[redacted]

OSE IMMUNO THERAPEUTICS	**Statement**

Product / Project	OSE-127
Subject	Cover page of the Statistical Analysis Plan v3.0 and the Version History page 2 of the SAP is mentioning the 28 February 2024 whereas the true date was the 28 February 2025
Author	[redacted]
Other participants	[redacted]
Date/time note written	04th of February 2026

Context :
The Statistical Analysis Plan (SAP) for project OSE-127 is planned to be submitted and loaded in ClinicalTrials.gov (ct.gov) as part of the study documentation package. During the preparation for this submission, a discrepancy was identified regarding the date reported on the SAP v3.0 cover page and in the version history section.

Description:
It was identified on 4 February 2026 that the cover page of the Statistical Analysis Plan, as well as the Version History table on page 2, mention the date 28 February 2024 for Version 3 of the SAP.

After verification, this date was confirmed to be incorrect. The correct and actual approval and finalization date of SAP Version 3 is 28 February 2025.

This discrepancy is limited to the date displayed on the SAP cover page and the Version History section. The SAP content, analyses definitions, endpoints, and planned statistical methodologies remain unchanged and were finalized and approved in 2025.

The incorrect date creates a technical issue for uploading the document into ClinicalTrials.gov, as the date is inconsistent with the study timeline and other regulatory documents.

The issue was identified prior to submission to ClinicalTrials.gov. A non-conformity will be generated in the quality system to document the deviation and its resolution.

Conclusion:
The incorrect date (28 February 2024) reported on the SAP cover page and Version History page is considered a documentation error only, with no impact on the scientific content, integrity, or validity of the Statistical Analysis Plan.

This note-to-file is issued to formally document the discrepancy and its root cause prior to submission to ClinicalTrials.gov. The SAP will be uploaded together with this note-to-file in ct.gov to ensure transparency and traceability.

No impact on patient safety, data integrity, statistical analyses, or study conclusions is expected.

[redacted]

OSE IMMUNO THERAPEUTICS	Statement

Name	Function	Signature	Date (dd-Mmm-yyyy)
[redacted]	[redacted]	[redacted]	04-févr.-2026
[redacted]	[redacted]	[redacted]	04-févr.-2026

STATISTICAL ANALYSIS PLAN
FOR FINAL RESULTS

Randomized, double-blind, Phase 2 study to evaluate the efficacy and the safety of OSE-127 versus placebo in subjects with moderate to severe active ulcerative colitis who have failed or are intolerant to previous treatment(s)

Protocol Number:	OSE-127-C201
IND or EudraCT Number:	2020-001398-59
Compound Number:	OSE-127
Indication:	Moderate to severe active ulcerative colitis
Phase:	2
Sponsor:	OSE Immunotherapeutics 22 boulevard Benoni Goullin 44200 Nantes France
Version - date:	V3.0 - 28 February 2024

Version History

[redacted]

Related Documents

[redacted]

Signature Pages

Title: Randomized double-blind phase 2 study to evaluate the efficacy and the safety of OSE-127 versus placebo in patients with moderate to severe active ulcerative colitis who have failed or are intolerant to previous treatment(s)

The undersigned have reviewed and revised this SAP and find it to be consistent with the study requirements:

Name	Position	Date Signature
[redacted]		

Table of Contents

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-Drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
C. diff	*Clostridium difficile*
CP	Conditional Power
CRA	Clinical Research Associate
CRP	C-Reactive Protein
CS	Clinically Significant
DSMB	Data Safety Monitoring Board
DTS	Data Transfer Specifications
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
FAS	Full Analysis Set
FFPE	Formalin Fixed Paraffin Embedded
GGT	Gamma Glutamyl-Transferase
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
IDMC	Independent Data Monitoring Committee
IE	Intercurrent Event
IND	Investigational New Drug (application)
ISF	Investigator Site File
IV	Intravenous
LDH	Lactic Dehydrogenase
LOCF	Last Observation Carried Forward
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCMC	Markov Chain Monte Carlo
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MMS	Modified Mayo Score
NCS	Not Clinically Significant

Abbreviation	Definition
OLE	Open-Label Extension
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PP	Per-Protocol
PrP	Predictive Power
PT	Preferred Term
RBC	Red Blood Cells
REP	Residual Effect Period
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Standard Deviation
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
UC	Ulcerative Colitis
UTC	Coordinated Universal Time
WBC	White Blood Cell

2. INTRODUCTION

The study OSE-127-C201 is a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with moderate to severe active ulcerative colitis (UC).

The **purpose** of this study is to assess the therapeutic efficacy of 2 doses of OSE-127 as well as its safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) in patients with UC.

The purpose of this Statistical Analysis Plan (SAP) is to describe the final statistical analyses. This SAP has been written in agreement with:

This Statistical Analysis Plan deals with the main analysis of the study (Selection Visit-W10 period) and the follow-up period (OLE) and details the planned analyses to be performed, in accordance with the main characteristics of the amended study protocol version 2.0 dated from 6 January 2022.

The main analysis of the study concerns the Selection Visit-W10 period and will be performed as soon as all efficacy and safety data of this period are available, and the mandatory steps required for study unblinding have been performed. Safety data collected during the Open Label Extension period that will be available at the time when database is locked for the main analysis will be the subject of an initial descriptive analysis. Then a full descriptive analysis including all data of the Open Label Extension period will be performed once all patients have completed Open Label Extension period and follow-up period.

2.1 STUDY OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To assess the efficacy of OSE-127 versus placebo on the reduction of the modified Mayo Score in moderate-to-severe UC patients who have previously failed or lost response or are intolerant to previous treatment(s)	• Mean change from baseline in the modified Mayo Score at Week 10 exploring the clinical symptoms (stool frequency and rectal bleeding sub-scores) additionally to the endoscopic sub-score
Key Secondary Objective	
• To assess the efficacy of OSE-127 versus placebo on the rate of clinical remission	• Number and proportion of patients in clinical remission at Week 10, defined as a modified Mayo score of ≤ 2 points and with no individual sub-score of > 1 point and a rectal bleeding at 0, therefore a stool frequency score of 0 or 1 and an endoscopic score of 0 or 1
Other Secondary Objectives	
• To assess the clinical efficacy of OSE-127 versus placebo on clinical response	• Number and proportion of patients with a clinical response at Week 10 defined as a reduction in the modified Mayo score of ≥ 3 points and of $\geq 30\%$ from baseline, with an accompanying decrease from baseline in the rectal bleeding sub-score of ≥ 1 point or an absolute rectal bleeding sub-score of ≤ 1 point
• To assess the efficacy of OSE-127 versus placebo on endoscopic remission and on endoscopic improvement	• Number and proportion of patients with an endoscopic remission at Week 10 defined by an endoscopic Mayo sub-score =0 • Number and proportion of patients with endoscopic response or improvement at Week 10 defined by an endoscopic sub-score of Mayo ≤ 1 point. • Mean change from baseline in the endoscopic activity measured at Week 10 by the Ulcerative Colitis Endoscopic Index of Severity (UCEIS)
• To assess the overall safety and tolerability of OSE-127 in patients with moderate to severe UC	• AEs, SAEs, AEs leading to the discontinuation of study treatment, target AEs of special interest, laboratory abnormalities, vital signs, ECG, and physical examination abnormalities

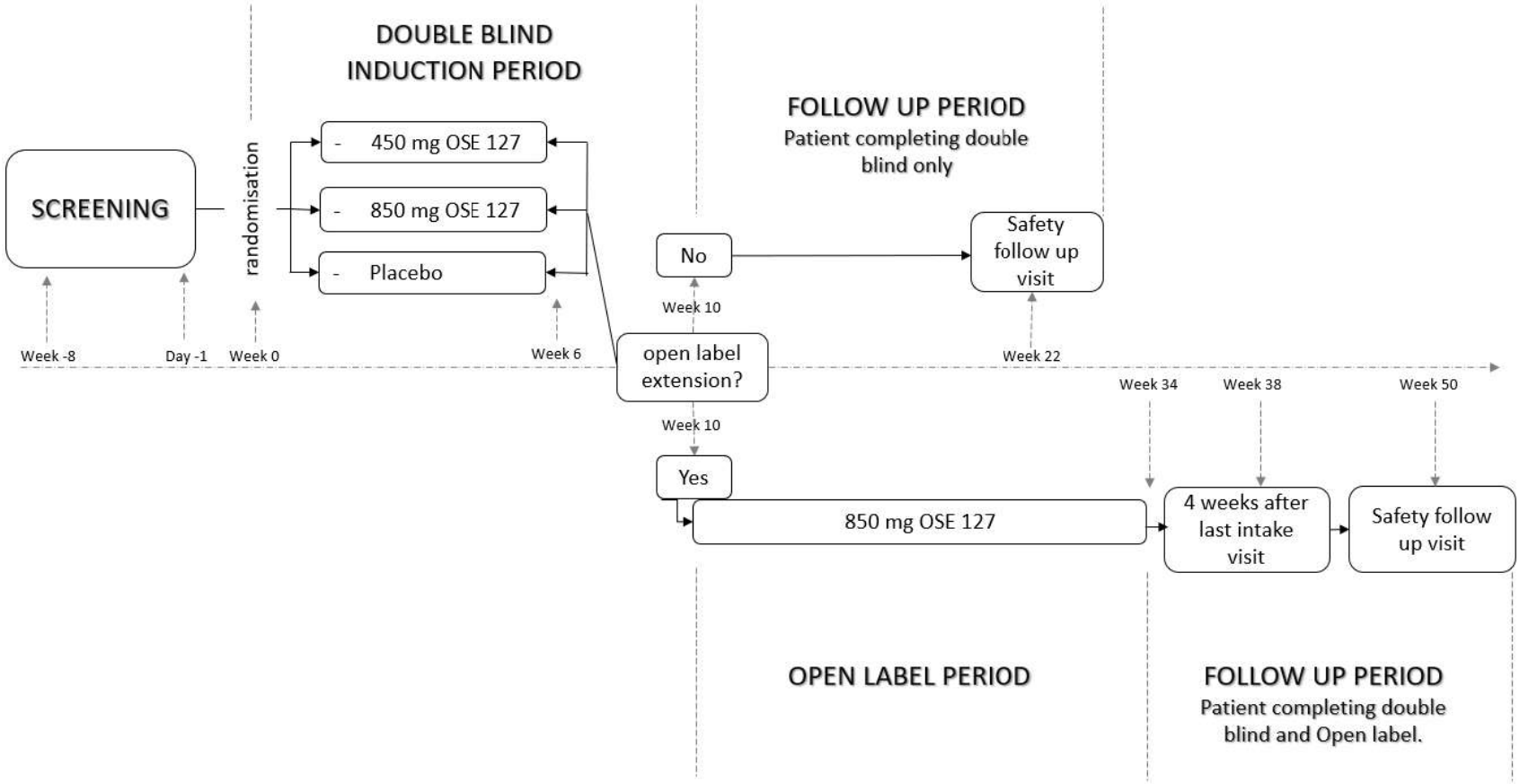
Objectives	Endpoints
Exploratory Objectives	
• To assess the efficacy of OSE-127 versus placebo on histologic remission and on histologic response	• Number and proportion of patients with a histological remission at Week 10 determined by a Nancy Histological Index score of 0 • Number and proportion of patients without acute histological inflammation at Week 10 defined by a Nancy Histological Index score of ≤ 1 • Mean change from baseline in the histologic activity measured at Week 10 by the score of Geboes and the Robarts Histopathology Index (RHI)
• To assess the efficacy of OSE-127 versus placebo on mucosal healing (i.e., endoscopic remission + histologic remission)	• Number and proportion of patients with mucosal healing (endoscopic remission and histologic remission) at Week 10 o Endoscopic remission defined by an endoscopic Mayo sub-score = 0 o Histologic remission defined by a Nancy Histological Index score of 0
• To assess the efficacy of OSE-127 versus placebo on Mayo score derived endpoints	• Activity of the disease measured by the UC-100 score at Week 10 • Evaluation of the 2-item patient reported outcomes (PRO2) (rectal bleeding and soft stools) at Week 2, Week 6, and Week 10
• To assess the activity of OSE-127 versus placebo on the change from baseline in C-reactive protein (CRP) and fecal calprotectin	• Median change from baseline in CRP at Weeks 10 and 22 • Median change from baseline in fecal calprotectin at Weeks 2, 6, and 10 • Number and proportion of patients with a 50% reduction in fecal calprotectin at Week 10 versus baseline
• To assess the efficacy of OSE-127 versus placebo for induction of clinical remission, clinical response, endoscopic improvement/remission, histologic improvement/remission and mucosal healing in the specific population of patients who had previously received biologics treatment	• Number and proportion of patients with clinical response, clinical remission or mucosal healing at Week 10 in the sub-population of patients who had previously received biologics

