EDISON

OSE Immunotherapeutics

Re-initiation of coverage

Milestones anticipated throughout FY23

Pharma and biotech

OSE Immunotherapeutics has announced its FY22 results, providing financial and operational updates as the company continues to advance its key clinical assets. A confirmatory and potentially pivotal Phase III study is planned for Tedopi, OSE's lead cancer vaccine candidate, which we expect to be initiated by end-FY23/early-FY24, and this would mark a significant clinical milestone, in our view. Additional upcoming catalysts for investor attention include readouts in Q423 for OSE-127, being investigated in a Phase II study in ulcerative colitis (UC). OSE-127 had previously been subject to a two-step licensing option granted to Servier. However, following negative readouts from a Phase II Servier-sponsored trial in primary Sjögren's syndrome (SS), OSE and Servier have mutually decided to terminate the option license agreement. We value OSE at €280.8m or €15.2 per share, with Tedopi as the primary contributor to this valuation, for which we expect commercialisation in 2028.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/21	26.3	(17.2)	(0.95)	0.0	N/A	N/A
12/22	18.3	(18.0)	(0.97)	0.0	N/A	N/A
12/23e	15.0	(17.8)	(0.96)	0.0	N/A	N/A
12/24e	15.0	(21.9)	(1.18)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Pivotal Phase III study next for Tedopi

While the readouts from the Phase III ATALANTE-1 trial were positive, they were not sufficient to satisfy the requirements for Tedopi's approval, which may be attributed to the study not achieving its full patient enrolment due to disruption during the COVID-19 pandemic. Following discussions with regulators (the FDA and EMA), a follow-on Phase III confirmatory and potentially pivotal trial is now planned in second-line non-small cell lung cancer (NSCLC) patients post immune checkpoint inhibitor (ICI) failure. We expect the new study to start by end-FY23/early-FY24, with readouts in FY25–26, and now estimate a conservative launch date for Tedopi in 2028 (vs our prior estimate of 2023).

Financing provides a runway into Q224

In December 2022 OSE drew down on the second tranche of €10m (bearing a 5% interest rate) of a facility agreed (€25m in total) with the European Investment Bank (EIB), with a final €5m remaining. In April 2023, OSE entered into an equity financing line agreement with Vester Finance, which has subscribed to a maximum of 2.8m shares over 24 months. We note that, should the shares be fully subscribed, existing shareholders may be diluted by up to 14.8%.

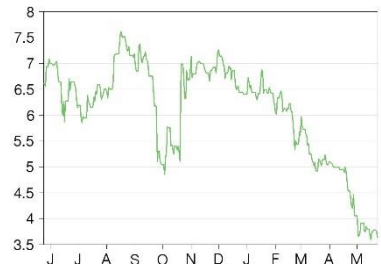
Valuation: €280.8m or €15.2 per share

We value OSE at €280.8m or €15.2 per share. Tedopi is the primary contributor to our valuation. We assume a licensing deal for Tedopi in 2027, worth up to €650m based on precedent deals for cancer vaccine technologies, and anticipate the commercialisation of this asset in 2028.

24 May 2023

Price	**€3.63**
Market cap	**€67m**
	€0.94/US$
Net debt (€m) at 31 December 2022 (excluding lease liabilities)	14.7
Shares in issue	18.5m
Free float	65%
Code	OSE
Primary exchange	Euronext Paris
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(19.9)	(33.9)	(45.8)
Rel (local)	(17.9)	(34.3)	(52.4)
52-week high/low		€7.60	€3.59

Business description

OSE Immunotherapeutics is based in Nantes and Paris in France and is listed on the Euronext Paris exchange. It is developing immunotherapies for the treatment of solid tumours and autoimmune diseases and has established several partnerships with large pharma companies.

Next events

Tedopi Phase III trial commencement	FY23
OSE-127 UC Phase II readout	FY23

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Edison profile page

Investment summary

Company description: Broad pipeline with established partners

OSE Immunotherapeutics is a French biotechnology company focused on the development of novel therapeutic agents for the treatment of cancer and autoimmune disorders. The company's leading clinical asset is Tedopi, a cancer vaccine being investigated for the treatment of NSCLC. Tedopi reported positive top-line data from the Phase III ATALANTE-1 trial, demonstrating efficacy and safety in NSCLC patients, and following discussions with US and EU regulators, the company is preparing a confirmatory and potentially pivotal follow-on Phase III study. Tedopi is also part of three ongoing investigator-sponsored Phase II studies in combination with ICIs or chemotherapy for the treatment of NSCLC, ovarian and pancreatic cancer. OSE has a further four clinical assets in its pipeline: OSE-127 for the treatment of UC, OSE-172/BI 765063 in colorectal cancer (out-licensed to Boehringer Ingelheim), FR-104/VEL-101 as a maintenance therapy following kidney transplantation (out-licensed to Veloxis Pharmaceuticals) and OSE-279 in solid tumours (fully owned by OSE).

Valuation: €280.8m or €15.2 per share

We value OSE at €280.8m or €15.2 per share on a risk-adjusted NPV analysis using a 12.5% discount rate, including net debt of €14.7m at end-December 2022. We have included five assets in our valuation of OSE: Tedopi in NSCLC, OSE-127 in UC, OSE-172/BI 765063, FR-104/VEL-101 and OSE-279. As the Tedopi pancreatic and ovarian cancer studies are investigator sponsored, we have excluded these indications from our valuation until their clinical development strategies become more apparent. We assume a full licensing deal for Tedopi is achieved in 2027 following the completion of the Phase III NSCLC study. Additionally, OSE-279 is currently in a first-in-human open-label Phase I dose-escalation and expansion study, and the solid tumour indication for which the treatment may be most effective is not yet known. However, OSE has stated that it intends to address orphan indications with significant unmet needs and, as such, for the purposes of our model we have assumed OSE-279 will be advanced in small cell lung cancer (SCLC).

Financials: Cash runway into Q224

In FY22, OSE reported revenues of €18.3m through payments received from licensing partners. Operating losses were €18.4m and the company ended the period with a gross cash position of €25.6m and net debt of €14.7m. OSE has a debt facility in place with the EIB worth up to €25.0m, of which OSE has, to date, drawn down a total of €20.0m bearing interest of 5%. The company has also secured an equity financing agreement with Vester Finance, which has committed to subscribing up to a maximum of 2.8m shares of OSE common stock (14.8% of existing share capital). Should the EIB debt financing facility be fully exercised, at our projected cash burn rates, and in line with management guidance, we forecast OSE to be operationally funded into Q224.

Sensitivities: Follow-on Phase III will require additional funding

OSE is subject to the regular commercial, development and regulatory risks associated with drug development. While the company has a later-stage clinical asset in Tedopi, the planned follow-on Phase III study will require OSE to raise further capital to fully fund the trial to completion. If this financing is realised through equity issuance, this may result in dilution to OSE's existing shareholders. The licensing deals with Boehringer Ingelheim and Veloxis diversify the impact of developmental risk and clinical trial expenditure for OSE. However, as with all licensing partnerships, these assets could potentially be returned to OSE in the event of clinical failures or strategic changes from partners, as was the case with Servier and OSE-127. Additionally, the successful commercialisation and launch of Tedopi, provided results from the follow-on Phase III

study are positive, are highly dependent on OSE securing a licensing deal with larger pharmaceutical partners. Failure to secure such a deal may delay or limit market uptake of Tedopi.

