# Lusvertikimab, a first-in-class IL7 receptor antagonist, in moderate to severe ulcerative colitis: results of a multicenter, randomized, placebo-controlled phase II study (CoTikiS)

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# Conflict of Interest

- A. Bourreille declares conflicts of interest with AbbVie, AlorIS pharma, BMS, BioMadvanced, Celltrion, Ferring, Galapagos, Gilead, MSD, Mauna Kea Technologies, Medtronic, OSE Immunotherapeutics, Janssen, Lilly, Pfizer, Roche, Takeda, Tillotts, Valneva
- A. Kierkus declares conflicts of interest with Danone, Nestle
- F. Corallo was an employee of OSE-Immunotherapeutics
- W. Reinisch declares conflicts of interest with  AbbVie, , Amgen, AOP Orphan, Boehringer Ingelheim, Bristol Myers Squibb, Calyx, Celltrion, Eli Lilly, Ferring, Gilead, Index Pharma, Janssen, Galapagos Medice, Medahead, Microbiotica, MSD, OSE-Immunotherapeutics, Roche, Pfizer, Sanofi, Sandoz, Sobi, Takeda, Teva.

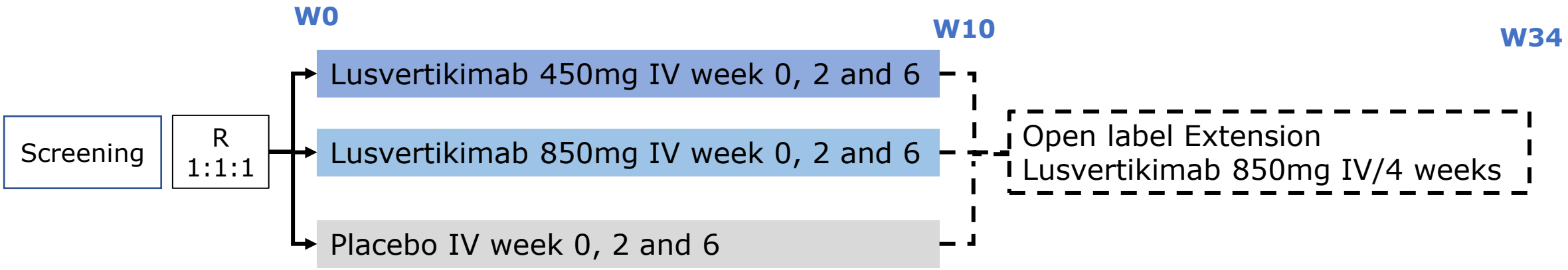
# Background

- IL-7 is mainly produced by epithelial and stromal cells
- IL-7Rα is expressed on T Lymphocytes, with the exception of Tregs
- IL-7 is a crucial survival and expansion factor for $CD4^+$ $T_{EM}$ lymphocytes and innate lymphoid cells[1]
- IL-7Rα blockade results in reduced human T cell homing to the gut and protects from colitis in transfer animal models[1,2]
- Lusvertikimab, a first-in-class antagonist of IL-7Rα, demonstrated its safety in a phase 1 study with ascending doses up to 10mg/Kg[3]

[1]Nemoto Y et al. J Immunol 2009
[2]Belarif L et al. J Clin Invest 2019
[3]Poirier N et al. J Immunol 2023

# Design

**Patients with a moderate to severe active UC defined by a Modified Mayo Score (MMS) between 4 and 9 (MES ≥ 2, RB ≥ 1, SF ≥ 1) who had failed or were intolerant to corticosteroids, IS, anti-TNFs, vedolizumab or ustekinumab**