Objectives	Endpoints
• To assess the immunogenicity of OSE-127 in patients with UC	• Measurement of anti-drug antibodies
• To assess the PD effects of OSE-127	• Blood Receptor Occupancy in a sub-population of patients of the study • Absolute lymphocyte count derived from blinded hematology laboratory results
• To identify potential biomarkers predictive of a therapeutic response to OSE-127	• Stool analysis for fecal biomarkers • Biopsies analysis for identification of mucosal and PD predictors of efficacy
• To assess the PK of OSE-127 in UC patients	• Measurement of OSE-127 concentrations in a sub-population of patients of the study • Correlation between efficacy outcomes and drug exposure

A Futility Analysis hold on December, 10th 2021 concluded that 450 mg OSE 127 was no longer a relevant dose. Arm was closed and randomization became 1:1. Hence modifications were performed using a protocol amendment (Version 2.0 dated 6 January 2022).

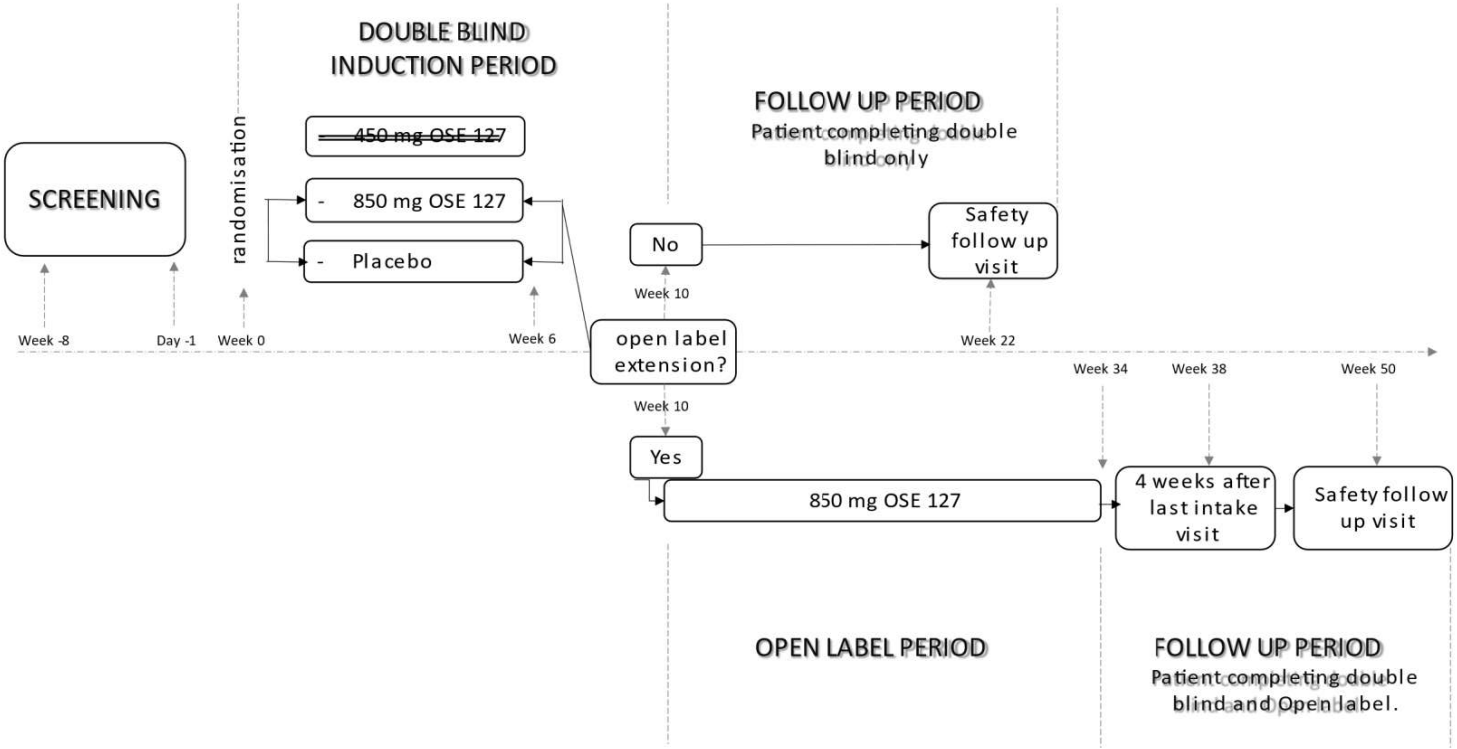
The study plan is shown Figure 1 (before Futility Analysis) and Figure 2 (after Futility Analysis). The investigation schedule is described in the protocol.

Figure 1 - Study plan before Futility Analysis



Notes: Patients who meet eligibility criteria after screening are randomized to treatment in a 1:1:1 ratio. The randomization will be stratified according to 2 variables: previous exposure to biologics (yes/no) and concomitant use of steroids (yes/no).
At week 10, patients not entering in the OLE phase will be followed for safety until Week 22.
The OLE phase is from Week 10 to Week 34. Patients having entered in the OLE phase will be followed for safety from Week 34 to Week 50.
[Extracted from Protocol V1.15 June 2020]

Figure 2 - Study plan after Futility Analysis



Protocol schema revised after FA

Notes: Patients who meet eligibility criteria after screening are randomized in a 1:1 ratio to the 2 remaining treatment arms (i.e. after the Futility Analysis outcome, the OSE-127 low dose arm has been cancelled since this dose was declared as futile). The randomization will be stratified according to 2 variables: previous exposure to biologics (yes/no) and concomitant use of steroids (yes/no). After the Futility Analysis outcome, only patients stratified to previous exposure to biologics will be randomized.
At week 10, patients not entering in the OLE phase will be followed for safety until Week 22.
The OLE phase is from Week 10 to Week 34. Patients having entered in the OLE phase will be followed for safety from Week 34 to Week 50.
[Extracted from Protocol V2.0 6 January 2022]

2.2 RANDOMIZATION

Before Futility Analysis, as per Global Protocol V1.0, patients were randomized to placebo, OSE-127 low dose (450 mg) or OSE-127 high dose (850 mg) in a 1:1:1 fashion. After Futility Analysis as per Global Protocol V2.0, patients were randomized to placebo or OSE127 high dose (850 mg) in a 1:1 fashion. Treatment assignments were obtained through an IWRS and disclosed to the investigational pharmacist or designee for dose preparation according to the Pharmacy Manual.

A stratification was applied through the IWRS according to 2 variables: previous exposure to biologics (yes/no) and concomitant use of steroids (yes/no).

The targeted proportion of biologics NON-naïve patients was to be within 50%-60% of the total population (i.e., the proportion of biologics naïve patients had to be within 40%-50% of the total population). As per Global Protocol V1.0, this ratio has been controlled during the first step of the study (i.e. before the Futility Analysis) by the Sponsor. Up to the 108 first inclusions, only 17 patients with previous exposure to biologics have been enrolled. This ratio being lower than 40%, the sponsor, after principal investigator agreement, has decided to stop inclusions in the subgroup of biologics-naïve patients. Therefore, only patients with previous exposure to biologics and primary non response or secondary loss of response were randomized from the 109th patient to the last randomized patient.

2.3 STUDY SAMPLE SIZE

Sample size calculation describes only the comparison between OSE-127 High Dose (850 mg) IV and Placebo intravenous (IV) with the target to have a percentage of previous exposure to biologics of 40% within this final analyzed population.

Group sample sizes of 44 per group are expected to achieve 85% power to reject the null hypothesis of equal means when the population mean reduction from baseline of the modified Mayo Score is 1 on placebo and 2.5 on active treatment (leading to a mean difference of 1.5) with a standard deviation (SD) for both groups of 2.3 and with a significance level (alpha) of 0.05 applying a 2-sided, 2-sample equal-variance t-test. Considering a dropout rate of 15%, the total sample size increases to 104. It is estimated that at the time of Futility Analysis, 72 patients have been randomized into the 2 arms that will be continued (placebo and OSE-127 high dose) with around 10 patients with previous exposure to biologics within these 2 arms. Therefore 32 additional biologics experienced patients have to be included in order to reach a number of 42 patients with previous exposure to biologics in the final analyzed population (i.e. 40% out of the 104 patients that will constitute the 2 remaining arms for final analysis).

3. STUDY SETS OF PATIENTS / TREATMENT GROUPS

The different sets of patients are described below:

The Safety Population (SAF)

All randomized patients who received any amount of study drug including those patients having received OSE-127 low dose during the first part of the study.

This set of patients is grouped for analysis according to the treatment they actually received, even if a randomization error is observed.

The Full Analysis Set (FAS)

The Full Analysis Set (FAS) for the Induction Phase consists of all randomized patients:

- With moderate to severe active ulcerative colitis who have failed or are intolerant to previous treatment,
- Who received any amount of blinded study drug.

This set of patients is grouped for analysis according to the planned treatment by the randomization including those patients who were randomized in the OSE-127 low dose group. Patients susceptible to be removed from FAS, if any, will be reviewed and discussed during Blinded Data Review Meeting (DRM).