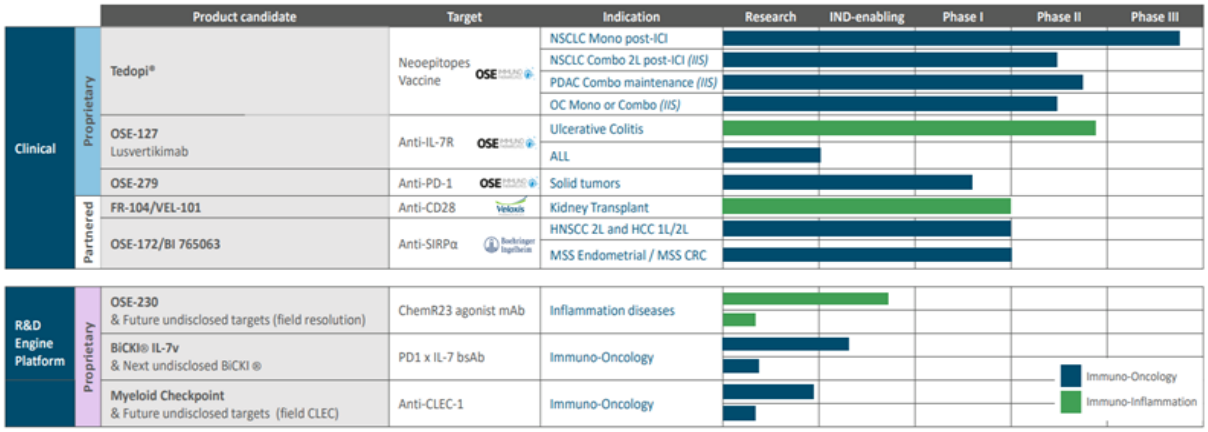
Active pipeline in immuno-oncology and -inflammation

OSE has multiple ongoing clinical programmes covering both immuno-oncology and immuno-inflammation disease areas (Exhibit 1). Spearheading OSE's development pipeline is Tedopi, a cancer vaccine comprised of a unique combination of neoepitopes, small peptides derived from tumour-specific antigens expressed by various cancer cells. Tedopi is being developed for the treatment of patients with NSCLC with secondary resistance to ICIs. The treatment works by directly activating tumour-specific T-cells, which, in turn, bind tumour-associated antigens presented on the surface of cancer cells by the HLA-A2 receptor (c 45% of NSCLC patients are HLA-A2 positive). Tedopi has shown encouraging data in clinical trials so far, and OSE is preparing a confirmatory and potentially pivotal Phase III trial to support the regulatory approval of the therapy. While positive clinical results were reported from the previous Phase III ATALANTE-1 study, we note that patient recruitment in the study was affected by the COVID-19 pandemic, with only 219 of the planned 363 patients enrolled in the study. This may account for why the ATALANTE-1 study alone was not sufficient to fulfil the requirements for regulatory approval. Following discussions with the regulators, OSE has now planned a follow-on pivotal study that will focus on second-line NSCLC patients who have acquired resistance to ICIs.

Another of OSE's proprietary assets is OSE-279, a high-affinity anti-PD-1 monoclonal antibody ICI therapy that blocks both PD-L1 and PD-L2. These are the ligands of PD1 overexpressed by tumour cells, and inhibition of which is a validated mechanism for tumour immune escape. OSE-279 is currently in a Phase I/II dose-escalation trial as a monotherapy for the treatment of solid tumours or lymphomas.

In addition to these immuno-oncology assets, OSE is working on the development of immuno-inflammation therapies. OSE-127 is the most advanced clinical candidate in this space, and is being evaluated for the treatment of UC. This candidate is a monoclonal antibody that acts as an antagonist of the interleukin-7 receptor (IL-7R), a cytokine on the surface of certain immune system T-cells, for the downregulation of inflammatory immune responses. OSE-127 has previously shown encouraging safety data across two Phase IIa studies, for SS (NCT04605978), and UC (NCT04882007). However, in Q223, negative readouts were reported from the Servier-sponsored trial in primary SS. Management attributed the lack of efficacy to uncertainty in the role of IL-7 biology in the disease. OSE and Servier have mutually decided to terminate the option license agreement, and the clinical development in primary SS will not be pursued. OSE will continue with the clinical development of OSE-127 in UC with full rights to the asset, and top-line results for this study are anticipated in Q423.

Exhibit 1: OSE Immunotherapeutics' pipeline



Source: OSE Immunotherapeutics corporate presentation

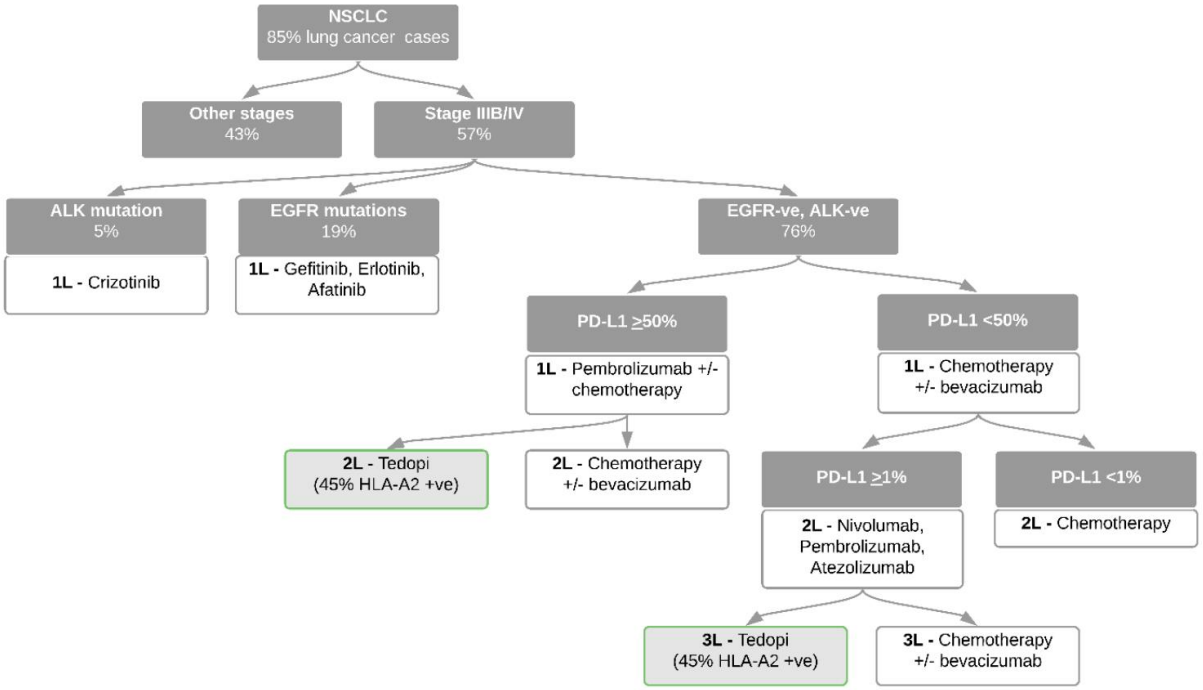
Tedopi confirmatory trial in focus in FY23

Patients with progressive disease showing secondary resistance to ICI treatment represent a significant unmet medical need, and with no approved therapies to address this, we believe this offers sizeable market opportunity. OSE has already conducted a randomised Phase III trial (ATALANTE-1) to evaluate Tedopi as second- or third-line treatment following ICI failure in HLA-A2 positive patients with locally advanced (stage IIIB) or metastatic (stage IV) NSCLC. The standard of care (SoC) for NSCLC patients is typically dependent on the following:

- The stage of the cancer (the size of the tumour and whether it has spread beyond the lungs to other areas of the body).
- Whether the cancer has mutations (for example, ALK or EGFR mutations).
- The general health of the patient.

