Meeting does not approve the resolution(s) for this purpose, the compensation will be determined in accordance with the compensation allocated for the previous fiscal year.

As of the date of this report, OSE Immunotherapeutics has two executive corporate officers: Dominique Costantini, Chairman of the Board of Directors and Alexis Peyrols, Chief Executive Officer, and nine directors including Dominique Costantini and Alexis P  yrols.

Dominique Costantini and Alexis Peyrols are paid by the Company under their employment contracts. Maryvonne Hiance and Nicolas Poirier, directors, are paid under their employment contract and not for their corporate office. The Directors of the Company receive a fixed annual compensation (formerly directors 'fees) allocated by the Board of Directors.

##### 1.4.1. Compensation policy for all corporate officers

- General principles

In accordance with the provisions of Article L. 22-10-8 of the French Commercial Code, this section sets out the principles and criteria for setting the fixed, variable and exceptional components of the total compensation and benefits in kind of executive corporate officers: Chairman of the Board of Directors and Chief Executive Officer of OSE Immunotherapeutics for the 2020 fiscal year.

On the basis of a report issued by the Board of Directors, a proposal will be submitted to the Combined General Shareholders' Meeting on June 24, 2021, to approve the compensation policy of executive corporate officers for the next fiscal year.

In the event that the Combined General Shareholders' Meeting of June 24, 2021, does not approve the resolution adopting the compensation policy for executive corporate officers, compensation will be set in line with the compensation allocated

in the previous fiscal year or, if no such compensation was allocated in respect of the previous fiscal year, in line with current Company practice.

In accordance with Article L. 22-10-8 of the French Commercial Code, the payment of variable and exceptional components of compensation will be subject to the approval by the General Shareholders' Meeting of the components of the compensation of the relevant individuals under the conditions set out in Article L. 225-100 of the French Commercial Code.

In accordance with the law of July 3, 2008, the disclosures presented herein are established by referring to the corporate governance code and additional recommendations regarding communication on the compensation of executive corporate officers of listed companies as defined by MiddleNext.

In accordance with Article 2 of the Internal Rules of the Board of Directors, in order to determine the level of compensation of its management as well as the information disclosed in this respect, the Board of Directors will draw on the following seven principles.

- Comprehensiveness: determining the compensation of executive corporate officers must be comprehensive: fixed part, variable part (bonuses), stock-options, free shares, attendance fees, retirement conditions and personal benefits must be factored in when assessing overall compensation.
- Balance between the different components of compensation: reasons must be given for each component of compensation which must be in the Company's general interest.
- Benchmark: insofar as possible, this compensation must be assessed based in the context of a given role and reference market and proportionate to the Company's position, while paying attention to its inflationary impact.
- Consistency: the compensation of the executive corporate officer must be consistent with that of other managers and employees within the Company.
- Legibility of rules: rules must be simple and transparent; performance criteria used to calculate the variable part of compensation or, where relevant, to allocate options or free shares, must be consistent with the business's objectives, be stringent, explicable and, where possible, long-term.
- Balanced: when determining compensation and the allocation of options or free shares, the right balance must be struck between the general interest of the Company, market practices and the performance of management.
- Transparency: annual information is provided to shareholders on the compensation received by management in accordance with applicable regulations.
- Policy on the distribution of directors' fees

All compensation received by directors for their term of office during the past fiscal year is presented in table 3 in section 13.1. of the 2020 Universal Registration Document.

If, following a change in its current composition, the Board of Directors was no longer composed in accordance with the first paragraph of Article L. 225-18-1 of the French Commercial Code, the payment of compensation to the Directors for their participation in the work of the Board would be suspended. The payment would be reinstated when the composition of the Board of Directors is legally restored, including the arrears since the suspension.

The Board of Directors may receive fixed annual compensation in the form of directors' fees, set by the General Shareholders' Meeting, the amount of which is charged to operating expenses.

The Board of Directors decides on the distribution of directors' fees among directors following a proposal by the Appointments and Compensation Committee. This distribution may take into account directors' specific experience, their actual participation at Board meetings or their actual participation at Committee meetings.

Under Article L. 225-46 of the French Commercial Code, they may also receive exceptional compensation for specific assignments or offices assigned by the Board.

#### 1.4.2. Compensation policy for executive corporate officers

The overall compensation of executive corporate officers is composed of the following:

- a portion of fixed compensation under their employment contract;
- variable compensation components under their employment contract.

These components are precisely defined by the Board of Directors but are not made public in full for reasons of confidentiality.

**1.4.2.1 Description of the principles and criteria on which the Chairman of the Board of Directors' compensation is based**

- a) No fixed or variable compensation

According to the Company's bylaws, the compensation of the Chairman of the Board of Directors of OSE Immunotherapeutics is set by the Board for the duration of his three-year term. However, the Chairman of the Board of Directors does not receive any fixed compensation in respect of his office, nor variable compensation.