The Per-Protocol (PP) Population

The per-protocol population is a subset of the FAS population. The per-protocol population consists of all patients who do not violate the terms of the protocol in a way that would impact the study primary outcome significantly. All decisions to exclude patients for the per-protocol population dataset will be made prior to the unblinding of the study according to the data review meeting specifications and will be reviewed and discussed before database lock during DRM. For the description of important protocol deviations, the following categories will be considered in accordance with ICH E3 guideline and ICH E3 Q&A:

- Selection/inclusion criteria not fulfilled.
- Patient having withdrawal criteria but not withdrawn.
- Incorrect treatment or dose received.
- Forbidden concomitant treatment.
- Endpoint assessment possibly affected.
- Safety possibly affected.
- Non-Respect of Study Procedures
- Randomization Issues

Analyses using the per-protocol population will be provided as a sensitivity analyses.

4. STATISTICAL METHODS

All data analyses and reporting procedures will use SAS v9.4 or higher.

All statistical programs employed in the analysis and reporting of the data as well as the outputs themselves will be validated by the [redacted] statistician in charge of the study and for primary criteria by another [redacted] statistician.

4.1 GENERAL CONSIDERATION

Descriptive statistics for parameters of interest will be provided by treatment group planned during induction phase and overall.

Descriptive statistics will be provided according to the nature of the criteria:

- Quantitative: number of data available and missing, number of observed values, minimum, maximum, median, mean, standard deviation and quartiles.
- Qualitative: number of missing values, number of observed values, frequencies, and percentages (of the number of available values) per modality.

Calculated statistics (median, mean, standard deviation and quartiles) will be displayed with one decimal more than min and max (which will be displayed with the same number of decimals as the record in the database), except other instructions.

The type I (α) error will be 5% (2-sided) for efficacy analyses and for each dose. Results on the OSE-127 low dose (450 mg) will only be descriptive.

For each relevant analysis, 6 columns corresponding to Placebo, High Dose, Low Dose, High Dose + Low Dose, High Dose + Placebo, Total will be produced. When edited, tests will always refer to a comparison between Placebo and High Dose.

From a statistical point of view, this study will not be comparative between the 2 doses of OSE-127, so comparison of confidence intervals (CIs) between the 2 doses will be exploratory.

Additionally to summary tables all data will be listed.

Durations in days between 2 timepoints T1 and T2 will be computed as T2 – T1 + 1.

Definitions:

Patients having taken at least one dose of IMP correspond to patients with at least one date of IMP infusion.

Baseline value will be defined as the last non-missing value prior to the first IMP intake but for MMS. Baseline MMS is specifically described in section 5.3.1. In case of patient randomised but not having taken at least one dose of IMP: value at baseline is defined as the last analysable value prior or equal to date of randomisation.

Considered periods are:

- Screening period = from ICF to Randomization
- Randomization period = from Randomization to first infusion (excluded)

- Induction period = First infusion - W10 period = first infusion until W10 infusion (excluded) or early termination before W10 or until W22 (last safety follow-up visit) if patient did not enter OLE
- OLE / FUP period = W10-W50 period = from W10 infusion until EOS

Last post-baseline value under treatment of the period will be defined as the last post-baseline non-missing value under treatment during the considered period.

Change from baseline to post-baseline visit under treatment is calculated as: Value at the post-baseline visit under treatment - Value at baseline.

Change from baseline to last post-baseline value under treatment is calculated as: Last post-baseline value under treatment - Value at baseline.

The Body Mass Index is calculated at a visit in the database as: BMI (kg/m^2) = Weight (kg) / (Height (cm) x 0.01)^2 using the height measured at the selection visit and the weight recorded at the corresponding visit. The result is rounded to one decimal place.

Visits Scheduled

W22 data collected for patients who are not included in OLE phase will not be presented together with W22 data collected for patients who are included in OLE. When W50 data will be displayed these W22 data will be pooled together with W50 data collected for patients who are included in OLE phase and may be referred as Last Follow-Up Visit.

W10 data collected for patients who are not included in OLE phase will be kept together with W10 data collected for patients who are included in OLE phase.

Data collected during W50 visit from a patient without any W34 visit will be considered as additional data.

4.2 HANDLING OF MISSING DATA

4.2.1 HANDLING OF INCOMPLETE DATES

For incomplete dates handling, the following conventions will be used.

Efficacy Data

- When day and month and year are missing, the date will be considered as missing.
- When only the day (respectively the month) is missing, it will be replaced by the 1st of the month (respectively June) of event.
- If the estimated date using this general rule is in contradiction with other available source data then a more appropriate case scenario rule will be used. To that aim the first infusion date will be taken into account.

Participation End Date / Early Termination Date

- Missing day will be replaced by 15
- Missing month or year will be missing

Concomitant Medications Start Date

- Missing month will be imputed to 1 (January)
- Missing day will be imputed to 1
- If missing year, date will be missing

Adverse Event Start Date

- For the adverse event start date (to derive the emergence of adverse event):
    - In case of completely missing date, it will be estimated by the first infusion date.
    - If the day and the month are missing:
        - If the year is the same as the year of an infusion date, it will be estimated by this infusion date,
        - If the year is not the same as the year of an infusion date, it will be estimated by the 1st January.
    - If only the day is missing:
        - If the month / year are the same as the month / year of an infusion date, it will be estimated by this infusion date,
        - If the month / year are not the same as the month / year of an infusion date, it will be estimated by the first day of the month.
- If after imputation, the estimated start date is after the end date, the estimated start date will be replaced by the end date.

Concomitant Medications or Medical History or Adverse Event End Dates

- Missing month will be imputed to 12 (December)
- Missing day will be imputed to last day of the month
- If missing year, date will be missing

4.2.2 MISSING DATA FOR EFFICACY ANALYSES

Definitions:

- Missing at Random (MAR): A variable is said to be missing at random if other variables (but not the variable itself) in the dataset can be used to predict missingness on a given variable.
- Missing Not at Random (MNAR): A variable is said to missing not at random if the fact that the data are missing is systematically related to the unobserved data, that is, the missingness is related to events or factors which are not measured by the researcher.
- Last Observation Carried Forward (LOCF) is a single imputation method which uses the last measured response as an endpoint by itself, not necessarily attached to a particular study time point.
- Baseline Observation Carried Forward (BOCF) is another single imputation approach which uses the baseline data as an endpoint by itself.

Handling of missing data for the modified Mayo score is described in section 0.

5. STATISTICAL ANALYSES

All baseline characteristics, efficacy and safety data will be presented using 6 columns: Low Dose, High Dose, Placebo, Low Dose + High Dose, High Dose + Placebo and Total (Low Dose + High Dose + Placebo) except baseline characteristics according to study part (see section 5.3.9) and randomization strata, main and sensitivity primary analyses and secondary analyses because of relevance.

5.1 DISPOSITION OF PATIENTS

Disposition of patients will be presented as follows:

- The numbers of randomized patients
- The numbers and percentages of patients included in the SAF
- The numbers and percentages of patients included in the FAS and numbers and percentages of patients excluded from the FAS + reasons for exclusion
- The numbers and percentages of patients included in the PP and reasons for exclusion from the PP

All following characteristics will be summarized for the FAS and by treatment group planned during induction phase and overall using descriptive statistics:

- For each visit, the numbers and percentages of patients who completed visit.

  For the Week 10 visit, visit is considered as fully completed if the actual 3 subscores constituting the primary endpoint at W10 *i.e.* Full Modified Mayo Score are available.
- Number and percentage of patients who prematurely withdrew from the induction phase and timing/reason for withdrawal
- Number and percentage of patients by total number of infusions and time between two IMP administrations by visit will be described by treatment group
- Number and percentage of patients who completed Week 10 but not included in open-label extension phase
- Induction duration (weeks), defined as time between the date of first study drug administration and
  - Date of Week 10 Endoscopy, if Week 10 Endoscopy is completed
  - Date of last visit before Week 10 Endoscopy, if Week 10 Endoscopy is not completed (lack of an actual primary endpoint at Week 10 i.e. Full Modified Mayo Score)
- Number and percentage of patients
  - in FAS who entered open-label extension phase
  - in SAF who entered open-label extension phase
- Number and percentage of patients who prematurely withdrew from the open-label extension phase (Week 34) and reason for withdrawal
- Number and percentage of patients who completed Week 34
- Study duration (weeks), defined as time between the date of randomization visit and date of end of study defined by the last visit for the patient (follow-up visit, premature end of study visit including visit performed over the phone -e.g. UKR….)

- Number and percentage of patients with at least one deviation / one major deviation / one minor deviation / one deviation by deviation name overall and by category. A listing of all deviations will be provided. Major deviations leading to exclusion from the FAS or from the PP will be defined as described in section 3.

A listing of patients who did not complete the induction period will also be provided with following information: gender, age, induction duration and duration between the endoscopy at baseline and 1st study drug administration, MMS at baseline (total and each of the 3 subscores), UC duration, previous exposure to biologics, concomitant steroids and reasons for discontinuation. Block ID if provided with the randomisation will also be displayed.

A listing of patients randomized during study part 1 and randomized during study part 2 will also be provided with following information: gender, age, induction duration and duration between the endoscopy at baseline and 1st study drug administration, MMS at baseline (total and each of the 3 subscores), UC duration, previous exposure to biologics, concomitant steroids and reasons for discontinuation. Block ID if provided with the randomisation will also be displayed.

5.2 BASELINE CHARACTERISTICS

All following baseline characteristics will be summarized, for the FAS by treatment group planned during induction phase and overall for the whole patient population as well as for study part 1 and study part 2 populations using descriptive statistics:

5.2.1 DEMOGRAPHIC AND UC BASELINE CHARACTERISTICS

- Age (years) at screening
- Gender (Male / Female)
- Weight (kg) at screening
- Tobacco consumption (Current / Former / No)
    - If current, type (Cigarettes / Cigars / Other)
    - If former, type (Cigarettes / Cigars / Other), and time since stop (defined in years as screening date – stop date + 1)

  Other type of consumption will be displayed in a listing.
- Alcohol consumption (Current / Former / No)
    - If current, number of drinks and frequency (Per day / Per week / Occasional)
    - If former, number of drinks, frequency (Per day / Per week / Occasional) and time since stop (defined in years as screening date – stop date + 1)
- Region of investigational centre
    - Ukraine
    - Russia
    - Country in UE (Union European): Belgium / Croatia / Hungary / Poland / Latvia / Bulgaria / Portugal / Spain
    - Other Country not in UE: South Africa / Belarus / Georgia / Serbia
- UC duration (years): Year of screening visit – Year of UC diagnosis + 1

- Previous exposure to biologics (Yes / No)
- Concomitant use of steroids (Yes / No)

There are some strata errors in iWRS due to site data entry errors. A description of strata recorded in the iWRS versus real strata will be provided. Real strata (eCRF Strata) will be taken into account in analyses.