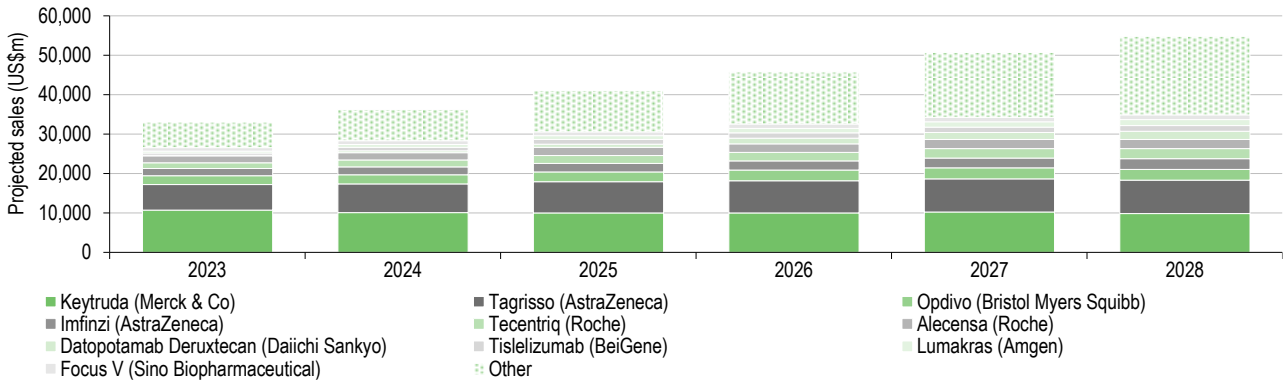
According to the World Health Organization, in 2020 there were 2.2m cases of lung cancer worldwide, and it is estimated that there will be 238.3k new cases of lung cancer in the United States alone in 2023. NSCLC is the most common type of lung cancer, accounting for c 85% of cases. For patients diagnosed with stage IIIB/IV NSCLC (without ALK and EGFR mutations), the typical first-line treatment regimen involves chemotherapy in combination with an ICI. However, in many cases patients may not respond to treatment (primary resistance) or they may develop resistance after an initial period of response (secondary resistance). We note that the NSCLC market is a highly competitive space and is dominated by ICIs such as Merck's blockbuster Keytruda (pembrolizumab). However, the existing strategy of positioning Tedopi in the post-ICI setting (Exhibit 2) may avoid direct competition with ICIs and provide an opportunity for OSE to garner a share of the growing NSCLC market, which is projected to reach $55bn by 2028 (source: EvaluatePharma, Exhibit 3).

Exhibit 2: Potential positioning of Tedopi in NSCLC based on guidelines



Source: Edison Investment Research; American Society of Clinical Oncology Clinical Practice Guideline Update 2017; Management of non-small cell lung cancer: The era of immunotherapy. Note: Some patients may also be addressable from other groups, eg, checkpoint inhibitors are recommended as a second-line treatment for patients with BRAF mutations (ASCO guidelines). Drugs approved since the guidelines were last updated have not been included in this figure.

Exhibit 3: Projected sales for the NSCLC market



Source: EvaluatePharma

In the ATALANTE-1 study, 219 patients were enrolled, of whom 118 met the definition of 'population of interest' with regard to exhibiting secondary resistance. Tedopi was compared to existing SoC chemotherapy treatments (docetaxel or pemetrexed) and results showed that the therapy significantly improved overall survival (OS) rates and maintained positive patient-reported outcomes (PROs), quality of life and safety. More specifically, highlights from this trial included:

- Tedopi demonstrated a 44.4% one-year OS rate versus 27.5% with the SoC chemotherapy.
- Only an 11% rate of adverse events was observed with Tedopi versus 35% with the SoC chemotherapy.

In terms of competition for new therapies, there are several other studies targeting second- or third-line NSCLC treatment options that are either ongoing or have been recently completed (Exhibit 4). In the selection of trials highlighted here, a range of technologies have been used, including

tyrosine kinase inhibitors and antibody-based therapies in combination with ICIs and chemotherapy agents. However, several of the trials failed to meet their primary endpoints of OS and progression-free survival (PFS), highlighting the challenge associated with this indication. Of note for positive results is the Southwest Oncology Group (SWOG) Cancer Research Network's Lung-MAP S1800A trial, which showed a median OS (mOS) of 15.0 months in the experimental arm versus 11.6 months for the control. For OSE's ATALANTE-1 trial, mOS was reported as 11.1 months with Tedopi versus 7.5 months with the control. We note that Tedopi is the only cancer vaccine from this selection of trials, which may offer market differentiation. In addition, Tedopi has demonstrated a desirable safety profile, offering further differentiation, in our view, in contrast to antibody-drug conjugates and traditional chemotherapy agents, which are typically associated with more adverse side effects.

Exhibit 4: Selection of ongoing clinical trials for second- or third-line NSCLC treatments

Trial	Company	N	Target population	Technology	Experimental arm	Control	Primary endpoint
Lung-MAP S1800A (Phase II)	SWOG Cancer Research Network	166	All comers 'Non-matched' NSCLC	Monoclonal antibody tyrosine kinase inhibitor + ICI	Ramucirumab + pembrolizumab	Docetaxel ± ramucirumab	OS Readout (mOS): 15.0 vs 11.6 months Hazard ratio: 0.61
SAPPHIRE (Phase III)	Mirati Therapeutics	532	Non-squamous Prior PD-1/L1 therapy for ≥4 months	Tyrosine kinase inhibitor + ICI	Sitravatinib + nivolumab	Docetaxel	OS Final analysis expected mid-2023
CONTACT-01 (Phase III)	Hoffmann-La Roche	366	All comers	Tyrosine kinase inhibitor + ICI	Cabozantinib + atezolizumab	Docetaxel	OS Readout: endpoint not met
LEAP-008 (Phase III)	Merck Sharp & Dohme LLC	405	All comers	Tyrosine kinase inhibitor + ICI	Lenvatinib + pembrolizumab	Docetaxel	PFS and OS Readout: endpoint not met
CARMEN-LC03 (Phase III)	Sanofi	554	Non-squamous CEACAM5 2+ expression	Antibody-drug conjugate	Tusamitamab-ravtansine	Docetaxel	PFS and OS Expected submission timeline: 2024
TROPION-Lung01 (Phase III)	Daiichi Sankyo	590	All comers	Antibody-drug conjugate	Datopotamab-deruxtecan	Docetaxel	PFS and OS Update expected in 2023
CANOPY-2 (Phase III)	Novartis	237	All comers	Monoclonal antibody IL-1β inhibitor + chemotherapy agent	Canakinumab + docetaxel	Docetaxel + placebo	OS Readout: endpoint not met
ATALANTE-1 (Phase III)	OSE	219	HLA-A2+	Peptide-based cancer vaccine	Tedopi	SoC (docetaxel or pemetrexed)	OS Readout (mOS): 11.1 vs 7.5 months Hazard ratio: 0.59

