# CLINICAL STUDY PROTOCOL

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 |
| Intervention: | OSE-127 |
| Compound Number: | OSE-127 |
| Indication: | Moderate to severe active ulcerative colitis |
| Phase: | 2 |
| Sponsor: | OSE Immunotherapeutics<br>22 boulevard Benoni Goullin<br>44200 Nantes<br>France |
| Principal/Coordinating Investigator | [redacted] |
| IND or EudraCT Number: | 2020-001398-59 |
| Version; date: | v2.0; 6 January 2022 |

*The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), with the Declaration of Helsinki, and with other applicable regulatory requirements.*

## SIGNATURE PAGES

### Declaration of Sponsor or Responsible Medical Officer

**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)

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

Date : 13 January 2022

Chief Medical Officer
OSE-Immunotherapeutics

**Declaration of the Principal or Coordinating Investigator**

**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)

This study protocol was subjected to critical review and has been approved by the Sponsor. The information it contains is consistent with the current risk/benefit evaluation of the investigational product as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, and the guidelines on Good Clinical Practice.

**Principal or Coordinating Investigator**

## Declaration of the Investigator

**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)

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidence. This documentation includes the study protocol, Investigator's Brochure, Case Report Forms, and other scientific data.

The study will not begin without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the protocol without the prior written approval of OSE Immunotherapeutics, the regulatory authority and the IRB or IEC, except where necessary to address an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol, including:

- To adhere to the Declaration of Helsinki, and the principles on Good Clinical Practice, the local laws and applicable regulatory requirements
- To obtain informed consent prior to performing any study procedures
- To use the study drug and all study materials only within the framework of this clinical study
- To comply with the obligations for reporting adverse events.

Signature of responsible Investigator of the local trial site

_____ _____

Name Date
Title
Institution

## Main Research Facilities

### Monitoring

| | |
|---|---|
| Company | [redacted] |
| Address | [redacted] |

### Biometry

| | |
|---|---|
| Company | [redacted] |
| Address | [redacted] |
| Tel | [redacted] |

### Pharmacovigilance

| | |
|---|---|
| Company | [redacted] |
| Address | [redacted] |
| Tel | [redacted] |
| Fax | [redacted] |
| Email | [redacted] |

# PROTOCOL AMENDMENT SUMMARY OF CHANGES

| **DOCUMENT HISTORY** | |
|---|---|
| **Document** | **Date** |
| | |
| | |
| Original Protocol | 15 June 2020 |

| **AMENDMENT X (DD-MMM-YYYY)** | | |
|---|---|---|
| **Overall Rational for the Amendment** | | **Brief Rationale** |
| **Section Number and Name** | **Description of Change** | |
| | | |
| | | |

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# 1 PROTOCOL SUMMARY

## Synopsis

**Protocol 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)

**Rationale:**

The study population (patients with moderate to severe ulcerative colitis [UC] who have failed or are intolerant to immunosuppressors, anti-tumor necrosis factor (TNF)-α, anti-integrin, ustekinumab and/or corticosteroids) was selected since this population consists of patients who are in need of alternative new therapies to avoid for as long time as possible the complications linked to the disease and in whom the safety profile of OSE-127 can be reliably assessed.

The double-blind, placebo-controlled design corresponds to a standard design in this disease and will allow the detection of differences between efficacy in active treatment versus a placebo.

Previous UC induction studies have evaluated initial endpoints at 8 to 12 weeks, and the present study proposes that Week 10 assessments for biologically naïve and experienced patients be used. Ten weeks is expected to be sufficient time for some degree of mucosal healing to occur and for clinical symptoms to improve. The use of endoscopy and histology maximizes objectivity in assessment of drug effect. Use of centrally read endoscopy will further reduce bias in assessment of endoscopic healing. At Week 10, an open-label administration of OSE-127 at Weeks 10, 14, 18, 22, 26, 30, and 34 will be offered to all patients regardless of their treatment allocation in the previous double-blind period. This will allow every patient, including those treated initially with the placebo, to be given the opportunity to receive the active treatment for a sufficient time. This administration will be done at the high dose level of OSE-127 (i.e., 850 mg).

**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 |

| Objectives | Endpoints |
|---|---|
| ***Other Secondary Objectives*** | |
| • To assess the clinical efficacy of OSE-127 versus placebo on the rate of 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 ≥ 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<br>• Number and proportion of patients with endoscopic response or improvement at Week 10 defined by an endoscopic sub-score of Mayo ≤ 1 point.<br>• 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 | • Adverse events (AEs), serious AEs (SAEs), AEs leading to the discontinuation of study treatment, target AEs of special interest, laboratory abnormalities, vital signs, electrocardiogram (ECG), and physical examination abnormalities |
| ***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<br>• Number and proportion of patients without acute histological inflammation at Week 10 defined by a Nancy Histological Index score of ≤ 1<br>• 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 |

| Objectives | Endpoints |
|---|---|
| | ○ Endoscopic remission defined by an endoscopic Mayo sub-score = 0<br>○ 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<br>• Evaluation of the 2-item 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 (Week 0) CRP at Weeks 10 and 22<br>• Median change from baseline (Week 0) in fecal calprotectin at Weeks 2, 6 and 10<br>• 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 |
| • To assess the immunogenicity of OSE-127 in patients with UC | • Measurement of anti-drug antibodies |
| • To assess the pharmacodynamic (PD) effects of OSE-127 | • Blood receptor occupancy in a sub-population of patients of the study<br>• 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<br>• Biopsies analysis for identification of mucosal and PD predictors of efficacy |
| • To assess the pharmacokinetics (PK) of OSE-127 in UC patients | • Measurement of OSE-127 concentrations in a sub-population of patients of the study<br>• Correlation between efficacy outcomes and drug exposure |

**Study Design:**

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with moderate to severe active UC.