- Mayo clinical subscores at randomization
- Modified Mayo Score at randomization (as described in section 5.3.1.1.)
- Endoscopic subscore at randomization
- Nancy score at baseline
- Robarts Histopathology Index at baseline
- Geboes integrated score at baseline
- CRP (the last available values prior to the first infusion date) as a quantitative variable and as a qualitative variable (Normal / Abnormal Not Clinically Significant / Abnormal Clinically Significant)
- Serum Albumin as a quantitative variable and as a qualitative variable (Normal / Abnormal Not Clinically Significant / Abnormal Clinically Significant)
- Faecal Calprotectin as a quantitative variable

5.2.2 RELEVANT MEDICAL HISTORY OR CURRENT CONDITIONS

Relevant medical history and current conditions will be coded in English using the Medical Dictionary for Regulatory Activities (MedDRA), validated version at the time of coding round during data-management process (Version 24.0).

A “medical history” event will be defined as an event with a start date strictly anterior to the first infusion date and an end date anterior or equal to the first infusion date. Otherwise (“ongoing at screening” ticked or end date posterior to the first infusion date) it will be considered as a “current condition” event.

Number and percentage of patients presenting at least one relevant medical history / current condition respectively will be displayed. For each relevant medical history / current condition term described according to its system organ class (SOC) and preferred term (PT), the corresponding number and percentage of patients will also be displayed.

5.2.3 MEDICATIONS HISTORY FOR UC

Number and percentage of patients presenting at least one previous medication for UC will be described using their prespecified therapeutic class (Biologics / Steroids / Immunosuppressors / Oral Aminosalicylates). Number and percentage of patients presenting at least one biologics will be displayed using their detailled therapeutic class.

For previous biologic medications, these results will also be displayed according to treatment outcome (Primary non-response / Secondary loss of response / Other / Unknown).

5.2.4 CHILDBEARING POTENTIAL AND PREGNANCY TEST

- Female of childbearing potential or procreative male (Yes / No)

- If no, reason (Sterilised / Hysterectomised / Menopaused / Vasectomised / Other)

  Other reason will be displayed in a listing.

- If yes, method of birth control (Combined hormonal contraception associated with inhibition of ovulation / Progestogen-only hormonal contraception associated with inhibition of ovulation / Intra uterine devices / Intra uterine hormone-releasing system / True sexual abstinence / Male partner sterilization / Condom / Other)

  Other method of birth control will be displayed in a listing.

- Pregnancy test at screening performed (Yes / No)
  - If no, reason will be displayed in a listing
  - If yes, specification (Serum / Urine) and result (Negative / Positive)

5.2.5 TUBERCULOSIS TESTS AT SCREENING

- Chest x-ray or negative quantiFERON TB Glod in Tube test performed within the last 3 months prior to screening excluding active or latent TB infection (Yes / No)
  - If yes, type of test (Negative Chest x-ray / Negative quantiFERON TB Gold in Tube test)
  - If not performed within the last 3 months prior to screening, test performed and type of test (Chest x-ray / QuantiFERON TB Gold in Tube test) and result (Negative / Positive)

5.2.6 COLON ENDOSCOPY AND BIOPSY FOR UC CONFIRMATION AT SCREENING

- Type of endoscopy performed (Full Colonoscopy / Only Rectosigmoïdoscopy)
  - If full endoscopy, local histopathology results expected (Yes / No)
- Histopathology report available confirming the diagnosis of UC (Yes / No)
  - If no, was the biopsy for UC histology confirmation performed (Yes / No)
    - If no, reason will be displayed in a listing.
    - If yes, diagnosis of active UC confirmed by local histopathology lab (Yes / No)

5.2.7 CONCOMITANT UC MEDICATIONS

Concomitant treatments for UC (steroids, ASA…) taken during induction period and OLE period will be described by ATC code and preferred name and by treatment group.

5.3 EFFICACY DATA

All efficacy analyses will be performed overall and by arms on the FAS population. Statistical test will be provided only for the comparison between OSE-127 High Dose (850 mg) and placebo.

In case of missing data for the Modified Mayo Score at Week 10, multiple imputation (see section 5.3.2.1) will be used as the **primary method** of imputation, and thus for the main analyses of primary endpoint (see section 5.3.2) and secondary endpoint based on MMS (see section 5.3.3).

Three sensitivity analyses will also be performed on primary endpoint:

- Analyses on PP
- Analyses on data using the imputation of MMS based on LOCF / BOCF (see section 4.2.2)
- Analyses on complete data (excluding patients with missing data for MMS at Week 10)

5.3.1 DERIVATION OF EFFICACY ENDPOINTS

5.3.1.1 MODIFIED MAYO SCORE CALCULATION

Definition

The modified Mayo score will be evaluated during the screening period and at Week 10.

The modified Mayo score consists of the following 3 subscores (Schroeder et al 1987):

- Stool frequency
- Rectal bleeding
- Findings of endoscopy

Each subscore is rated on a scale from 0 to 3, indicating normal to severe activity, as defined below:

Parameter	Clinical Evaluation (single choice)	Score
Stool frequency per day	Normal number of stools	0
	1-2 more than normal	1
	3-4 more than normal	2
	≥ 5 more than normal	3
Rectal bleeding (indicate the most severe bleeding of the day)	No blood seen	0
	Streaks of blood with stool less than half the time	1
	Obvious blood with stool most of the time/ half of the time or more	2
	Blood alone passes	3
Endoscopic findings	Normal mucosa or inactive disease	0
	Mild activity (erythema, decreased vascular pattern, mild friability)	1
	Moderate activity (marked erythema, lack of vascular pattern, friability, erosions)	2
	Severe activity (spontaneous bleeding, large ulcerations)	3

Source: Schroeder 1987

The modified Mayo score is calculated as the sum of the 3 subscores of stool frequency, rectal bleeding and findings of endoscopy. Thus, the Modified Mayo score may take on values in the range of 0 to 9.

For the stool frequency and rectal bleeding data are based on the results from the most recent consecutive 3-day period (average sub-score rounded to the nearest integer) within the 1 week before the randomization/W10 visit excluding the following:

- The day(s) of the preparation for an endoscopy, if completed after preparation started (Day of endoscopy – 1 day)
- The day of the endoscopy
- The 48 hours immediately following the endoscopy (Day of endoscopy + 2 days)

For both MMS (baseline/W10), if 3 days that meet the criteria defined above are not available within the 7 days prior to the randomization/W10 endoscopy, then available data of stool frequency subscore and rectal bleeding subscore within the 14 days before randomization will be chosen. The actual calculation of scores will be done on the **3 most recent available scores** (whether they are consecutive or not).

For W10 MMS, if the date of W10 endoscopy is different from the date of W10 visit, the W10 endoscopy date will be taken into account for ePRO identification provided that the W10 administration (first infusion within OLE) is posterior to the W10 endoscopy. Note that this rule is different from the rule used for the futility analysis where W10 visit date was taken into account instead of W10 endoscopy date when the 2 dates were different.

The endoscopic sub-score is established by the centralized reading platform on the colonoscopy and/or the flexible sigmoidoscopy conducted prior to randomization and at Week 10.

Moreover, the following rules will be taken into account:

- If two PRO are reported the same day with the same value and if there is less than 6 hours between the PRO, it will be considered as a doublon and only the first PRO will be kept.

- Coordinated Universal Time (UTC) will be used when comparing PRO date/time to randomization date/time whereas local date/time will be used when comparing PRO date/time to endoscopy date.

It was discussed during DRM and agreed to consider a partial MMS imputation for patients who received 3 infusions with missing endoscopy results at Week 10 when both PRO for ‘rectal bleeding’ and ‘stool frequency’ are available and provided that no IE 2 or IE6 had occurred before. For each clinical subscore, the 3 PRO values within the 14 days before the theoretical Week 10 date included (= randomization date + 70 days) will be selected, and only missing endoscopic score will be imputed for these patients. Number and percentage of patients meeting that condition will be presented.

Primary Endpoint Derivation

Absolute variation of modified Mayo score between baseline and Week 10 will be derived as modified Mayo score at week 10 - modified Mayo score at randomization.

5.3.1.2 CLINICAL REMISSION AT WEEK 10

Clinical remission at Week 10 is defined as a modified Mayo score of ≤ 2 points and with no individual sub-score > 1 point and a rectal bleeding at 0, therefore a stool frequency score of 0 or 1 and an endoscopic score of 0 or 1.

- Clinical remission = Yes, if at week 10:
  - Modified Mayo score ≤ 2 points
  - **AND** rectal bleeding sub-score = 0
  - **AND** stool frequency sub-score = 0 or 1
  - **AND** endoscopic findings = 0 or 1
- Clinical remission = No, in all other cases

  Modified Mayo score will be based on Modified Mayo score obtained in section 5.3.1.

5.3.1.3 CLINICAL RESPONSE AT WEEK 10

Clinical response at Week 10 is defined as a reduction in the modified Mayo score of ≥ 3 points and of ≥ 30% from baseline, with an accompanying decrease from baseline in the rectal bleeding sub-score of ≥ 1 point or an absolute rectal bleeding sub-score of ≤ 1 point.

- Clinical response = Yes, if at week 10:
  - Modified Mayo score at Week 10 - Modified Mayo score at baseline ≤ -3
  - **AND (**Modified Mayo score at Week 10 - Modified Mayo score at baseline) / MMS Baseline *100 ≤ -30%
  - **AND**
    - Rectal bleeding at Week 10 - Rectal bleeding at baseline ≤ -1
    - **OR** Rectal bleeding at Week 10 ≤ 1
- Clinical response = No, in other cases

  Modified Mayo score will be based on Modified Mayo score obtained in section 5.3.1.

5.3.1.4 ENDOSCOPIC REMISSION AT WEEK 10

Endoscopic remission at Week 10 is defined by an endoscopic Mayo sub-score = 0

- Endoscopic remission = Yes, if endoscopic findings = 0 at week 10
- Endoscopic remission = No if endoscopic findings > 0 at week 10,

5.3.1.5 ENDOSCOPIC IMPROVEMENT AT WEEK 10

Endoscopic improvement at Week 10 is defined by an endoscopic sub-score of Mayo ≤ 1 point.

- Endoscopic improvement = Yes if endoscopic findings ≤ 1 at week 10
- Endoscopic improvement = No if endoscopic findings > 1 at week 10

5.3.1.6 CHANGE FROM BASELINE IN THE ENDOSCOPIC ACTIVITY AT WEEK 10

Change from baseline in the endoscopic activity at Week 10 is measured by the Ulcerative Colitis Endoscopic Index of Severity (UCEIS).

The UCEIS is an endoscopic scoring system which includes assessment of vascular pattern, bleeding, and ulcers (Travis SPL 2012). The UCEIS consists of the following three descriptors (in following table) and will be calculated as a simple sum: vascular pattern (scored 0–2), bleeding (scored 0–3), and erosions and ulcers (scored 0–3). The range in the UCEIS scores is 0 to 8. Higher scores indicate more severe disease.