Source: Edison Investment Research

In February 2023, OSE announced that it had received positive recommendations for a further confirmatory Phase III trial for Tedopi as a second-line monotherapy (against the SoC) in advanced or metastatic NSCLC. Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) provided scientific advice for this confirmatory, and potentially pivotal, Phase III trial. We believe that this trial will build on the ATALANTE-1 trial, by acquiring more data in a larger NSCLC patient population, but also with the focus being on Tedopi as a second-line monotherapy as opposed to a second- or third-line treatment. This new study is designed for HLA-A2+ patients with secondary resistance to immunotherapy (IO)/ICIs after a first-line of chemo-IO, followed by failure to maintain IO for at least 12 weeks (the threshold for secondary/acquired resistance defined by international expert consensus recommendations). Management has communicated that this study aims to recruit c 400 patients and is expected to commence by end-2023 with a conclusion in 2025–26. We believe that readouts from this confirmatory trial may represent a significant catalyst for the company, and we now expect a launch for this asset in 2028 (commercial approval previously expected in 2023), provided the data continue to be positive.

Tedopi combination approaches offer broad oncology potential

In addition to the Phase III trials evaluating Tedopi as a monotherapy, OSE is also engaged in three Phase II trials, led by external clinical oncology groups, which seek to expand the clinical utility of

Tedopi in various oncology indications through combination approaches: with Opdivo (NSCLC), with chemotherapy (pancreatic cancer) and with Keytruda (ovarian cancer). If Tedopi can demonstrate improved survival rates in these combinations, this has the potential to increase the commercial impact of the cancer vaccine, in our view. Updates for each of these trials are expected in 2024. While we recognise that these studies are important in providing further clinical validation for Tedopi, we note that investigator-sponsored trials may not necessarily align with OSE's future clinical development strategy for the cancer vaccine.

OSE-279: a new checkpoint inhibitor in the clinic

In December 2022, OSE announced the first patient dosing in the Phase I/II trial for OSE-279. This monoclonal antibody ICI therapy is being evaluated in the Phase I/II, first-in-human, multicentre, dose-escalation/expansion study aiming to determine the maximum tolerated dose and/or recommended Phase II dose of OSE-279 as a monotherapy in solid tumours or lymphomas. Secondary objectives for this study include the assessment of anti-tumour activity, safety, investigating the pharmacokinetic/pharmacodynamic profile of the treatment and measuring receptor occupancy. Management anticipates an update on this study in 2024.

We note that this is a highly competitive space, with several ICIs already approved in the market that are designed to target PD-1 or PD-L1 (Exhibit 5). The global ICI market was estimated to be worth $31.4bn in 2021 and is projected to be worth $148.1bn by 2030. However, we believe that OSE will look to differentiate itself in this space by evaluating OSE-279 in combination with other proprietary assets, such as Tedopi, or with external partnerships, to obtain novel treatment options. Management anticipates that such combinations may have potential in overcoming the challenges associated with cancer resistance mechanisms.

Exhibit 5: Approved PD-1 and PD-L1 targeting ICIs

Drug	Company	Checkpoint target	Launch year	Estimated sales 2028 (US$)
Pembrolizumab (Keytruda)	Merck & Co	PD-1	2014	31.6bn
Nivolumab (Opdivo)	Bristol Myers Squibb	PD-1	2014	12.9bn
Cemiplimab (Libtayo)	Regeneron Pharmaceuticals	PD-1	2018	1.1bn
Atezolizumab (Tecentriq)	Roche	PD-L1	2016	6.9bn
Avelumab (Bavencio)	Merck KGaA	PD-L1	2017	947m
Durvalumab (Imfinzi)	AstraZeneca	PD-L1	2017	4.6bn

Source: Cancer Research UK; EvaluatePharma

BiCKI platform tested by clinical development of OSE-279

While OSE-279 is under clinical development as a therapy for the treatment of solid tumours or lymphomas, it also forms the backbone of the company's bifunctional checkpoint inhibitor platform (BiCKI). As a reminder, BiCKI is a bispecific ICI fusion protein platform to address primary and secondary cancer resistance mechanisms. ICIs are an effective SoC for many cancer patients, however, in a significant proportion of cases (dependent on the cancer type), patients may show either primary or secondary resistance to the treatment. It has been reported that this resistance could be caused by sustained tumour antigen stimulation, resulting in the exhaustion of T-cells and a dampening of anti-tumour responses. OSE believes that its bispecific approach can stimulate the effective T-cells while disarming the ineffective T-cells, thus circumventing immuno-resistance mechanisms.

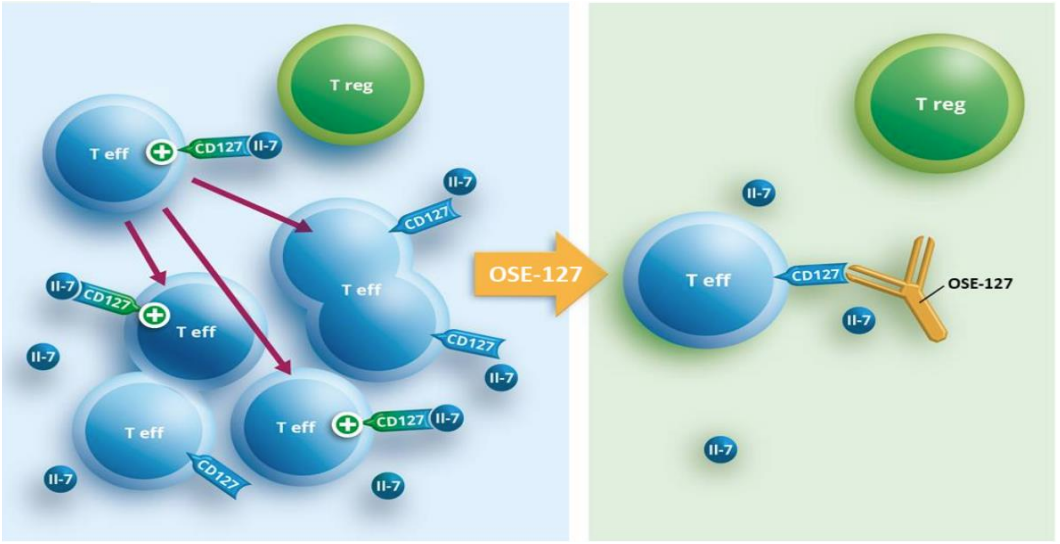
BiCKI antibodies are based on a humanised anti-PD-1 monoclonal antibody ICI backbone (OSE-279) and are engineered with proteins such as interleukin-7 (IL-7), a cytokine shown in separate preclinical studies to improve immune functions and cancer IO efficacy. This pairing of OSE-279 with IL-7 has formed OSE's first candidate from the BiCKI platform, called BiCKI-IL-7. The candidate targets PD1 and simultaneously delivers IL-7 pro-survival cytokine to tumour-specific T-

cells expressing PD1. At the American Association for Cancer Research (AACR) 2023 annual meeting, the company presented an update, which summarised that BiCKI-IL-7 showed significant anti-tumour efficacy in various in vivo models. OSE hopes to file an investigational new drug (IND) application in 2024 in solid tumours, and if successful, commence clinical trials in 2025. We believe that the clinical trial data from OSE-279 alone will make a significant contribution to the potential success of this IND application.