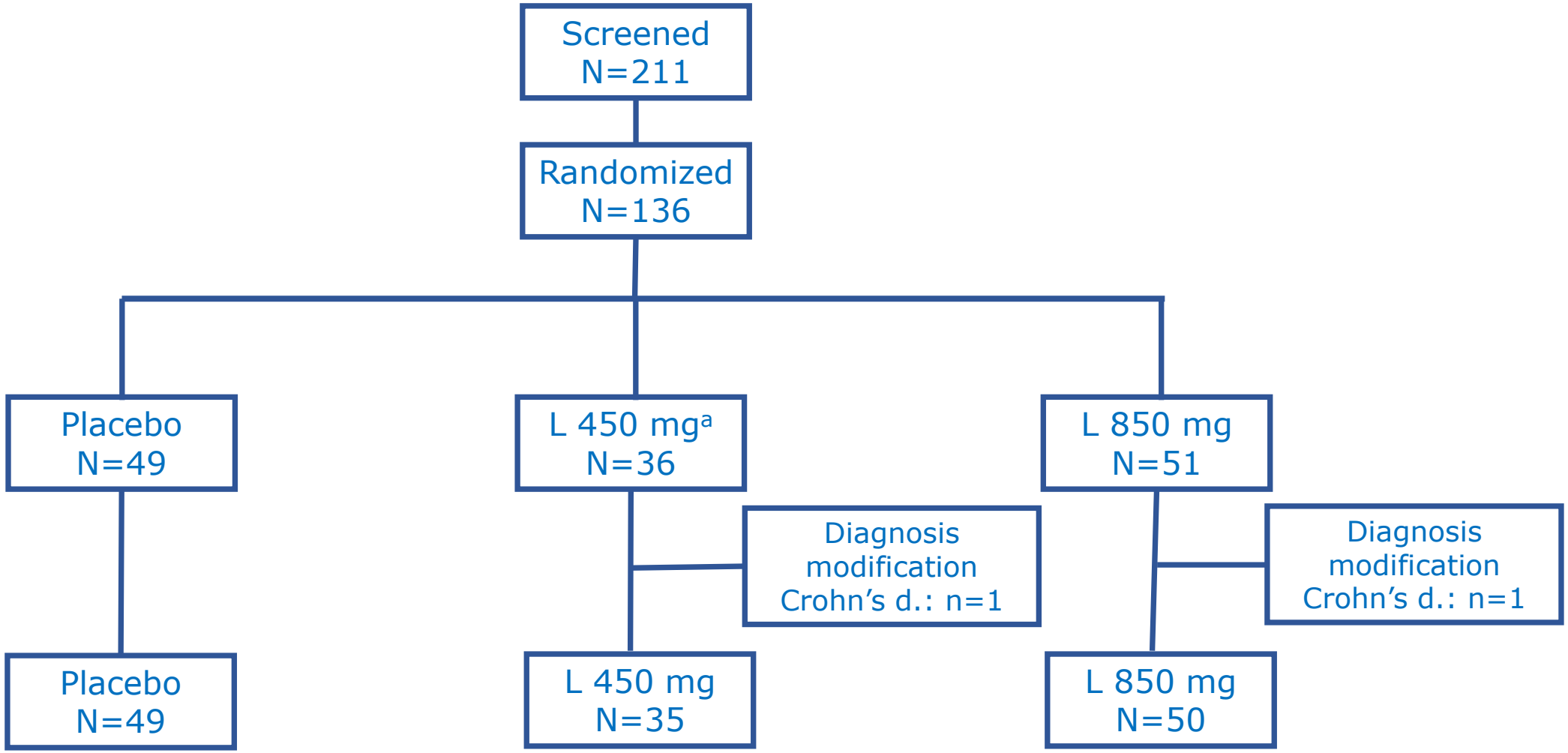



- **Primary endpoint (W 10)**: efficacy of Lusvertikimab on the reduction of the MMS
- **Secondary endpoints (W 10)**:
  - Clinical Remission: MMS ≤2 with no sub-score >1 and RB 0, SF ≤ 1, Mayo Endoscopic subscore (MES) 0 or 1
  - Endoscopic Remission: MES of 0
  - Endoscopic Response: UCEIS changes from baseline
  - Histological Response: Nancy index of 0 or 1
  - Histo-endoscopic Mucosal Improvement: Nancy index ≤ 1 and MES ≤ 1
  - Biological responses: F-calprotectin and CRP changes from baseline
  - Overall safety and adverse events

# Methods

- Efficacy analyses were performed using the FAS population
- Safety and adverse events were assessed in all patients who received any amount of the study drug
- Sample sizes of 44 per group were expected to achieve 85% power to reject the null hypothesis of equal means between placebo and Lusvertikimab 850 mg, leading to a mean difference of -1.5 with a standard deviation (SD) for both groups of 2.3
- MMS changes from baseline were analyzed by ANCOVA with treatment, baseline score, stratification criteria (bio exposed 40%) at randomization as covariates
- Interim futility analysis was planned after 50 patients had completed the Induction Phase. If the conditional and the predictive power were <20% for one or both doses, the study arm was to be discontinued for futility