Descriptor	Points	Definition
Vascular pattern	Normal (0)	Normal vascular pattern with arborization of capillaries clearly defined, or with burring or patchy loss of capillary margins
	Patchy obliteration (1)	Patchy obliteration of vascular pattern
	Obliteration (2)	Complete obliteration of vascular pattern
Bleeding	None (0)	No visible blood
	Mucosal (1)	Some spots or streaks of coagulate blood on the surface of the mucosa ahead of the scope which can be washed away
	Luminal mild (2)	Some free liquid blood in the lumen
	Luminal moderate or severe (3)	Frank blood in the lumen ahead of the endoscope or visible oozing from mucosa after washing intraluminal blood or visible oozing from hemorrhagic mucosa
Erosions and ulcers	None (0)	Normal mucosa, no visible erosions or ulcers
	Erosions (1)	Tiny (≤ 5 mm) defects in the mucosa, of a white or yellow color with a flat edge
	Superficial ulcer (2)	Larger (≥ 5 mm) defects in the mucosa, which are discrete fibrin-covered ulcers in comparison with erosions, but remain superficial
	Deep ulcer (3)	Deeper excavated defects in the mucosa, with a slightly raised edge

Source: Travis SPL 2012

Change from baseline in the endoscopic activity at Week 10 will be derived as:

UCEIS at week 10 - UCEIS at baseline.

5.3.2 PRIMARY ENDPOINT ANALYSIS

5.3.2.1 MAIN ANALYSIS

Primary efficacy estimand

The primary estimand of interest is the effect of the treatments on the clinical disease activity in all patients assuming non-occurrence of intercurrent events (IE) (hypothetical strategy as defined below). The motivation for this choice is to assess the full efficacy potential, that is, the pharmacologic effect of OSE-127 if all patients adhere to it (without any intercurrent events).

The attributes of the primary estimand are defined as follow:

Treatment: OSE-127 high dose or placebo

Population : FAS

Variable: Absolute variation of modified Mayo score between baseline and Week 10 (primary efficacy endpoint).

Summary measure: difference in means between treatments.

Intercurrent events (IE):

- **IE1: Study drug discontinuation for ulcerative colitis worsening** (Early Termination before W10 for Disease Worsening)

- **IE2: Initiation / increase of authorized / prohibited medication** (identified and validated during DRM using a specific listing programmed for this purpose).

- **IE3: Study drug discontinuation for AE related to study drug** (AE with Action Taken regarding Study Treatment equals to Drug Withdrawn and Relationship to Study Treatment equals to Possible or Probable or Definitely Related)

- **IE4: Study drug discontinuation for other reasons** (non-medical reason, AE not related…) (Early Termination before W10 for other reason than Disease Worsening or than AE with Action Taken regarding Study Treatment equals to Drug Withdrawn and Relationship to Study Treatment equals to Possible or Probable or Definitely Related)

- **IE5: Switch of treatment group** (error of dispensation) (determined by unblinded monitoring)

- **IE6: Decrease or stop of authorized medication** (identified and validated during DRM using specific listing programmed for this purpose)

The rate of these IEs is assumed to be below 10%. IEs will be handled by an **hypothetical strategy** aimed at estimating what the outcome at W10 would have been if no IE would have occurred, considering that patients with IE would have the same efficacy outcomes as those patients who completed their treatment in the same group without IE. At this early stage of OSE-127 clinical development in UC it was decided to apply an hypothetical strategy instead of a Treatment Policy strategy which is recommended in the European Guidelines for the development of new medicinal products in Ulcerative Colitis if the therapeutic intent is to induce remission in the short term.

Note: In case a patient is concerned by several IEs or if the IE can be classified in 2 different categories of IEs, the first event occurring will be considered. If several IE occurred the same day, IE will be considered to be more conservative in the following order: IE1; IE2; IE3; IE4; IE5, IE6.

Mayo Score Analysis

- Subscores and modified Mayo scores distributions at baseline and Week 10 will be described as quantitative variable.
- Subscores and modified Mayo scores change as a qualitative variable (Improvement > 0 / No Change = 0 / Worsening < 0)
- Absolute variation of modified Mayo score will be described as quantitative variable for each treatment dose (450 mg OSE-127 and 850 mg OSE-127) and for placebo.
- Week 10 changes from baseline will be plotted

Primary Endpoint Analysis

- The treatment difference (only between high dose 850 mg OSE127 and placebo) will be assessed with an ANCOVA model which includes terms to adjust for the baseline Modified Mayo Score value, real stratification factors (eCRF strata) and treatment group. The average of the adjusted difference in the mean change from baseline to W10 between the

treatments will be reported with the standard errors of the mean, two-sided 95% confidence interval, and P-value obtained from the multiple imputed datasets and analysis (see section below).

- The assumptions underlying the model, as for instance, the normality and homoscedasticity of residuals and detection of outliers will be checked. The assumptions of normality and homoscedasticity of residuals will be investigated using some graphs and descriptive statistics. The detection of outliers will be done using graphics.
- If the model is not running due to too few patients (< 5) in any of the strata, the model mentioned above will be modified. Thus, the two stratification factors in the model will be replaced by the following composite factor: Concomitant use of steroids or Previous exposure to biologics or both (yes/no).

  The following statistical hypotheses being considered:

  - H0 (null): No difference in primary endpoint between OSE-127 and placebo
  - H1 (alternative): Difference in primary endpoint between OSE-127 and placebo

Missing data / intercurrent events handling

The primary analysis for the primary estimand will be conducted using only data obtained prior to IEs. Values observed post IE2 and IE6 will not be used in the primary analysis. Post IE values will be imputed according to the Missing At Random (MAR) assumption (multiple imputation by treatment group). This is aligned with the primary estimand and the hypothetical strategy. Missing data not linked to intercurrent events will be imputed according to the MAR assumption with a multiple imputation by treatment group.

Multiple Imputation of Modified Mayo Score at Week 10 for Main Analysis

If the Modified Mayo Score at W10 is missing or if one or 2 subscores are missing, the missing subscores (rectal bleeding, stool frequencies and endoscopic) will be imputed as follow:

- Step 1: Missing values will be identified and replaced by a random sample of plausible values (between 0 to 3) imputations (completed datasets). Multiple completed datasets are generated via imputation model based on the Missing At Random (MAR) assumption within each treatment group, whatever the reason is for patient withdrawal.

  A total of 100 completed datasets will be created.
- Step 2: From these 100 completed datasets modified Mayo score at W10 and change of modified Mayo score at W10 from baseline will be calculated in each of the imputed datasets.
- Step 3: The 100 completed datasets will be analyzed using the ANCOVA model as described above.
- Step 4: Treatment effects from these 100 analyses will then be combined using Rubin's Method. SAS codes are described in Appendices (section 9). The variance of the estimator is the combination of the between- and within-imputation variability (Carpenter and Kenward, 2007).

Statistical elements: Finally, the following elements will be provided in a summary table:

- Estimate (standard error) of the difference between adjusted treatment arm means
- Two-sided 95% CI of the estimate
- Two-sided p-value

The covariates and baseline characteristics which can be predictive of the primary endpoint will be included in a multiple imputation procedure and will include the following:

- Age (years) at screening
- Gender (Male/Female)
- UC duration (years)
- Modified Mayo Score at baseline (at randomization data)
- Previous exposure to biologics (Yes/No) (eCRF stratification factor)
- Concomitant use of steroids (Yes/No) (eCRF stratification factor)

5.3.2.2 SENSITIVITY ANALYSES

PP Analysis

Main analysis (section 5.3.2.1) will be performed on the PP population.

Other Imputation Method Analysis

Main analysis (section 5.3.2.1) will be performed replacing multiple imputation method by BOCF / LOCF imputation of Modified Mayo Score at Week 10.

To that aim, missing modified Mayo score at W10 will not be directly imputed, the 3 subscores will be imputed as follow:

- Endoscopic subscore will be imputed by the Baseline Observation Carried Forward (BOCF) (see section 4.2.2)
- The stool frequency and rectal subscores will be imputed by the Last Observation Carried Forward (LOCF) (see section 4.2.2):

  These 2 subscores will be calculated from the three last available values collected in the same way as process described in section 5.3.1.

Complete Data Analysis

Main analysis (section 5.3.2.1) will be performed on complete data (excluding patients with missing or partially missing data for MMS at Week 10).

Composite Strategy

In order to assess the sensitivity to hypothetical strategy, values post IE1, IE2 and IE3 will be imputed using the composite strategy, meaning worst mean of 3 consecutive values for rectal bleeding and stool frequency (rounded to the nearest integer) between randomization and last available data and endoscopic value at baseline will be used to derive MMS score at W10. The other IE and missing data will be handled as in the primary analysis.

MNAR Assumption

In order to assess the sensitivity to MAR assumption, values post IE1, IE2 and IE3 will be imputed to the Missing Not At Random (MNAR). The other IE and missing data will be handled as in the primary analysis.

5.3.3 SECONDARY ENDPOINTS ANALYSES

Secondary endpoints will be analysed (proportion, logistic or ANCOVA models) applying derivation described in section 5.3.1 and applying multiple imputation (from 100 completed datasets) as for

primary criteria, using estimands. Treatment effects from these 100 analyses will then be combined using Rubin's Method. SAS codes are described in Appendices (section 7).

For binary secondary endpoints, comparison between 850 mg OSE 127 and placebo will be analyzed using a logistic model with treatment, baseline score, stratification criteria at randomization as factors. The response function will be the log odds (logit) of the proportion of patients responding with associated p-value. The fitted curve will be shown graphically with CIs for each dose. Estimates of the treatment differences in response function and associated 95% CI for OSE-127 High Dose (850 mg) against placebo will be computed from the model. These results will be back-transformed to give point estimates of the difference in proportions and associated 95% CI.

Secondary safety and tolerability endpoints are described in section 5.3.5.

Following parameters will be summarized for each treatment doses (450 mg OSE127 and 850 mg OSE 127) and for placebo.

5.3.3.1 ANALYSES OF KEY SECONDARY ENDPOINT

Number and proportion of patients in clinical remission at Week 10

Secondary efficacy estimand

The attributes of the secondary estimand are defined as follow:

- Treatment: OSE-127 high dose or placebo
- Population: FAS
- Variable: clinical remission at Week 10.
- Summary measure: difference in proportion between treatments.
- Intercurrent events (IE): IE1, IE2, IE3, IE4, IE5, IE6 previously defined

Missing data and intercurrent events will be handled as for the primary analysis.

The same sensitivity analyses as for the primary endpoint will be applied:

- Analysis on PP population
- Analysis using BOCF / LOCF imputation methods
- Complete Data Analysis
- Composite Strategy Analysis: values post IE1, IE2 and IE3 will be imputed using the composite strategy, meaning clinical remission at W10 will be no.
- MNAR Assumption Analysis

5.3.3.2 ANALYSES OF OTHER SECONDARY ENDPOINTS

- Number and proportion of patients with a clinical response at Week 10
- Number and proportion of patients with an endoscopic remission at Week 10

- Number and proportion of patients with endoscopic improvement at Week 10

These 3 endpoints will be handled as the key secondary endpoint.