OSE continues in UC with full rights to OSE-127

OSE-127 is the company's most advanced clinical asset in the immuno-inflammation space. This candidate is an antibody therapy acting as an IL-7R antagonist, more specifically, targeting CD127, a cytokine modulating the proliferation, apoptosis and activation of CD4 and CD8 T-cells. To our knowledge, this is a novel and differentiated mechanism of action (Exhibit 6).

Exhibit 6: OSE-127 mechanism of action



Source: OSE Immunotherapeutics corporate presentation

OSE-127 was initially developed in partnership with Servier through an option license agreement, with Servier sponsoring a Phase II study in primary SS, while OSE was fully funding development in a Phase II trial in UC. Servier had the option to assume full development in both indications after completion of the Phase II clinical trials. However, in May 2023, following negative results (as communicated by OSE's management) from the Phase II primary SS study and a strategic realignment of Servier's portfolio, OSE and Servier mutually decided not to pursue the option license agreement. The full trial data is still to be disclosed, but the Servier decision means that OSE will miss out on the potential receipt of a €15m opt-in licensing milestone payment and potentially subsequent developmental, regulatory and commercial milestone payments worth up to €272m.

OSE remains committed to the development of OSE-127 in UC, having recaptured the full value of the asset, as the ongoing Phase II study continues to recruit patients. UC is a chronic inflammatory bowel disease affecting approximately 160–290 people per 100,000 each year worldwide, and current treatment options for the disease are associated with having a significant burden on patients' lives. The trial is expected to be fully enrolled (n=150) by end Q323. The top-line results after induction (primary endpoint at week 10) are anticipated in December 2023, and this update could represent a significant inflexion point, in our view. Additional data will be reported in H124 assessing OSE-127's use as a maintenance treatment after six months of therapy.

In preclinical research in the immuno-oncology space, OSE is also investigating OSE-127 as a potential treatment for acute lymphoblastic leukaemia (ALL). The CD127 receptor is overexpressed in ALL, hence it is a prime target for the IL7-R antagonist OSE-127. At AACR 2023, the company presented an update concluding that OSE-127 may be a promising option for ALL patients due to its dual mechanism of action. The antibody both blocks the oncogenic IL7-R fuel pathway and triggers macrophage-driven phagocytosis of leukemic cells. This could be encouraging for a clinical programme for OSE-127 in this indication, provided preclinical research continues to be supportive.

FR-104 focused on kidney transplantations

OSE also intends to progress with the development of FR-104, which is in clinical development with Veloxis, as a maintenance therapy following kidney transplantations. OSE has already received €13.9m from Veloxis and is set to receive up to €315.0m further in milestone payments. The long-term management of maintenance immunosuppression in kidney transplant patients continues to be an unmet medical need. The current SoC involves the use of calcineurin inhibitors and mycophenolate as immunosuppressive therapies, either with or without corticosteroids. While this approach is often associated with excellent short-term results, long-term exposure to these therapies contributes to allograft rejections. This commonly observed attrition, and the fact that current the SoC has been in place for over 20 years, highlights the opportunity for novel long-term treatment options, in our view.

FR-104 is a monoclonal antibody fragment that inhibits CD28, a T-cell co-receptor, delivering stimulatory signals from antigen-presenting cells to the T-cells. FR-104 has potential clinical applications in multiple autoimmune diseases and particularly with kidney transplants. As a comparison, we note that Bristol Myers Squibb's belatacept is a T-cell surface glycoprotein CD28 antagonist approved by the FDA in 2011, with the patent expiring in 2023. Belatacept is considered a more modern treatment option following kidney transplants and reached peak sales of $37m in 2021 and 2022 according to EvaluatePharma; we believe this serves as precedent for OSE's therapeutic approach with FR-104. Competition in this space is somewhat varied, and many approved therapies now have expired patents. However, Hansa Biopharma's idefirix appears the most modern therapy, with the associated patent expiring in 2029 (Exhibit 8).

Exhibit 7: Competition in the kidney transplant maintenance therapy space

Drug	Generic name	Company	Mechanism of action	Patent expiry year	Estimated sales 2028 (US$m)
Idefirix	Imlifidase	Hansa Biopharma	Immunoglobulin inhibitor	2029	459
Prograf	Tacrolimus	Astellas Pharma	Calcineurin inhibitor	2009	431
Thymoglobulin	Anti-thymocyte globulin	Sanofi	T-cell inhibitor	-	281
CellCept	Mycophenolate mofetil	Roche	IMPDH inhibitor	2009	222
Zortress	Everolimus	Novartis	mTOR inhibitor	2020	203
Myfortic	Mycophenolic acid	Novartis	IMPDH inhibitor	2014	118
Simulect	Basiliximab	Novartis	IL-2R antibody	2020	116
Nulojix	Belatacept	Bristol Myers Squibb	T-cell surface glycoprotein CD28 antagonist	2023	12

Source: Evaluate Pharma

Results from the Phase I trial (n=64) involving healthy volunteers showed that FR-104 demonstrated effective engagement with CD28 with a response of up to 57 days, and a desirable safety profile with no signs of cytokine elevation. OSE plans to initiate a Phase II trial in 2023 and share initial readouts in 2024.

OSE-172 continues to progress

OSE-172/BI 765063, a SIRPα-targeting ICI, is in clinical development with Boehringer Ingelheim (BI). OSE has already received €65.3m from BI and is set to receive up to €1.1bn further in milestone payments. The drug operates in a similar way to T-cell ICIs in the tumour microenvironment. However, instead of inhibiting T-cells, it aims to inhibit the checkpoints between tumour cells and myeloid cells. Further details on the mechanism of action of OSE-172, as well as an overview of preclinical data, can be found in our initiation note. The candidate is currently involved in various Phase I trials:

- NCT03990233 (in Europe): a dose-escalation and accrual expansion study covering multiple indications:
  - OSE-172 as a monotherapy for the treatment of solid tumours (n=50) – dose escalation.
  - OSE-172 in combination with BI's ICI ezabenlimab (a PF1 inhibitor still in clinical development) for the treatment of solid tumours (n=18) – dose escalation.
  - OSE-172 in combination with ezabenlimab for the treatment of microsatellite stable (MSS) endometrial cancer (n=10) and MSS colorectal cancer (CRC) (n=30) – ongoing accrual expansion study.
- NCT04653142 (in Japan): an ongoing accrual expansion study evaluating OSE-172, with and without ezabenlimab, for the treatment of solid tumours (n=36).
- NCT05249426 (in the United States, Europe and Japan): an ongoing accrual expansion study evaluating OSE-172 with and without different combinations of ezabenlimab, chemotherapy, cetuximab or a VEGF/Ang2 inhibitor for the treatment of head and neck squamous cell carcinoma and hepatocellular carcinoma (HCC) (n=150).