For fiscal year 2021, Ms. Costantini will receive her salary as Director of Development on the basis of a gross annual remuneration of €302,500 (for 151.67 hours of work per month).

For fiscal year 2021, its objectives were set as follows: to succeed in the continued clinical development of the Company's portfolio, to drive R&D and scientific recognition, and to implement the growth strategy. Variable compensation equivalent to no more than three months' salary is to be paid in cash.

- b) No exceptional compensation

Other than her compensation in respect of her unemployment contract (see a) above), the Chairman of the Board of Directors is not entitled to severance pay or to any compensation in respect of a non-compete clause.

- c) Benefits

The Chairman of the Board of Directors has been receiving directors' fees since March 28, 2019. She receives no other benefits.

**1.4.2.2 Description of the principles and criteria on which the Chief Executive Officer's compensation is based**

According to the Company's bylaws, the compensation of the Chief Executive Officer of OSE Immunotherapeutics is set by the Board.

- a) No fixed or variable compensation

The Chief Executive Officer does not receive any compensation in respect of his corporate office.

For fiscal year 2021, Alexis Peyroles will receive his salary as Director of Operations on the basis of a gross annual remuneration of €350,000.

For fiscal year 2021, the Board of Directors of December 8, 2020, following the recommendation of the Appointments and Compensation Committee on the same day, set the objectives of Alexis Peyroles as follows: to succeed in the continued clinical development of the Company's portfolio, drive R&D and scientific recognition, and to set up the strategy for the future growth strategy. Variable compensation is 50% of the fixed compensation per objective, half of which is to be paid in shares.

- b) No exceptional compensation

Other than compensation in respect of his employment contract (see a) above), the Chief Executive Officer is not entitled to severance pay nor to compensation in respect of a non-compete clause.

c) Allocation of securities giving access to capital

In 2020, Alexis Peyroles vested 150,000 free shares at the end of the vesting period (on June 27, 2020) and 22,625 free shares at the end of the vesting period (on December 18, 2020). In addition, the Board of Directors allocated to him 161,363 free shares (150,000 on June 17, 2020, and 11,363 on December 8, 2020, corresponding to the variable portion of his compensation based on the 2020 targets). He received other allocations in respect of previous years as described in the annual financial report included in the Universal Registration Document.

In accordance with Article L. 225-197-1 II of the French Commercial Code and standard Company practice in terms of the allocation of free shares to management, Alexis Peyroles has committed to holding 5% of the free shares allocated to him as registered shares until the end of his corporate office within the Company.

d) Allocation of directors' fees

As a director, Alexis Peyroles received €16,685 in directors' fees for 2020.

e) No other benefits

Alexis Peyroles receives no other benefits.

#### 1.4.2.3 Description of the principles and criteria for the remuneration of the Vice-Chairman and Director

According to the Company's bylaws, the compensation of directors is decided by the Board of Directors, within the budget for directors' fees.

f) No fixed or variable compensation

The position of Vice Chairman of the Board of Directors, held by Maryvonne Hiance, does not give the right to any specific compensation.

Maryvonne Hiance assumed an operational role of Strategic Advisor within Executive Management under a contract dated May 31, 2016. At its meeting on June 26, 2019, the Board of Directors wished to amend the title and position in her employment contract to Director of Public Affairs; this change was made without a salary raise. Compensation under this employment contract is calculated on the basis of €120,000 in gross annual salary. The employment contract took effect on May 31, 2016, concurrently with the completion of the merger. Variable compensation equal to up to three months' salary is provided for based on the achievement of certain targets.

g) No exceptional compensation

Other than her compensation in respect of her unemployment contract (see a) above), the Vice Chairman of the Board of Directors is not entitled to severance pay or to any compensation in respect of a non-compete clause.

h) Allocation of securities giving access to capital

In 2020, Maryvonne Hiance vested 25,000 free shares at the end of the vesting period (on June 27, 2020). In addition, the Board of Directors allocated to her 10,000 founders' warrants on June 17, 2020.

In accordance with Article L. 225-197-1 II of the French Commercial Code and standard Company practice in terms of allocating free shares to management, Maryvonne Hiance has committed to holding 5% of the free shares allocated to her as registered shares until the end of her corporate office within the Company.

i) Allocation of directors' fees

As a director, Maryvonne Hiance received €22,724 in directors' fees for 2020.

j) No other benefits

Maryvonne Hiance receives no other benefits.

**1.4.2.4 Description of the principles and criteria for the compensation of the Chief Scientific Officer, who also represents the employee shareholders.**

The remuneration of the director representing employee shareholders is the same as that allocated to the directors.

k) No fixed or variable compensation

The Director representing the employee shareholders does not receive any compensation for his or her corporate office.