# Patient Disposition




[a]lusvertikimab 450mg was dropped at a prespecified futility analysis after 58 patients; it was later shown not to be futile

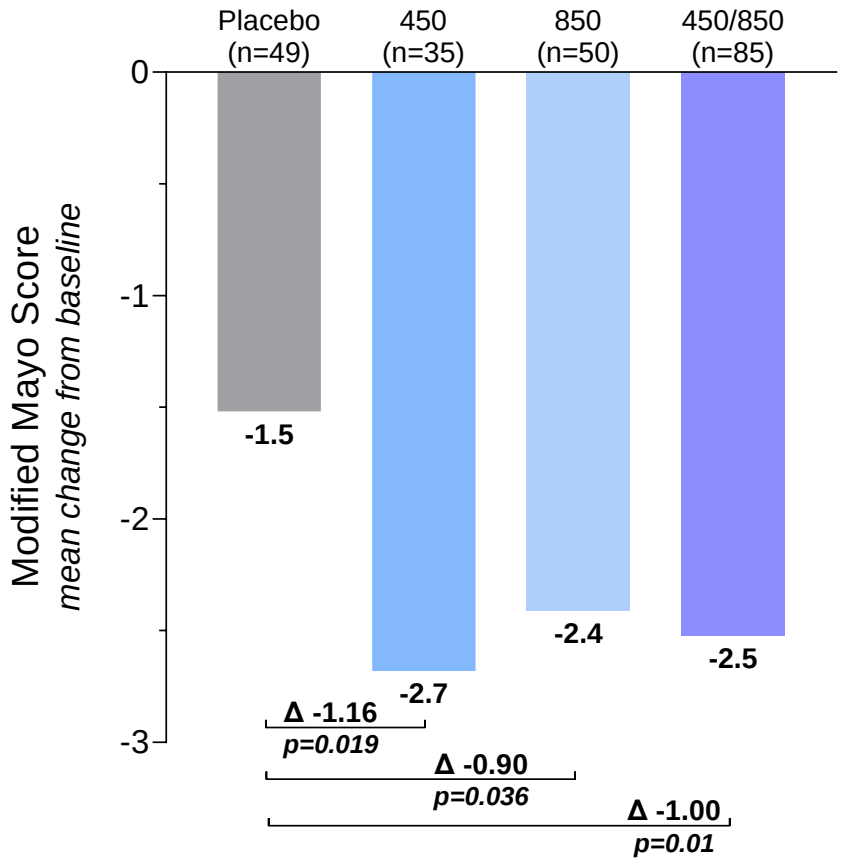
# Patients demographics and baseline disease characteristics

| | Placebo (n=49) | Lusvertikimab[a] 450 mg (n=35) | Lusvertikimab 850 mg (n=50) |
|---|---|---|---|
| Age: mean (SD) | 42.7 (15.9) | 38.8 (10.5) | 42.5 (15.1) |
| Sex: Male, n (%) | 28 (57.1%) | 22 (62.9%) | 27 (54.0%) |
| Never Smoker, n (%) | 39 (79.6%) | 25 (71.4%) | 43 (86.0%) |
| UC Duration (Years) Mean (SD) | 8.2 (7.5) | 7.2 (6.5) | 9.3 (8.6) |
| Modified Mayo Score (MMS) Mean (SD) | 6.6 (1.2) | 6.0 (1.4) | 6.5 (1.0) |
| MMS, n (%) | | | |
| 5-6 | 21 (42.9%) | 17 (48.6%) | 25 (50.0%) |
| 7-9 | 26 (53.1%) | **13 (37.1%)** | **25 (50.0%)** |
| Mayo Endoscopic Subscore Mean (SD) | 2.5 (0.5) | 2.4 (0.5) | 2.6 (0.5) |
| Mayo Endoscopic Subscore 3, n (%) | 26 (53.1%) | **15 (42.9%)** | **32 (64.0%)** |
| UCEIS Mean (SD) | 4.6 (1.3) | 4.4 (1.3) | 4.8 (1.2) |
| Nancy Histological Index 3 or 4, n (%) | 31 (65.9%) | **20 (58.8%)** | **34 (70.8%)** |
| FCP (μg/g) Mean (SD) | 1459.5 (1865.0) | 1088.0 (1600.5) | 1191.8 (1603.3) |
| C-Reactive Protein (mg/L) Mean (SD) | 8.6 (13.6) | 9.4 (16.7) | 11.2 (18.1) |
| Previous Exposure to Biologics | 19 (38.8%) | **5 (14.3%)** | **19 (38.0%)** |
| Previous Biologics >2 : n (%) | 5 (10.2%) | **0 (0%)** | **6 (12%)** |
| Concomitant Use of Steroids, n (%) | 23 (46.9%) | 18 (51.4%) | 25 (50.0%) |