- Change from baseline in the endoscopic activity at Week 10 as quantitative variable

  For this change, the difference between 850 mg OSE-127 and placebo will be assessed with an ANCOVA model which includes terms to adjust for the endoscopic subscore at randomization, stratification factors and treatment group. The average of the adjusted difference in the mean change from baseline to W10 between the treatments will be reported with the standard errors of the mean, two-sided 95% confidence interval, and P-value obtained from the multiple imputed datasets and analysis (see section above).

5.3.4 EXPLORATORY ENDPOINTS

[redacted]

5.3.4.1 MAYO SCORE DERIVED ENDPOINTS

5.3.4.1.1 UC-100 Score

- UC-100 score measuring activity of the disease will be described at Week 10 as a quantitative variable. The UC-100 is a composite score consisting of scores from the modified Mayo stool frequency sub-score (as defined in section 5.3.1), the modified Mayo endoscopic sub-score (as defined in section 5.3.1), and the RHI (defined in section 5.3.4.3). The composite score is calculated as follows: (1 + 16 × Mayo Clinic stool frequency sub-score [0 to 3] + 6 × Mayo Clinic endoscopic sub-score [0 to 3] + 1 × RHI score [0 to 33]). Scores range from 1 (no disease activity) to 100 (severe disease activity). Complete case results will be displayed. This analysis will be performed only if main analysis is significant.

5.3.4.1.2 PRO2

- Evaluation of the 2-item PRO2 (rectal bleeding and stool frequency) will be described at Week 2, Week 6, Week 10, Week 14, Week 18, Week 22, Week 26, Week 30, Week 34, Week 38 and Week 50 as a qualitative variable and a quantitative. Partial Modified Mayo Score (pMMS) defined as the sum of rectal bleeding subscores and stool frequency subscores will also be described at the same timepoints. For W2 and W6, the 3 closest values from W2 and W6 visits will be used with the same rules as for primary endpoint analyses. Evolution of rectal bleeding, stool frequency and partial Modified Mayo scores will also be graphically presented over time.
- The change from baseline of partial Modified Mayo score will be presented and a mixed model for repeated measures (MMRM) will be performed including terms to adjust for the score at randomization, stratification factors and treatment group. Kenward-Roger method for approximating the denominator degrees of freedom and correcting for bias in the estimated variance-covariance of the fixed effects. The average of the adjusted difference in the mean change from baseline to each timepoint between the treatments will be reported with the two-sided 95% confidence interval and graphically displayed.

5.3.4.2 C-REACTIVE PROTEIN (CRP) AND FECAL CALPROTECTIN

- CRP value will be described at baseline and at Week 10 as well as the change from baseline.
- Fecal calprotectin value will be described at baseline and at Week 2, Week 6 and Week 10 as well as the change from baseline.
- Number and proportion of patients with at least a 50% reduction in fecal calprotectin at Week 10 versus baseline will be described as a qualitative variable.

5.3.4.3 HISTOLOGICAL DATA

- Nancy score (0 to 4) will be described at Week 0 and at Week 10
- Shift tables between Week 0 and Week 10 Nancy scores will be produced according to the following modalities:
  - Score 0 to 0 / 0 to 1 … / 4 to 3 / 4 to 4
  - Improvement (Score W10 < Score W0) / Stable (Score W10 = Score W0) or Aggravation (Score W10 > Score W0) /
  - Histological remission defined as Nancy score = 0 at W10 (Score = 0 / Score > 0)
  - Acute Inflammation: Score ≤ 1 at W0 to Score > 1 at W10 / Score ≤ 1 at W0 to Score ≤ 1 at W10 / Score > 1 at W0 to Score > 1 at W10 / Score > 1 at W0 to Score ≤ 1 at W10
  - Histological Improvement defined as Nancy score ≤ 1 at W10 (Score ≤ 1 / Score > 1)
  - Nancy score at W10 according to Nancy Score = 4 at W0
- Robarts Histopathology Index (RHI) will be described at Week 0 and at Week 10, as well as absolute change from W0 at W10.
- Geboes Integrated Score will be described at Week 0 and at Week 10, as well as absolute change from W0 at W10
- Mucosal Healing at W10 defined as an endoscopic subscore = 0 and a Nancy score = 0
- Histo-Endo Mucosal Remission (HEMR)
  - With Nancy defined as an endoscopic subscore = 0 and a Nancy score = 0 or 1
  - With Geboes defined as an endoscopic subscore = 0 and a Geboes score ≤ 2B.0
  - With Robart defined as an endoscopic subscore = 0 and a RHI ≤ 3
- Histo-Endo Mucosal Improvement (HEMI)
  - With Nancy defined as an endoscopic subscore = 0 or 1 and a Nancy score = 0 or 1
  - With Geboes defined as an endoscopic subscore = 0 or 1 and a Geboes score ≤ 3.1
  - With Robart defined as an endoscopic subscore = 0 or 1 and a RHI ≤ 9

As sensitivity analyses, these variables will be provided:

- On patients without any missing W0 data
- On specific populations of patients defined in section 5.3.6 (stratification variables – eCRF strata)

- On the subset of patients with a fecal calprotectin value > 250 µg/g at W0
- Without patients with a MMS score = 4 at randomization (only Nancy score, RHI, Geboes integrated score and mucosal healing)
- With the addition of the Geboes Continuous Score described at Week 0 and at Week 10, as well as absolute change from W0 at W10

5.3.5 SAFETY DATA

All safety analyses will be described on the safety population by treatment group.

All safety analyses will be performed in the Safety Set:

- by treatment group during the induction period (W0-W10)
- by initial treatment during OLE (W10-W50 periods). Those patients having received OSE-127 (either in low or high dose) since W0 will be interpreted separately.
- and overall.

5.3.5.1 GENERAL CONSIDERATIONS

Adverse Events (AE) will be coded to the SOC and PT using MedDRA central coding dictionary, Version 24.0.

Treatment-emergent adverse events (TEAEs) are defined as AEs that occurs from the time the patient receives his/her first dose of study drug until end of the residual effect period (REP), meaning a period of 16 weeks after the last dose of trial medication. In the case where it is not possible to define an AE as treatment emergent or not, the AE will be classified by the worst case, i.e. treatment emergent. When an AE occurs after written consent has been obtained but before the first dose of study drug, the AE will be considered a non-treatment emergent AE. In this study, worsening of gastro-intestinal symptoms identified from the screening history and physical examination are considered related to the underlying condition (efficacy endpoints). Thus, these symptoms will not be considered as AEs unless their course, intensity or other specific features are such that the Investigator, according to his/her best medical judgment, considers these events as exceptional in the context of this medical condition.

Also, when a SOC of AE is “Investigations” and the AE occurs on the same day as the first dose of the study drug (after confirmation in the eCRF that the blood collection was performed before the study drug administration), then the AE is classified as a non-Treatment Emergent. AE with another SOC than “Investigations” occurring on the same day as the first dose of the study drug is considered as well as a non-Treatment Emergent when action taken regarding study treatment is “Not Applicable”

Serious Adverse Events (SAEs) are those events recorded as “Serious” on the AE page of the eCRF.

An adverse event of special interest (AESI) includes**:**

- Allergy (local at the site of infusion and general)
- Infections defined as AE recorded with a SOC “Infections and infestations”
- Lymphopenia $<500 \times 10^6$/L

An overdose is reported in AE forms and is identified by SOC = Injury, poisoning and procedural complication and PT = Overdose.

Severity of AE will be classified as mild/ moderate/ severe. TEAEs of study medication with a missing severity will be classified as severe.

Relationship, as indicated by the Investigator, will be classified as 'Unrelated', 'Unlikely', 'Possible' or 'Probable', 'Definitely'. TEAEs with a missing relationship to study medication will be assigned a relationship of 'unknown' except for overdoses.

A "related to study treatment" AE is defined as an AE with a relationship to study treatment of 'Possible', 'Probable', 'Definitely', unknown and **"not related"** if the relationship is unlikely related or unrelated.

A death will be reported in the "Adverse Event" database for AEs with fatal outcome or seriousness criteria as fatal.

5.3.5.2 SUMMARY OF ADVERSE EVENTS

Brief AEs summary tables will provide the number and percentage of patients with at least one the following events as well as the total number of AEs for induction phase, OLE period and for the entire study period:

- any TEAE,
- TEAE related to the study treatment,
- Serious TEAE,
- Serious TEAE related to the study treatment,
- Severe TEAE,
- Severe TEAE related to the study treatment,
- TEAE leading to death
- Related TEAE leading to death
- TEAE leading to drug withdrawn
- TEAE leading to drug interruption
- TEAE leading to study discontinuation
- AESI:
    - Allergy (local at the site of infusion and general),
    - Infections
    - Lymphopenia $<500 \times 10^6/L$
- Overdoses

5.3.5.3 DESCRIPTION OF ADVERSE EVENTS

Number and percentage of patients with at least one AE will be presented by SOC and PT for induction phase and OLE period, separately. Analysis will be presented for all AE displayed in summary of AE (Section 5.3.5.2).

Subjects are only counted once within each SOC or PT.

Within each AE frequency table, the SOCs will be ordered in alphabetical order, and the PTs will be listed in descending order of frequency.

5.3.5.4 DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

By-patients Listings of deaths (including cause of death), AESI, pre-treatment AE, post-follow up AE and all SAE (emergent or not) and overdoses will be provided.

5.3.5.5 VITAL SIGNS

Following vital signs will be considered:

- Systolic Blood Pressure (SBP) in mmHg (normal value range is [90-149])
- Diastolic Blood Pressure (DBP) in mmHg (normal value range is [45-90])
- Heart rate in b.p.m (normal value range is [40-100])
- Respiratory rate in b.p.m (normal value range is [8-18])
- Body temperature (°C) ; Temperature in F will be converted using the formula: °C = (50 F – 32) * 5/9
- Weight (kg)
- BMI (kg/m^2)

Descriptive statistics on value at baseline, on value at each post-baseline visit under treatment (Induction and OLE), on last post-baseline value under treatment and on change from baseline to last post-baseline value under treatment (pre-dose data). These analyses will be performed on both periods (Selection Visit-W10 and W10-W34).

5.3.5.6 ELECTROCARDIAGRAMMS

ECG parameters will be described at each timepoint under treatment (Induction and OLE):

- 12-lead ECG performed (Yes / No)
    - If no, reason will be displayed in a listing
    - If yes, result (Normal / Abnormal NCS / Abnormal CS). Listing of abnormal parameter values will be produced.

Shift tables between baseline condition (Normal / Abnormal NCS / Abnormal CS) and worst value during study (Normal / Abnormal NCS / Abnormal CS) will be presented (worst change).

5.3.5.7 LABORATORY TESTS

As per eCRF, all laboratory parameters are fully recorded at screening and Week 0. Then only the abnormal values (clinically and non-clinically significant) are collected at the next timepoints except for Hemoglobin, WBC, absolute neutrophils and absolute lymphocytes counts within the V.2.0 Global Version of the protocol.