Nicolas Poirier initially signed an open-ended employment contract with the Company as Chief Scientific Officer on May 31, 2016. Compensation under this employment contract is calculated on the basis of a gross annual amount of €180,000 increased to a gross annual amount of €200,000 from July 1, 2020. Variable compensation is also provided for.

l) No exceptional compensation

Other than compensation in respect of his employment contract (see a) above), Nicolas Poirier is not entitled to severance pay nor to compensation in respect of a non-compete clause.

**m) Allocation of securities giving access to capital**

In 2020, Nicolas Poirier vested 25,000 free shares at the end of the vesting period (March 26, 2020) and 25,000 free shares at the end of the vesting period (June 27, 2020). The Board of Directors also allocated to him 100,000 free shares on June 17, 2020.

In accordance with Article L. 225-197-1 II of the French Commercial Code and standard Company practice in terms of allocating free shares to management, Nicolas Poirier has committed to holding 5% of the free shares allocated to him as registered shares until the end of his corporate office within the Company.

n) Allocation of directors' fees

As a director, Nicolas Poirier received €18,937 in directors' fees for 2020.

o) No other benefits

Nicolas Poirier receives no other benefits.

**1.4.3. Directors' compensation policy**

The General Shareholders' Meeting of June 14, 2017, set the total directors' fees allocated to the Board of Directors at two hundred thousand euros (€200,000) net for previous years, pending any subsequent resolution passed by the Ordinary General Shareholders' Meeting.

At its meeting on June 26, 2019, the Board of Directors voted to allocate directors' fees to the directors as follows:

- €2,500 per meeting attended in person (one meeting is scheduled per quarter);
- €1,500 per meeting attended by video conference or other means of telecommunication subject to the internal rules;
- Travel and lodging costs incurred by each Committee participant for meetings of the Board of Directors held outside of Europe will be covered for an amount of €2,500 per meeting, while costs incurred for meetings in Europe will be covered for an amount of €500 per meeting.

At its meeting on March 28, 2019, the Board voted to include the Chairman of the Board and Directors and Chief Executive Officers among the directors entitled to these directors' fees.

Due to the COVID-19 epidemic making it difficult or impossible to hold physical meetings, the Chief Executive Officer, in agreement with the members of the Appointments and Remuneration Committee, has adapted the above rules. It has decided that the participation of Directors who have attended Board meetings by audio or video conference since March 2020 will be remunerated in the same way as those who participated in person, and that this rule would also apply to all meetings of the Board and its committees for the duration of the health emergency.

Members of the Board of Directors received a total of €148,500 net in directors' fees from the Company for fiscal year 2020.

A breakdown of the compensation awarded to corporate officers is presented in summary form in Section 13.1 "Overall gross compensation for members of the Board of Directors and General Management."

#### 1.4.3 Pensions and other benefits

##### 1.4.3.1 Compensation, payments and benefits due or likely to become due as a result of taking or leaving a corporate office or a change in duties

The Company has not provisioned sums for the purpose of payment of pensions, retirement and other benefits for the benefit of corporate officers and/or executive corporate officers who do not benefit elsewhere (or have not benefited) from severance or a hiring bonus within the Company.

#### 4.2.2.2 Other benefits

At December 31, 2020, the Company provisioned for retirement benefits as well as for bonuses for corporate officers and/or executive corporate officers who are not otherwise entitled (or have not previously been entitled) to severance or a hiring bonus.

#### 1.5 Information on corporate officers

##### Agreements covered by Articles L. 225-38 et seq. of the French Commercial Code

See Section 17.1.2 of the Universal Registration Document.

##### 1.6 Governance and list of offices and positions held by each corporate officer

See Section 12 (Governing, management, supervisory bodies and executive management) and 13 (Compensation and benefits) of the Universal Registration Document.

#### 5 Items likely to have an impact in the event of a public offering

In accordance with Article L. 22-10-11 of the French Commercial Code, the following items may have an impact in the event of a takeover bid:

The Company's capital structure	See Note to the Financial Statements Number 4: Capital, Section 18.1.6 of the Universal Registration Document
The restrictions contained in the Bylaws on exercising voting rights and share transfers or agreement clauses brought to the attention of the Company in accordance with Article L. 233-11 of the French Commercial Code.	See (iv) Shareholding disclosure thresholds (Article 16 of Bylaws)
Any direct or indirect investments in the Company's share capital of which it is aware under Articles L. 233-7 and L. 233-12 of the French Commercial Code.	None
The list of holders of any securities conferring special control rights and description of these securities.	None
The control mechanisms provided for in any employee shareholding plan when control rights are not held by employees.	None
Shareholder agreements of which the Company is aware and which may include restrictions on share transfers and on exercising voting rights.	None
Rules governing the appointment and replacement of members of the Board of Directors as well as changes to the Company's Bylaws.	See Report on corporate governance and legal and statutory provisions
The powers of the Board of Directors, in particular issuing or buying back shares.	See Appendix C - Corporate governance report, Sections 1.1.2 (Functioning of the Board of