Preliminary results have shown a good safety profile in all cases, one case of partial response (PR) in HCC (associated with a 45% clinical benefit rate as a monotherapy), and three PRs in MSS endometrial cancer and CRC in combination with the ICI. More recently, at AACR 2023, the company presented an update based on a biomarker analysis to characterise the impact of OSE-172 on the tumour microenvironment. This analysis showed that high levels of myeloid cells expressing SIPRα in the tumour microenvironment correlated with longer survival; this was not true with CD47 tumour cell expression. Furthermore, myeloid-derived suppressor cells signature in the tumour microenvironment at baseline also correlated with clinical responses, and collectively these results are supportive of OSE-172's mechanism of action, in our view. Management expects to provide more detailed updates for these studies across 2023, and will start preparing for Phase II trials in 2024.

Sensitivities

OSE is subject to the regular development, regulatory and commercial risks associated with drug development. It is highly likely that the company will be required to source additional financing to fund the follow-on Phase III study for Tedopi, which brings about a potential dilution risk for shareholders should funding be raised through an equity issue. Additionally, funding risk is further heightened considering the current tight capital market situation, particularly for biotechs and drug development companies.

The licensing deals with BI and Veloxis diversify the impact of developmental risk and clinical expenditure for OSE. However, these assets could potentially be returned to OSE in the event of clinical development failures or strategic changes from partners. Additionally, the successful commercialisation and launch of Tedopi, provided results are positive in the follow-on Phase III study, is highly dependent on OSE securing a licensing deal with larger pharmaceutical partners.

Any challenges in securing a partner could postpone product development and/or adversely affect the economics of a potential licensing transaction.

Valuation

Our updated valuation of OSE is €280.8m or €15.2 per share. Given the progress OSE has made over the last year, the updated strategy for Tedopi (preparation of a potentially pivotal Phase III trial) and the initiation of new trials in new indications, we have revised our rNPV model and R&D assumptions. Exhibit 9 provides a detailed description of the assumptions we have used in our rNPV model. Key changes from our previously published model include:

- **Tedopi in NSCLC:** with the planned initiation of a second, potentially pivotal, Phase III study in second-line NSCLC in 2023, we expect trial readouts in 2026 followed by the filing of a new drug application (NDA) in 2027 and market launch in 2028. We have also incorporated a licensing deal into our model for Tedopi, which we assume will be achieved in 2026 with deal terms based on precedent cancer vaccine transactions.
- **OSE-279 in solid tumours:** OSE has communicated that it will look to target orphan indications with strong unmet medical needs once the programme enters Phase II/III trials. As such, we have assumed an indication where PD-L1 therapies have been validated as SoC but where improvements in existing treatment options remain highly sought after. We have therefore modelled a patient population using extensive disease small cell lung cancer (ED-SCLC) as a proxy indication. We will revisit these assumptions once additional data emerge from the trial (first update expected in 2024). Our assumptions for this new asset are further detailed in Exhibit 9.
- **OSE-127 in UC:** with the termination of the Servier licensing agreement, we now include a new licensing deal for OSE-127 in UC. We assume OSE will secure a licensing deal in 2025, following the readouts of the ongoing Phase II study, with a partner assuming all subsequent developmental costs. Our assumptions are further detailed in Exhibit 9.
- **FR-104/VEL-101 in kidney transplantation**: we have adjusted the timing of anticipated milestone payments from OSE's licensing partner Veloxis. This is based on expected readouts from the Phase II study in kidney transplantation in 2025–26.
- **OSE-172/BI 765063**: we have adjusted the timing of anticipated milestone payments from OSE's licensing partner, BI. This is based on an expected update from the Phase II study in solid tumours in 2025–26. As such, we have pushed our expected launch date out to 2028 (previously 2027).

Our underlying assumptions for OSE's assets are stated in Exhibit 9.

Exhibit 8: rNPV assumptions

Asset	Indication	Assumptions
Tedopi	2L NSCLC	■ **Target market**: We assume, of lung cancer cases, an incidence of NSCLC of c 85%, and c 75% of these will not possess EGFR or ALK mutations. We assume c 50% of NSCLC patients will show disease progression following first-line ICI treatment (secondary resistance) with c 45% of patients being HLA-A2 positive and eligible for Tedopi. We assume a peak market penetration of 25% in this NSCLC subset population.
		■ **Pricing and licensing**: As in our prior reports, we assume pricing of $70k per patient per year in the US with a 30% discount in the EU. We assume OSE will secure a licensing deal for Tedopi in 2027, receiving up to c $200m (€185m) in upfront payments, a further c $500m (€470m) in developmental and sales milestones and low double-digit royalties on net sales.
		■ **Trial timelines and R&D cost:** We assume c US$20m (€18.5m) to fund a pivotal Phase III study.
		■ **Probability of success**: We assume a probability of approval of c 50% based on historical clinical phase transition success rates of 50% from Phase III to NDA and 95% from NDA to approval in oncology solid tumours.*
OSE-172/ BI 765063	Multiple cancer indications (MSS CRC)	■ **Target market**: We assume a population of c 150,000 patients diagnosed with CRC, of whom 85% are classified as MSS. This population remains stable over the valuation period. Treatment is being assessed in third-line MSS CRC; c 30% of patients progress to this stage of treatment. We assume peak market penetration of 10% in CRC.
		■ **Pricing and licensing**: As in our prior reports, we assume pricing of $70k per patient per year in the US with a 30% discount in the EU. Our licensing assumptions are based on deal terms with BI: worldwide rights in multiple cancer indications for €1.1bn in R&D and commercial milestones + royalties.
		■ **Trial timelines and R&D cost:** Financed by BI with Phase I/II updates in 2023 and 2024 and Phase II update in 2024.
		■ **Probability of success**: We assume a probability of approval of c 15% based on historical clinical phase transition success rates of 30% from Phase II to Phase III, 50% from Phase III to NDA and 95% from NDA to approval in oncology solid tumours.*
OSE-279	Solid tumour and haematological indications (SCLC)	■ **Target market:** We assume OSE will target an orphan solid tumour indication with a large unmet need where PD-(L)1 therapies are clinically validated in SoC treatment regimes. We model a patient population using relevant statistics for ED-SCLC. We assume an incidence of 15% of SCLC cases in lung cancer and 70% with ED-SCLC. PD-L1 expression levels in SCLC patients are not a prerequisite for eligibility of SoC ICI treatments. We assume peak market penetration of 20% in SCLC.
		■ **Pricing and licensing:** We assume pricing of $35k per patient per year in the US based on existing prices for marketed ICIs. We assume that OSE will secure a licensing deal in 2025, which we have based on our assessment of past licensing deals for Phase II oncology antibody assets indicated across solid tumour types (median 4 exploratory indications per deal). Given that we use only one indication in our model, we have split the deal economics and model c $50m (€46m) in upfront payments, a further c $190m (€176m) in developmental and sales milestones and low double-digit royalties on net sales in SCLC.
		■ **Trial timelines and R&D cost:** €2.5m in FY23, €2.5m in FY24 and €2.5m in FY25 (based on industry average Phase II trial costs). We assume a licensing deal is secured by end-FY25 and that the licensee will assume all subsequent development and commercialisation costs and the initiation of further clinical studies.
		■ **Probability of success**: We assume a probability of approval of c 15% based on historical clinical phase transition success rates of 30% from Phase II to Phase III, 50% from Phase III to NDA and 95% from NDA to approval in oncology solid tumours.*
OSE-127	Ulcerative colitis (UC)	■ **Target market**: As in our prior reports, we assume total treated UC patients of approximately 690,000 in the US and 610,000 in Europe. We have assigned a conservative peak market penetration of 2% to reflect the likelihood that OSE-127 will be a second-/third-line therapy for more severe patients, and that a proportion of patients will be in remission.
		■ **Pricing and licensing**: We assume pricing of $30k per patient per year in the US based on current existing costs of anti-interleukin biologics (Actemra and Kevzara), with a 30% discount in the EU. Our licensing assumptions are based on precedent deal terms for IL-7R targeting drugs including Q32 Bio's partnership with Horizon and Zura Bio's deal with Pfizer. We assume OSE will secure a licensing deal for OSE-127 in 2025, receiving up to c $30m (€27m) in upfront payments, a further c $620m (€560m) in developmental and sales milestones and low double-digit royalties on net sales.
		■ **Trial timelines and R&D cost**: €5.0m in FY23 with a licensing partner financing subsequent trials following Phase II readouts in 2023.
		■ **Probability of success**: We assume a probability of approval of c 15% based on historical clinical phase transition success rates of 30% from Phase II to Phase III, 60% from Phase III to NDA and 95% from NDA to approval in autoimmune disorders.*
FR-104	Kidney transplantation	■ **Target market**: The annual number of kidney transplantations in the US is 25k. The organ transplantation market is highly populated with generic immunosuppressant therapies. However, with current limitations associated with such treatments there is scope for FR-104 to potentially offer differentiation and we assign a market penetration of 10%.
		■ **Pricing and licensing**: We assume pricing of $20k per patient per year in the US with a 30% discount in the EU based on the cost per patient for the FDA-approved CD80- and CD86-targeting fusion protein post kidney transplantation, Belatacept (Nulojix). Our licensing assumptions are based on deal terms with Veloxis: worldwide rights for €315m in R&D and commercial milestones + royalties.
		■ **Trial timelines and R&D cost:** Financed by Veloxis with Phase I/II updates in 2024 and Phase II readouts in 2025.
		■ **Probability of success**: We assume a probability of approval of c 15% based on historical clinical phase transition success rates of 30% from Phase II to Phase III, 60% from Phase III to NDA and 95% from NDA to approval in autoimmune disorders.*