Following parameters will be considered:

- Red blood cell count
- Hemoglobin
- WBC
- Absolute neutrophils
- Absolute lymphocytes
- Absolute eosinophils
- Absolute basophils
- Absolute monocytes
- Platelet count
- Glucose
- Total cholesterol
- Triglycerides
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase
- ASAT
- ALAT
- GGT
- Sodium
- Potassium
- Creatinine
- LDH
- Viral testing
- Hematocrit
- Mean Corpuscular Haemoglobin (MCH)
- Mean Corpuscular Haemoglobin Concentration (MCHC)
- Mean Corpuscular Volume (MVC)
- Total protein
- Albumin
- Cholesterol HDL
- Cholesterol LDL
- Indirect bilirubin
- Chloride

The summaries will include all laboratory assessments collected no later than Week 50 visit. All laboratory assessments will be listed and those collected during 16 weeks after study treatment discontinuation will be flagged in the listings.

All laboratory values will be converted into SI units. Lymphocytes, neutrophils, WBC, Platelet count, ASAT, ALAT,GGT, urea and creatinine will have a CTCAE grade calculated using appropriate common terminology criteria for AEs (CTCAE – V5.0 – Grade 0 to Grade 4). Worst grade post-baseline will be presented. Worst Grade amongst W2-W6-W10 according to Grade at W0 will be presented for absolute lymphocyte counts. A listing of laboratory values will be provided by laboratory parameter, by patient.

All laboratory data will be displayed at each visit, as well as absolute and relative changes.

A separate listing will display notable laboratory abnormalities (at least one abnormal CS and shift from baseline of abnormal CS). The frequency of these notable laboratory abnormalities will be displayed by parameter.

Moreover absolute lymphocytes and absolute neutrophils (Abnormal Clinically Significant / Abnormal Not Clinically Significant / Normal and Upper Normal Range / Lower Normal Range for Abnormal Values) will be displayed at each timepoint in Safety Population, in patients with concomitant use of steroids and in patients without any concomitant used of steroids.

For patients included in Part II, a table will describe absolute lymphocytes, neutrophils, WBC and hemoglobin mean values at each timepoint.

A listing of absolute lymphocyte values for patients with at least one abnormal value from Week 0 will also be displayed.

Figures of hemoglobin, white blood cells, absolute neutrophils, absolute lymphocytes, displaying pre-infusion dose versus worst abnormal value post-dose by patient during induction phase will be edited. Figure of absolute lymphocytes displaying pre-infusion dose (W0) versus worst abnormal value post-dose (including additional visits) by patient during OLE until W50 will be edited.

5.3.5.8 PHYSICAL EXAMINATION

The following variables will be described at screening and at each timepoint under treatment (Induction and OLE):

- Physical examination performed (Yes / No)
  - If no, reason will be displayed in a listing
  - If yes, each examination (Eyes / Ears / Nose / Throat / Neck / Lung-Thorax / Hear-Cardiovascular system / Musculoskeletal system / Extremities / Skin and mucosae / Lymph nodes) condition (Normal / Abnormal NCS / Abnormal CS) will be described. Abnormalities description and other body system examined will be displayed in a listing.
- At all other visits, symptom-directed physical examination performed (Yes / No)
  - If no, reason will be displayed in a listing
  - If yes, CS change since the last visit (Yes / No)

Physical examination will be described, in terms of value at baseline, value at each post-baseline visit under treatment as well as in terms of change from baseline to each post baseline visit under treatment.

5.3.5.9 ADDITIONAL VISITS

Additional visits data (date, reason, exam performed and other related data) will be displayed in a listing.

5.3.5.10 CONCOMITANT MEDICATION

Concomitant medication is defined as all treatments taken on the day of first infusion or after.

Incidence of concomitant medications related to all diseases except UC will be presented by preferred drug name and ATC class (Who drug dictionary, version March 2020 or higher).

5.3.5.11 TREATMENT EXPOSURE AND COMPLIANCE

All following parameters will be described:

Total duration of exposure (from first infusion to last infusion): average number of administrations of IMP, and average duration of follow-up in weeks will be summarized by treatment group as part of the safety tables.

Induction / OLE / Overall phases:

- Number of infusions started
- Relative exposure (%): (number of infusions / number of planned infusions)*100

  Where number of Planned infusion is 3 for the induction period, 7 for the OLE period and 10 for the overall period.
- Cumulative volume infused (mL), derived as the sum of volumes infused for each infusion started

5.3.6 SUBGROUP ANALYSES

All the efficacy analyses will be repeated in the following specific populations of patients (stratification variables – eCRF strata):

- who had previously received biologics treatment
- who had not previously received biologics treatment
- who use corticosteroids at inclusion (randomization)
- who do not use corticosteroids at inclusion (randomization)

If primary criteria appear to be significant in one of this specific population, baseline characteristics, secondary endpoints and safety analyses (summary of adverse events) will be edited in this specific population.

Subgroups analyses of primary estimand will be performed on the FAS to determine whether treatment effect is consistent among subgroups. More specifically, results of the subgroup analyses will be displayed in a forest plot including:

- For each subgroup level, the sample size, the estimate of the treatment effect (LS Means) with its 95% confidence interval as obtained for a stratified ANCOVA model within each subgroup level.
- A p-value for the interaction test obtained from the ANCOVA model including terms for "subgroup", "treatment", "treatment by subgroup" interaction.
- A vertical reference line displayed at the level of the overall treatment effect.
- The subgroup analysis will not be performed in subgroups with less than 10 patients (for variables with more than 2 levels, the level with the sample size below 10 may be collapsed with one of the adjacent levels, if appropriate).

Additionally, multivariate ANCOVA models, stratified for the same stratification factors as used for the randomization, will be used on the FAS set to explore the potential joint influences of the other factors. If deemed appropriate backward selection of variables will be used.

The following variables will be used to define subgroups:

Stratification criteria (corrected stratas)
- Concomitant use of steroids (yes/no)
- Previous exposure to biologics or both (yes/no)

Other criteria
- Gender (male/ female)
- Age (< 65 vs. ≥ 65)
- Smoking status: never, former, or current smoker

- Alcohol status: never, former, or current
- BMI at screening (<20, [20;25[, [25;30[, ≥30 kg/m²)
- Rectal Bleeding at screening
- UC duration (years)
- Modified Mayo Score at baseline
- CRP
- Fecal calprotectin
- Serum Albumin

5.3.7 HANDLING OF MULTIPLICITY AND SECONDARY CRITERIA

Since it is a phase II proof of concept study all secondary endpoints pvalues will be provided.

5.3.8 COVID / UKRAINE IMPACT

It has been assessed that the politic situation observed in Ukraine (UKR) will have no impact on the data integrity of the trial. Even though some centers were inaccessible to on-site monitoring, the main efficacy assessment (W10) of the last UKR patient occurred before the conflict. In addition, the Primary and Secondary Efficacy Endpoints are based both on ePROs remotely collected by patients and on endoscopy features assessed centrally by a reading platform, therefore independently of local data collection. Moreover only one Ukrainian patient did not perform W10 visit.

COVID will have an impact on efficacy results because some patients withdrew from the study before W10 due to COVID occurrence. However multiple imputation will be used to handle this issue.

5.3.9 STUDY PART EFFECT

At the time of protocol amendment following Futility Analysis (FA), only 17 patients with previous exposure to biologics have been enrolled. Because this ratio was lower than expected, it has been decided to stop inclusion in the subgroup of biologic-naïve patients. Moreover in the second part of the study (after the protocol amendment), recruitment was closed in several countries. New sites and countries were opened to allow to complete the recruitment.

To analyse the impact of these decisions, disposition of patients, baseline and disease characteristics will be edited in this subgroup (Part I / Part II). Moreover primary endpoint ANCOVA will be analysed on biologics patients using this variable (Part I / Part II) as covariate as a sensitivity analysis.

6. CHANGES FROM PROTOCOL

A specification was added regarding primary endpoint: “If 3 days (within the week prior to the indicated visit) that meet the criteria defined above are not available, then the stool frequency subscore and rectal bleeding subscore using available data even if not in the 1-week window” will be taken into account.

Clarification was made regarding MMS computation to considere Week 10 visit date as the Week 10 endoscopic date.

Countries as covariates were removed from ANCOVA models since there are too many countries.

No hierarchical procedure will be performed for secondary endpoints since it is a phase II proof of concept study; all p values will be provided.

7. CHANGES FROM SAP V1.0

This section describes all analyses performed after the database lock / unblinding. They were conducted as exploratory analyses to reinforce the existing results.

This section also details more precisely final multiple imputation models.

7.1.1 PRIMARY AND SECONDARY EFFICACY ANALYSES

Considering that OSE-127 low dose was declared as futile in the futility analysis hold on 2021, inferential models were initially in the SAP V1.0 on OSE-127 high dose versus Placebo. OSE-127 low dose analyses were descriptive. The main ANCOVA model was OSE-127 high dose versus Placebo only and multiple imputation was performed on this population pooling the 2 groups for the imputation. Results from these analyses were presented in the Press Release in July 2024.

Given the results, consistent for each tested dose of OSE-127 and consistent within each recruitment period of the study (before or after futility analysis - part I or II), a global ANCOVA model / logistic model (depending on the endpoint) was performed to estimate treatment effect over placebo of each OSE-127 dose, fed by complete sets of data from a single multiple imputation model by treatment. Combined treatment effect of OSE-127 all dose versus placebo was also estimated with these models, considering as weight the number of patients treated with each dose. These methodologies were used for all planned analyses (instead the analyses planned in the SAP) as described in sections 5.3.2 and 5.3.3, including supplementary ones described below, to analyze OSE-127 high dose versus Placebo effect and OSE-127 low dose versus Placebo effect. Because of convergence issues in some subgroups (due to small headcounts) some adjustments and differences in proportions were not performed (statistics not evaluable).

Updated corresponding SAS codes are displayed in section 9.1.

Considering it is a phase II proof of concept study no multiplicity approach was considered regarding OSE-127 high dose and OSE-127 low dose comparisons.

7.1.2 SUPPLEMENTARY ANALYSES

7.1.2.1 SUBGROUPS ANALYSES

Part I Effect

All primary and secondary efficacy analyses were run on patients recruited during study Part I (before futility analysis Q42021) and comparing OSE-127 low dose patients versus Placebo patients.

All primary and secondary efficacy subgroup analyses, restricted to patients who had not previously received biologics treatment and patients who do not use corticosteroids at inclusion (due to number of patients) were provided on patients from Part I and comparing OSE-127 low dose patients versus Placebo patients.

Futility Analysis Effect

Baseline characteristics (section 5.2) were performed on patients who took part in the futility analysis and patients who did not took part in the futility analysis, all restricted to patients from Part I.

Initially Planned Subgroups

Primary and secondary analyses (sections 5.3.2.1 and 5.3.3), as well as demographic and UC baseline characteristics (section 5.2.1) were finally performed on all subgroups defined in section 5.3.6. Other baseline characteristics and safety data were not useful.