	Directors) and 1.1.4 (Restrictions on the powers of the Chief Executive Officer and Board of Directors)
Any agreements entered into by the Company that are amended or terminated in the event of a change of control of the Company, unless this disclosure would seriously harm its interests, notwithstanding any legal disclosure duty.	See Note 4 to the consolidated financial statements: Capital (Section 18.1.6 of the Universal Registration Document)
Agreements providing for severance payments for the Board of Directors or employees should they resign or be dismissed without proper cause or if their employment is terminated as a result of a public offering.	None

### The Board of Directors

## Appendix D - Cross-reference tables

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**INFORMATION FROM THE PROVISIONS OF APPENDICES 1 AND 2 OF THE COMMISSION DELEGATED REGULATION (EU) 2019/980 OF MARCH 14, 2019 SUPPLEMENTING REGULATION (EU) 2017/1129 OF THE EUROPEAN PARLIAMENT AND THE COUNCIL**

The cross-reference table below can be used to identify in the Universal Registration Document the information required under Appendices 1 and 2 of the Delegated Regulation (EU) 2019/980 of March 14, 2019.

<b>Commission Delegated Regulation (EU) 2019/980 of March 14, 2019, supplementing Regulation (EU) 2017/1129 (Appendices 1 and 2)</b>		<b>Universal Registration Document</b>
<b>Number</b>	<b>Section</b>	<b>Reference</b>
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1.2	Statement of the persons responsible	1.2
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1.4	Statement regarding third-party information	1.4
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<b>3</b>	<b>Risk factors</b>	<b>3</b>
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4.2	The Company's place of registration, its registration number and legal entity identifier	4.2
4.3	Date and term of incorporation of the Company	4.3
4.4	Domicile, legal form, legislation, country of incorporation, address, telephone number and website	4.4
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5.6	Competitive position	5.6
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<b>6</b>	<b>Organizational structure</b>	<b>6</b>
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#### CROSS-REFERENCE TABLE FOR THE MANAGEMENT REPORT

The cross-reference table below can be used to identify the information in this Universal Registration Document which comprises the management report to be published in accordance with the provisions of Article L. 225-100 of the French Commercial Code.

Management report	Paragraph in this document
Presentation of the Company's position during the past fiscal year (Article L. 232-1 II)	Appendix A, 1.2
Major events between the reporting date and the publication of the management report (Article L. 232-1 II)	Appendix A, 1.3
Foreseeable changes to the Company's position (Article L. 232-1 II)	Appendix A, 1.3
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Objective and comprehensive analysis of business development	Appendix A
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Information on the use of financial instruments (Article L. 225-100-1 1° to 3° and 6°)	18.1.6 (3., note 13)
Main features of the internal control and risk management procedures concerning the preparation and processing of accounting and financial information (Article L. 225-100-1 5°)	Appendix A, 8
Adjustments in the event that securities giving access to capital are issued (Article L. 228-99)	N/A
Executive corporate officers' requirements to hold shares until the termination of their positions by the Board of Directors when deciding on the allocation of free shares (Article L. 225-197-1 II para. 4)	Appendix C, 4.3
Non tax-deductible expenses and reintegrated expenses following a tax adjustment (Articles 223 quater and 22 quinque of the French General Tax Code).	N/A
Identity of the direct or indirect holders of more than one-twentieth, one-tenth, three-twentieths, one-fifth, one-quarter, one-third, one-half, two-thirds, eighteen-	16.1.1

twentieths, nineteen-twentieths of the share capital or voting rights (Article L. 233-13)	
Share buy-back transactions (Article L. 225-211 para. 2)	N/A
Securities transactions carried out by management (Article 223-26 of the General Regulations of the French Financial Markets Authority)	14. Appendix A, appended to the report
Employee shareholding (Article L. 225-102)	15.2
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Payment terms for customers and suppliers (Article L. 441-6-1 para. 1)	Appendix A, 2.5

#### CROSS-REFERENCE TABLE FOR THE ANNUAL FINANCIAL REPORT

The cross-reference table below can be used to identify any information in this Universal Registration Document which makes up the annual financial report to be published in accordance with articles L. 451-1-2 of the French Monetary and Financial Code and 222-3 of the General Regulations of the French Financial Markets Authority.

Number	Section	Paragraph in this document
1	Separate financial statements	18.1.5
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4	Statement by natural persons who take responsibility for the annual financial report	1.1
5	Statutory Auditors' report on the separate financial statements	18.1.1.2
6	Statutory Auditors' report on the consolidated financial statements	18.1.1.1