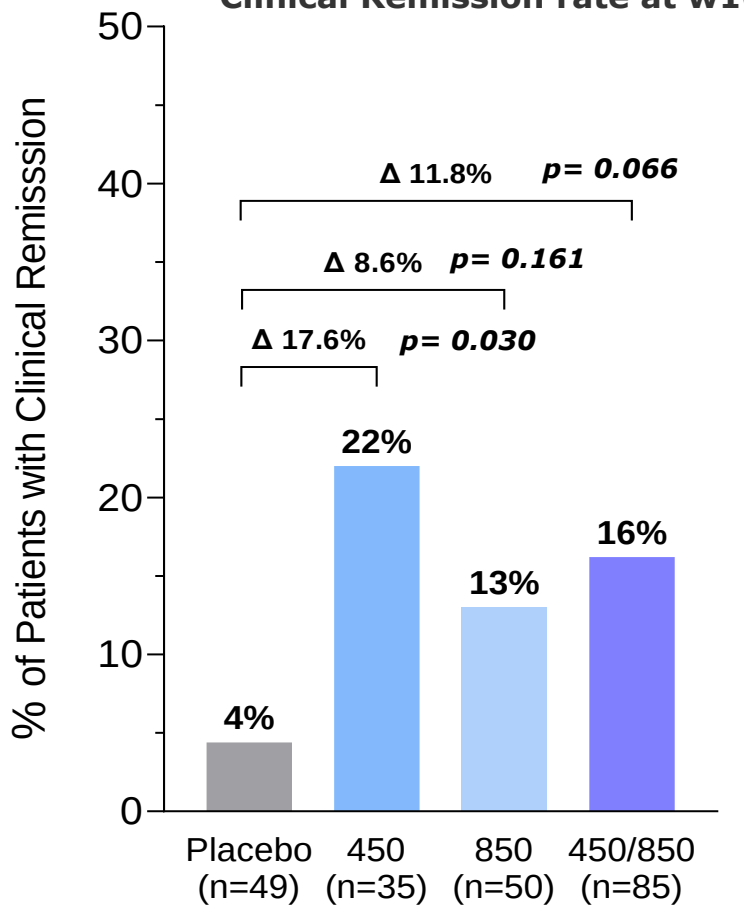
[a] lusvertikimab 450mg was dropped at a prespecified futility analysis after 58 patients. It was later shown not to be futile