Source: Edison Investment Research. Note: *Clinical phase transition success rates are based on 2021 Clinical Development Success Rates I Pharma Intelligence (informa.com) as well objective analysis of data reported from the clinical programme.

We apply an unchanged discount rate of 12.5% to our rNPV calculations. In addition, our valuation reflects a net debt position of €14.7m at end-December 2022. A breakdown of our valuation is shown in Exhibit 10.

Should the follow-on Phase III study for Tedopi generate positive data, the asset would be supported by data from two Phase III trials; we believe this could add significant value and potential deal value for future licensing opportunities. In our view, a comparable deal of note is the worldwide licensing agreement signed in 2020 between Roche and Nykode, worth up to $715m (upfront and

near-term payments of $200m), for the Scandinavian biotech's personalised cancer vaccine, VB10.NEO. At the time of the agreement, VB10.NEO was in the Phase I portion of a Phase I/II basket trial that included patients with advanced or metastatic melanoma, NSCLC, clear renal cell carcinoma urothelial cancer or squamous cell carcinoma of the head and neck.

While we have not included indications other than NSCLC in our valuation of Tedopi, we note that it is being investigated in both pancreatic and ovarian cancer in two separate Phase II studies, potentially broadening its application. As such, we believe this could enhance the potential deal value that could be commanded from future licensing opportunities for Tedopi and have modelled a licensing deal equivalent to Nykode's, with an upfront payment of €182m ($200m) in 2027, following completion of the second Phase III study.

Exhibit 9: Sum-of-the-parts OSE valuation

Product	Launch	Peak sales (€m)	NPV (€m)	NPV/share (€)	Probability	rNPV (€m)	rNPV/share (€)
Tedopi – NSCLC	2028	561	358.9	19.4	50%	164.8	8.9
OSE-127 – ulcerative colitis	2027	828	276.6	14.9	15%	49.6	2.7
BI 765063 – multiple cancer indications (MSS CRC)	2028	534	181.2	9.8	15%	29.5	1.6
FR104 – Veloxis deal milestones (kidney transplantation)	2028	96	132.7	7.2	15%	26.4	1.4
OSE-279 – multiple cancer indications (SCLC)	2029	373	147.9	8.0	15%	25.3	1.4
Net cash/(debt)			(14.7)	(0.8)	100%	(14.7)	(0.8)
Valuation			**1,082.6**	**58.4**		**280.8**	**15.2**

Source: Edison Investment Research

Financials

OSE reported operating expenses for FY22 of €36.7m, a 14.5% decrease year-on-year and lower than our estimate of €41.1m. This decrease was primarily driven by a 12% reduction in R&D expenses due to the winding down of the Phase III ATALANTE-1 study. However, these lower operating expenses were offset by a reduction in revenue related to licensing agreements (€18.3m in FY22 vs €26.3m in FY21) resulting in an operating loss for FY22 of €18.4m (FY21: €16.6m). Net cash flow from operating activities stood at €18.3m in FY22, a significant increase from €9.9m in FY21. The figure was negatively affected by changes to working capital (€3.1m) as well as financial charges associated with the repayment of debt obligations (€3.1m).

The costs associated with many of OSE's ongoing clinical programmes are absorbed either through the company's licensees (Veloxis, BI) or by academic institutions and investigator-sponsored studies. As such, with the conclusion of the OSE-sponsored Phase II study in UC of OSE-127/S95011 in FY23, we expect operating expenses for the company to decrease slightly year-on-year in FY23. However, we estimate costs will increase in FY24 as the Phase III Tedopi study is initiated. We estimate operating cash outflows of €16.2m in FY23, increasing to €20.2m in FY24.

OSE ended the year with a gross cash position of €25.6m and a net debt position of €14.7m. We note that OSE has entered into financing agreements with the EIB as well as, more recently, with Vester Finance. The debt facility with the EIB includes a €25m loan agreement, of which OSE has received €20m to date. The first €10m tranche was drawn down in July 2021 and the second €10m in December 2022. In combination with each of the €10m loans (which bear a 5% interest rate), 1.4m OSE shares (7.56% of share capital) are available to the EIB through warrants. The warrants attached to the first tranche (850,000 shares) may not be exercised until after 9 July 2026 and those attached to the second tranche (550,000 shares) may not be exercised until after 16 December 2027 (except if there is an early exercise event such as a change in control), at which point the EIB and OSE retain put and call options, respectively, with various conditions attached. In

our view, these agreements somewhat limit the dilution risk associated with these warrants. OSE also recently entered into an equity financing agreement with Vester Finance, which has subscribed to a maximum of 2.8m shares (15.1% of the share capital) of the company over a maximum period of 24 months. OSE has committed to a minimum use of the equity financing facility of €0.6m. Shares will be issued based on the average stock market price prior to the issue date and at a maximum discount of 6%. With an FY22 gross cash position of €25.6m and, assuming OSE fully exercises its debt and equity committed financing, management has guided that it expects this to provide a cash runway into Q224. Our model assumes a similar runway, even without the use of the Vester Finance equity financing line.