Fecal Calprotectin Subgroup

Given that FCP is a biomarker of active disease and 250 µg/g is considered as a threshold of active UC (Turner et al 2021 and Jukik et al 2021), primary and secondary analyses (sections 5.3.2.1 and 5.3.3) were displayed comparing OSE-127 850 mg patients versus Placebo patients and OSE-127 450 mg patients versus Placebo patients among patients with a fecal calprotectin value > 250 µg/g at W0. Evolution of fecal calprotectin and CRP over time (section 5.3.4.2) were also displayed among patients with a fecal calprotectin value > 250 µg/g at W0.

Histologic data analyses (section 5.3.4.3) were also displayed among patients with a fecal calprotectin value > 250 µg/g at W0.

7.1.2.2 OTHER SENSITIVITY EFFICACY ANALYSES

Primary analysis (section 5.3.2.1) was performed comparing OSE-127 high dose patients versus Placebo patients removing patients with a MMS score equals to 4 at randomization.

Primary analysis (section 5.3.2.1) was performed comparing OSE-127 low dose patients versus Placebo patients removing patients with a MMS score equals to 4 at randomization.

7.1.2.3 C-REACTIVE PROTEIN (CRP) AND FECAL CALPROTECTIN ANALYSES

Number and percentage of patients with a fecal calprotectin < 50 / ≥ 50 and < 250 / ≥ 250 were described at each timepoint in the FAS and in the subset of patients with a fecal calprotectin value > 250 µg/g at W0.

Number and percentage of patients with a normal CRP value at W10 were displayed.

7.1.2.4 ABSOLUTE LYMPHOCYTE COUNTS ANALYSES

Number and percentage of patients with a normal value at baseline and with at least one value upper normal range / at least one value lower normal range with ALC ≥ 500 10^6/L / at least one value lower normal range with ALC < 500 10^6/L were described. The same results were displayed for patients with an abnormal value at baseline. These tables were displayed for several periods : from W0 to W10 (included), from W10 (excluded) to W34 (included), from W34 (excluded) to W50 (included), from W0 to W34 (included), from W0 to W50 (included), from W10 (excluded) to W50 (included).

7.1.2.5 MAINTENANCE ANALYSES DURING OLE PERIOD

Analyses during OLE period differed according to patient remission status at W10: pMMS at W10 equals to 0 or 1 versus pMMS at W10 > 1. The following analyses were hence produced:

- pMMS analyses (section 5.3.4.1.2) were displayed on patients with pMMS at W10 equals to 0 or 1.

Maintenance of efficacy was defined as a pMMS = 0 or 1 during OLE excluding first assessment after W10 to see efficacity more than 4 weeks after OSE-127 injection (from W14 until W38). Relapse was defined as a pMMS > 1 on 2 consecutive assessments or, in case of a lonely assessment, with a rectal bleeding subscore > 0. Number and percentage of patients in maintenance or relapse were described by treatment group and overall for patients with a pMMS at W10 equals at 0 or 1, hereafter defined as baseline.

Kaplan-Meier analyses and curves overall and by treatment group were also produced to analyze time to relapse (weeks) defined as the time between W10 and first visit until W38 with a confirmed relapse.

- pMMS analyses (section 5.3.4.1.2) were displayed on patients with a baseline pMMS at W10 > 1. Response was defined as a pMMS = 0 or 1 during OLE excluding first assessment after W10 to see efficacity more than 4 weeks after OSE-127 injection (from W14 until W38). All other patients were considered as failure. Number and percentage of patients in response or failure were described.

  Kaplan-Meier analyses and curves overall and by treatment group were also produced to analyze time to response (weeks) defined as the time between W10 and first visit until W38 with a pMMS = 0 or 1.

For Kaplan-Meier analyses, patients without event were censored at the minimum date between W38 and end of study (or last visit reached if no end of study visit). Kaplan-Meier estimates and their corresponding 95% CI were displayed. Number of patients at risk, number of censored patients, as well as number of events were produced.

As secondary results these 4 analyses were repeated replacing baseline (pMMS at W10) by:

- MMS at W10
- endoscopic score at W10
- rectal bleeding subscore at W10
- stool frequency subscore at W10

As sensitivity analyses, these results will be provided:

- On specific populations of patients defined in section 5.3.6 (stratification variables – eCRF strata)
- On the subset of patients with a fecal calprotectin value > 250 µg/g at W0

8. REFERENCES

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9. APPENDICES – SAS CODES

SAS code to impute missing value in 100 datasets

Multiple imputation by fully conditional specification (FCS) will be used. FCS is a powerful and statistically valid method for creating imputations in datasets which include both categorical and continuous variables. It specifies the multivariate imputation model on a variable-by-variable basis and offers a principled yet flexible method of addressing missing data.

[redacted]

Under MAR Assumption

[redacted]

Under NMAR Assumption

[redacted]

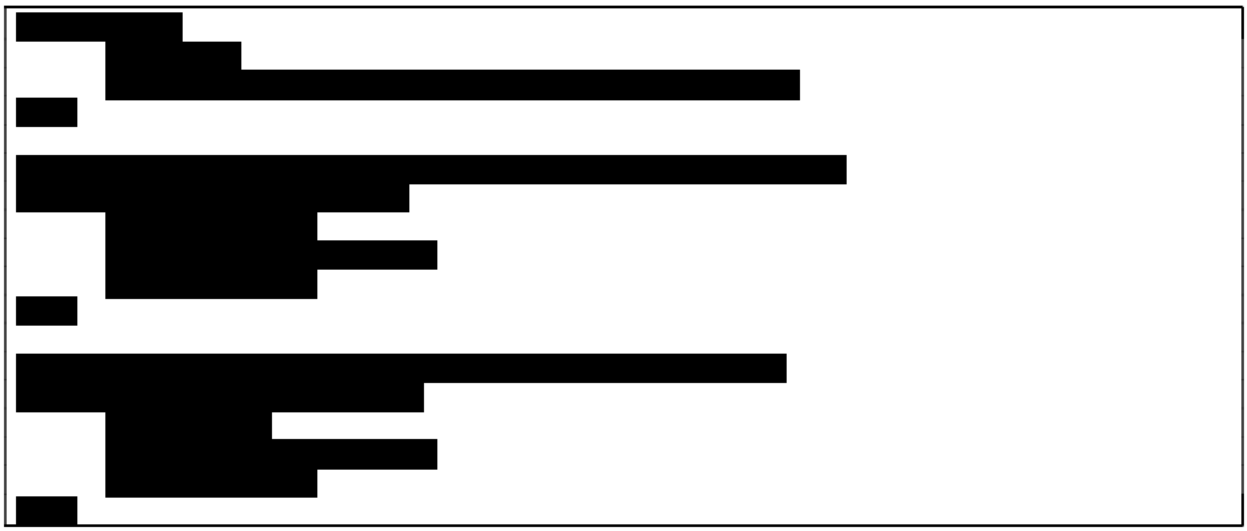
The seed numbers will be identified in the SAS programs to allow for reproducibility.

Minimum and/or maximum options will be used if results appear to be out of plausible range of values.

SAS code for ANCOVA analysis

[redacted]

SAS code for combining estimates from each imputed data set (MMS change)



SAS code for combining estimates from each imputed data set (Remission)

[redacted]

9.1 CHANGES FROM SAP V1.0

Syntaxes under MAR assumption of the first multiple imputation models, depending on the selection, were:

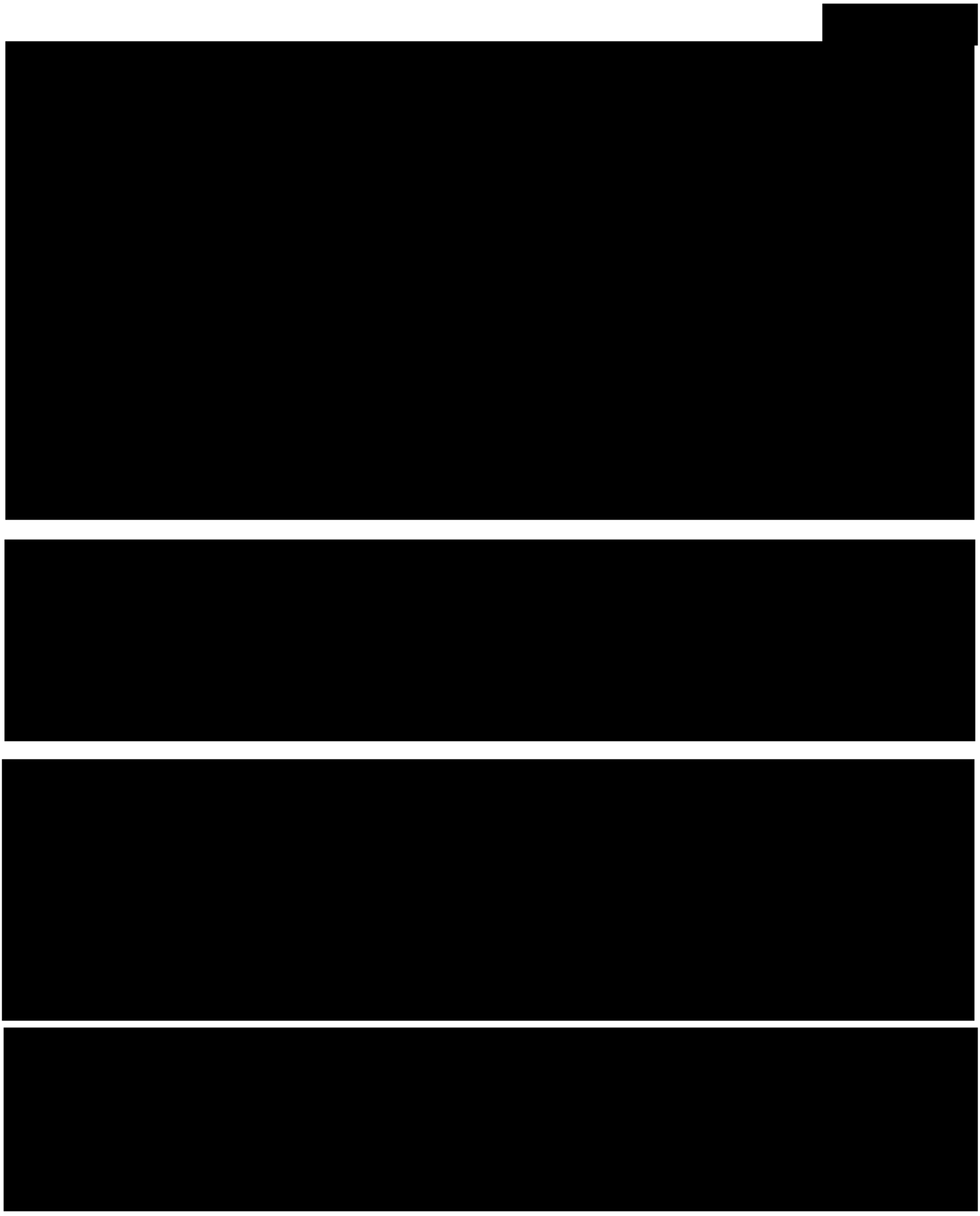
[redacted]

Final multiple imputation model syntax under MAR assumption was:

[redacted]

Final ANCOVA model syntax was:

Final logistic model syntax was:



[redacted]