# Changes in MMS (primary endpoint) and Clinical Remission rate at w10

**Primary endpoint: changes in MMS at w10**

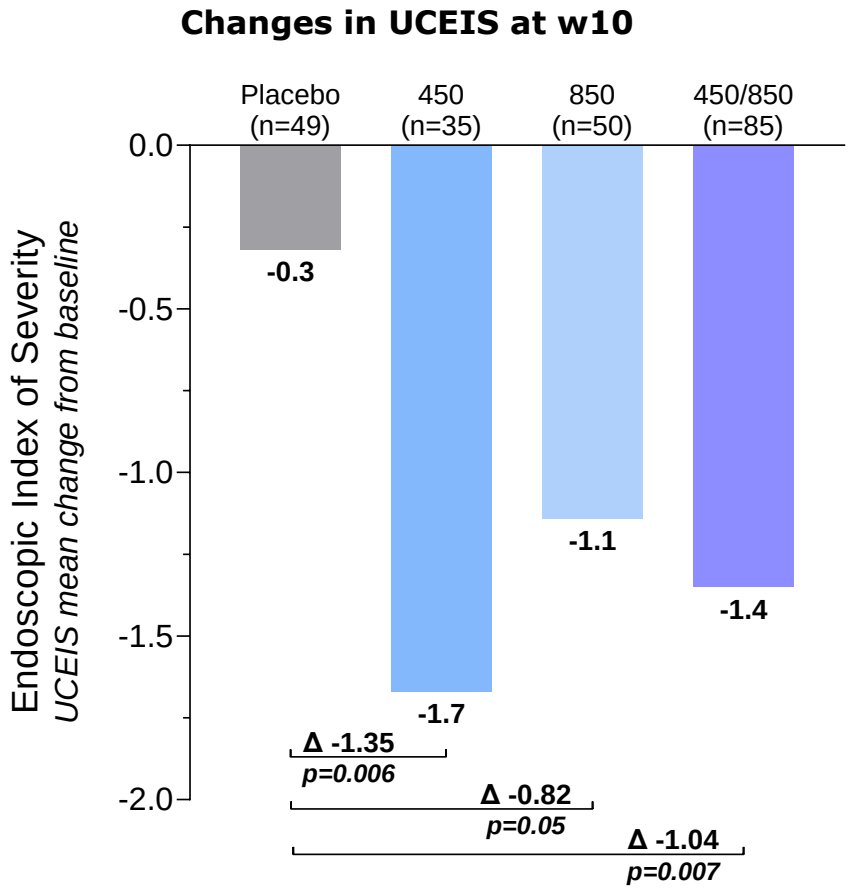



**Clinical Remission rate at w10**

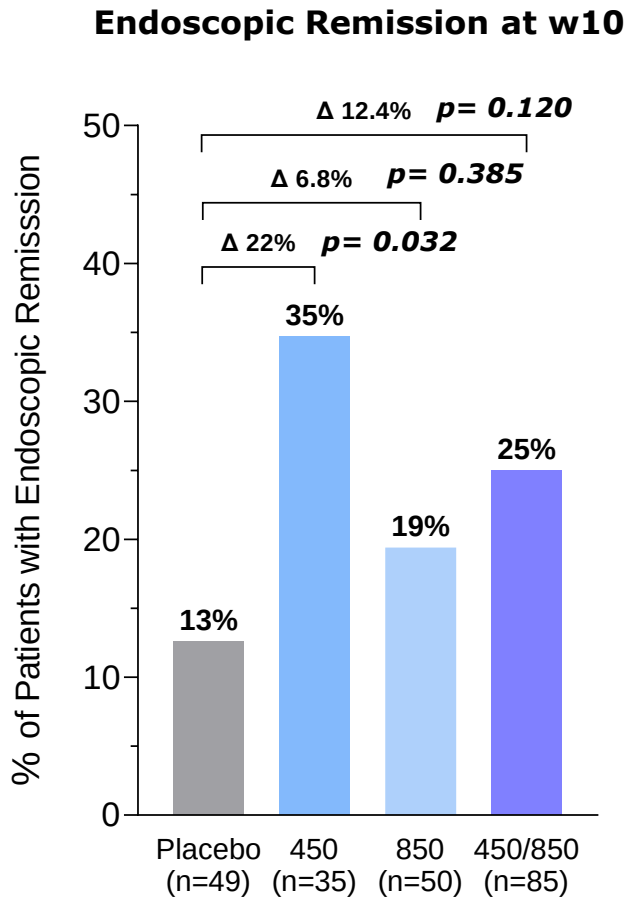



**Clinical Remission**:
MMS ≤2 with no sub-score >1 and RB 0, SF ≤ 1, MES 0 or 1