In our model we assume OSE secures an out-licensing deal for Tedopi by end-2027. We assume the company receives licensing milestones associated with Tedopi, including development milestones associated with existing deals with Veloxis and BI before reaching steady, revenue-generating operating profitability following the commercial launch of Tedopi in FY28. We estimate the company would be required to raise a total of c €65m in funds to reach this point. We account for this raise as illustrative debt in our model. Alternatively, if the funding is realised through an equity issue instead (assuming at the current trading price of €4.05/share), OSE would have to issue 16.0m shares, resulting in our per share valuation coming down to €8.3 from €15.2 currently (shares outstanding would increase from 18.5m to 34.5m).

Exhibit 10: Financial summary

€000s	2020	2021	2022	2023e	2024e
Year end 31 December	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS					
Revenue	10,432	26,306	18,302	15,000	15,000
Cost of Sales	0	0	0	0	0
Gross Profit	10,432	26,306	18,302	15,000	15,000
Research and development	(22,355)	(30,550)	(22,500)	(22,382)	(27,670)
EBITDA	(18,259)	(13,601)	(14,991)	(13,061)	(18,514)
Operating Profit (before amort. and excepts.)	(18,989)	(16,625)	(18,477)	(14,254)	(19,749)
Intangible Amortisation	(457)	(687)	(742)	(844)	(844)
Exceptionals	0	0	0	0	0
Other	0	0	0	0	1
Operating Profit	(19,446)	(17,312)	(19,219)	(15,098)	(20,592)
Net Interest	(258)	(589)	455	(3,537)	(2,103)
Profit Before Tax (norm)	(19,247)	(17,214)	(18,022)	(17,792)	(21,852)
Profit Before Tax (reported)	(19,247)	(17,214)	(18,022)	(17,792)	(21,852)
Tax	2,692	364	263	0	0
Profit After Tax (norm)	(19,247)	(17,214)	(18,022)	(17,792)	(21,852)
Profit After Tax (reported)	(16,555)	(16,850)	(17,759)	(17,792)	(21,852)
Average Number of Shares Outstanding (m)	15.6	18.2	18.5	18.5	18.5
EPS - normalised (c)	(123.72)	(94.82)	(97.27)	(96.03)	(117.94)
EPS - reported (€)	(1.06)	(0.93)	(0.96)	(0.96)	(1.18)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	N/A	N/A	N/A
Operating Margin (before GW and except.) (%)	N/A	N/A	N/A	N/A	N/A
BALANCE SHEET					
Fixed Assets	57,141	57,670	54,580	53,636	52,752
Intangible Assets	52,600	51,122	48,784	47,940	47,096
Tangible Assets	947	926	743	643	603
Investments	3,594	5,622	5,053	5,053	5,053
Current Assets	39,832	44,205	37,200	77,995	78,317
Stocks	0	0	0	0	1
Debtors	1,074	772	403	423	444
Cash	29,368	33,579	25,620	66,395	66,696
Other	9,390	9,854	11,177	11,177	11,177
Current Liabilities	14,128	16,762	16,268	16,695	17,143
Creditors	10,286	9,607	8,539	8,966	9,414
Short term borrowings	50	1,611	3,093	3,093	3,093
Other	3,792	5,544	4,636	4,636	4,636
Long Term Liabilities	21,481	37,224	42,855	100,071	120,913
Long term borrowings	16,552	30,801	37,231	95,175	116,619
Deferred tax liabilities	2,080	1,748	1,514	1,514	1,514
Other long term liabilities	2,849	4,675	4,110	3,382	2,780
Net Assets	61,364	47,889	32,657	14,865	(6,987)
CASH FLOW					
Operating Cash Flow	(19,276)	(9,919)	(18,252)	(16,191)	(20,191)
Net Interest	273	634	(3,066)	0	0
Tax	(2,742)	(696)	(499)	0	0
Capex	(210)	(472)	(274)	(250)	(350)
Acquisitions/disposals	0	0	0	0	0
Financing	24,062	265	11,052	57,944	21,444
Other	(273)	0	0	0	0
Dividends	0	0	0	0	0
Net Cash Flow	1,834	(10,188)	(11,039)	41,503	903
Opening net debt/(cash)	(16,083)	12,766	1,167	(14,704)	(31,873)
HP finance leases initiated	0	0	0	0	0
Other	0	0	0	0	0
Closing net debt/(cash)*	12,766	1,167	(14,704)	(31,873)	(53,016)

Source: company accounts, Edison Investment Research. Note: *Excluding lease liabilities.

Contact details	Revenue by geography
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Management team

CEO and CSO: Dr Nicolas Poirier	Chief Development & Strategy: Dr Dominique Costantini
Dr Poirier began his career at Tcl pharma before joining Effimune in 2012, starting as a project manager before becoming director of R&D programmes. Following the merger of OSE Pharma and Effimune in 2016, Dr Poirier became chief scientific officer and a member of the management team of the newly formed OSE Immunotherapeutics. In addition to continuing his role as CSO, Dr Poirier was appointed CEO in 2022 following the departure of Alexis Vandier. Dr Poirier currently sits on the Strategic and Scientific Advisory Committee (COSSF) of the French biomedical industry association (MabDesign). He holds a PhD in Immunology and a double master's degree in biotechnology and pharmacology.	With more than 25 years of experience in management positions in the pharmaceutical industry (HMR, now Sanofi), Dr Costantini has overseen many therapeutic innovations and has been involved in the development of numerous medicines. In 1997, she founded and led as CEO BioAlliance Pharma (now Onxeo), a biotech company specialising in oncology and supportive care. In 2012, she founded and was CEO of OSE Pharma, a biotech company in cancer immunotherapy. She served as CEO and director of the company, subsequently renamed OSE Immunotherapeutics, until April 2018. She is a medical doctor (Paris V University), specialising in immunology.
CFO: Anne-Laure Autret-Cornet	
Ms Autret-Cornet started her financial career at Deloitte, spending seven years within the firm's audit function before moving to Effimmune as administrative and financial manager in 2013. Following the merger of OSE Pharma and Effimmune in 2016, she was appointed CFO for OSE, and she has now held the position for seven years. Ms Autret-Cornet graduated from ESSCA Management School and received a 'Corporate Finance' certificate from HEC Paris in 2020.	

Principal shareholders	(%)
Loria Emile	16.71
Costantini Dominique	10.48
Peyroles Alexis	4.80
Hiance Maryvonne	2.22
Poirier Nicolas	1.01
CCR-Gestion SA/France	0.48
BFC Fund Management AG/Lichtenstein	0.06

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