# Secondary endpoints: Endoscopic Improvement and Endoscopic Remission rates at w10



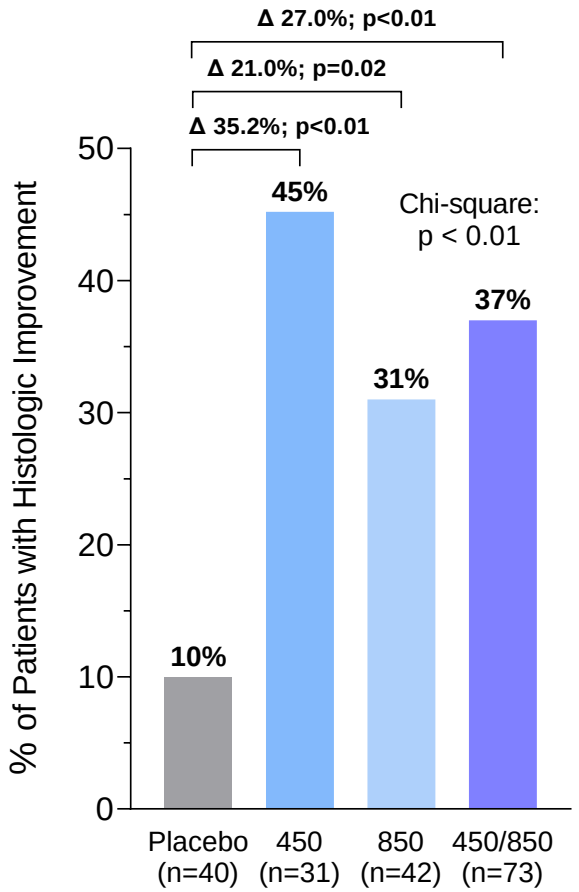

**Endoscopic improvement:**
UCEIS changes from baseline




**Endoscopic Remission:**
Mayo endoscopic subscore (MES) of 0

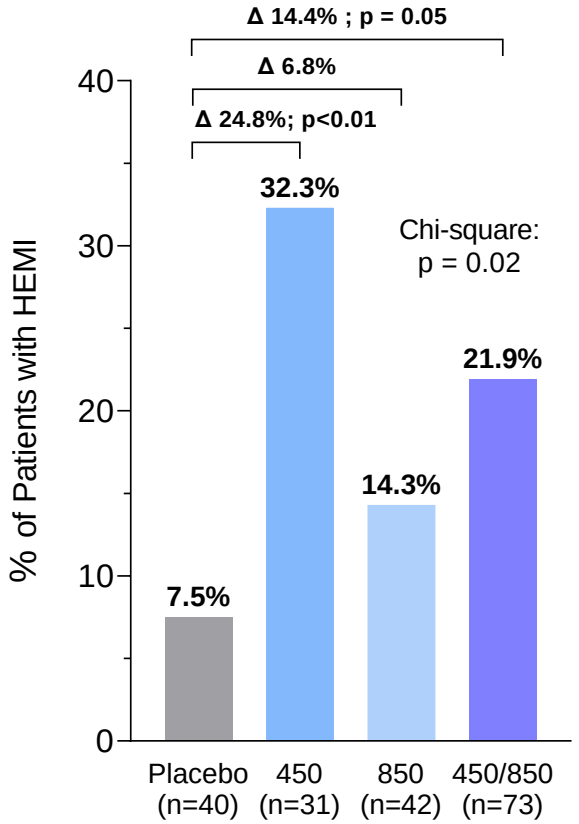
# Secondary endpoints: Histological Improvement and Histo-endoscopic Mucosal Improvement (HEMI) rates at w10

**Histological Improvement at w10**



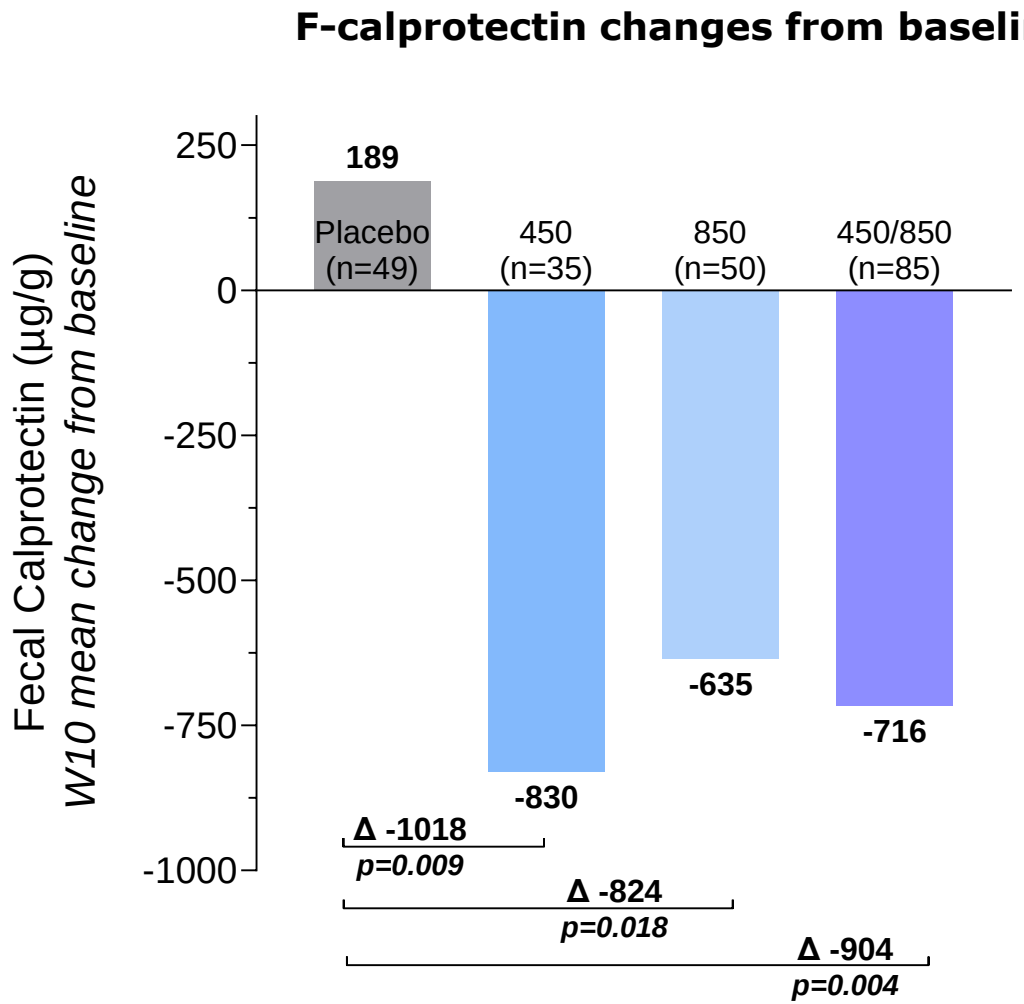

**Histological Improvement**
Nancy Histological Index (NHI) : ≤ 1

**Histo-Endoscopic Mucosal Improvement at w10**




**Histo-Endoscopic Mucosal Improvement:**
NHI ≤ 1 + MES ≤ 1

# Secondary endpoints: F-calprotectin changes from baseline at w10



# Safety

| | L450 mg (N=36) N(%) [E] | L850 mg (N=51) N(%) [E] | Placebo (N=49) N(%) [E] | Total (N=136) N(%) [E] |
|---|---|---|---|---|
| At least one TEAE | 17 (47.2%) [33] | 20 (39.2%) [42] | 16 (32.7%) [29] | 53 (39.0%) [104] |
| Lymphopenia | 4 (11.1%) [5] | 2 (3.9%) [2] | 1 (2.0%) [1] | 7 (5.1%) [8] |
| Anaemia | 1 (2.8%) [1] | 0 | 2 (4.1%) [2] | 3 (2.2%) [3] |
| Ulcerative colitis | 1 (2.8%) [2] | 2 (3.9%) [2] | 3 (6.1%) [4] | 6 (4.4%) [8] |
| Pyrexia | 2 (5.6%) [2] | 0 | 1 (2.0%) [1] | 3 (2.2%) [3] |
| Covid-19 | 1 (2.8%) [1] | 0 | 2 (4.1%) [2] | 3 (2.2%) [3] |
| Upper Respiratory Tract Infection | 0 | 2 (3.9%) [2] | 1 (2.0%) [1] | 3 (2.2%) [3] |
| Hypertension | 0 | 1 (2.0%) [1] | 2 (4.1%) [2] | 3 (2.2%) [3] |

- Lymphopenia ($<1*10^9$/L) was more frequent with Lusvertikimab (6/87: 6.9%) than with placebo 1/49: 2%)
- Lymphopenia $<0.5*10^9$/L occurred in 4.6% (4/87), was transient, not associated with a higher rate of infection and did not lead to treatment discontinuation

# Conclusions

- Lusvertikimab demonstrated clinical, endoscopic, histological and biological efficacy vs placebo at week 10 at both 450 and 850mg doses
- Lusvertikimab was well tolerated with transient lymphopenia occurring in 6.9% and lymphopenia $<0.5*10^9/L$ in 4.6% of patients, without a higher rate of infections
- Based on these data, Lusvertikimab deserves its potential place in the therapeutic armamentarium of UC and should be evaluated in a phase III study

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