The study includes 4 periods: screening, induction, optional extension, and follow-up.

Screening Phase: 8 weeks maximum

Following the screening period, eligible patients will be randomized and enter the 10-week placebo -controlled induction phase. The randomization will be stratified 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 had 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). Up to the 108 first inclusions, only 17 patients with previous exposure to biologics have been enrolled. Therefore, only patients with previous exposure to biologics and primary non response or secondary loss of response will be randomized from the 109$^{th}$ patient to the last randomized patient.

Induction Phase: Week 0 to Week 10

**In the first step of the study** (i.e. before the outcome of the pre-specified Futility Analysis, Global Protocol V1.0), patients were randomly assigned on Week 0 in a 1:1:1 ratio to receive 1 of the following regimens:

- Placebo intravenous (IV) infusion at Week 0, Week 2, and Week 6
- OSE127 Low Dose (450 mg) IV infusion at Week 0, Week 2, and Week 6
- OSE127 High Dose (850 mg) IV infusion at Week 0, Week 2, and Week 6

**Following the pre-specified Futility Analysis** within this amended protocol (Global Protocol V2.0), patients will be randomly assigned on Week 0 in a 1:1 ratio to receive 1 of the 2 following regimens:

- Placebo intravenous (IV) infusion at Week 0, Week 2, and Week 6
- OSE127 High Dose (850 mg) IV infusion at Week 0, Week 2, and Week 6

Infusions will be delivered in an in-patient clinic for 1 hour, with a 2 hour post-infusion surveillance. Clinical examination will be performed and vital signs will be checked before each infusion. Vital signs will be recorded every 30 minutes during the infusion and during the 2-hour post-infusion surveillance period.

At Week 10, all the patients will have a visit to record all the components of the primary and main secondary endpoints (see flowchart).

Open-Label Extension Phase (OLE): Week 10 to Week 34

At Week 10 all the patients will be asked to participate in an open-label extension period and those willing to continue the study in accordance with the clinical investigator will receive additional infusions at Weeks 10, 14, 18, 22, 26, 30, and 34 at the high dose level of OSE-127 (i.e., 850 mg).

Study drug will be administered as described above during the Induction Phase.

Safety Follow up Phase: Week 10 to Week 22 or Week 34 to Week 50

If the patient does not participate in the OLE, the safety follow-up period during which no study treatment will be administered will start after Week 10 and will last 12 weeks after the end of the induction phase (Week 10 to Week 22 corresponding to 16 weeks after the last administration). In such case, 1 mandatory follow-up visit will be conducted at Week 22.

If the patient participates in the OLE Phase, the safety follow-up period will last 16 weeks after the last administration (Week 34 to Week 50) and 2 mandatory follow-up visits will be conducted at Week 38 and at Week 50.

An independent Data Safety Monitoring Board (DSMB) will be set up to primarily take care of the safety of the participating patients by reviewing the safety and tolerability data of the investigational drug on a regular basis.

An interim futility analysis has been completed as planned in the V1.0 Global Protocol of the study after 30% of the patients had completed the Induction Phase (see statistical section).

**Study Population:**

*Inclusion Criteria:*

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|---|---|
| 1. | Provision of signed and dated informed consent document indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrollment |
| 2. | Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures |
| 3. | Willingness to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose |
| 4. | Male or female 18 to 75 years of age, inclusive |
| 5. | Diagnosis of moderate to severe active UC* made at least 3 months before the screening visit. The diagnosis of UC must have been confirmed by endoscopy, with a minimal extent of 15 cm from anal margin and histology (i.e., histopathology report available in the patient's fil, however a biopsy for a local histopathology assessment at screening can substitute this requirement).<br><br>*Moderate to severe active UC is defined by a modified Mayo score between 4 and 9, inclusive. The modified Mayo score is defined by the addition of the rectal bleeding sub-score, the stool frequency sub-score, and the endoscopic sub-score. Thus, to be included, a patient must have the following:<br><br>a. a rectal bleeding score ≥ 1,<br><br>b. a stool frequency score ≥ 1 (sub-score calculated before bowel preparation), and<br><br>c. an endoscopic sub-score ≥ 2 |

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| 6. | Previous or current biologic therapy for UC with **documented** history of a **primary non** clinical response or **a secondary loss of response** to **at least**:<br>- **1** of the following agents used at a dose and regimens approved for the treatment of UC for sufficient time (including approved biosimilars):<br>• Anti-TNF-α agents<br>• Vedolizumab<br>• Ustekinumab<br>- **Or to 1 of the following investigational biologic agents (i.e. not yet approved in UC)** used at a therapeutical dose **(in such situations, pre-screening discussions with the Medical Monitor of the study will allow to define if the conditions of non-response are met):**<br>• Mirikizumab<br>• Rizankizumab<br>• Guselkumab<br>• Other biologic … |
| 7. | Patient currently receiving 1 or more of the following medication(s) for UC is eligible, provided that he/she has been receiving such treatment(s) for at least 4 weeks and with no change in dose or frequency in the 2 weeks prior to screening:<br>a. Oral aminosalicylates anticipating that the dose at screening has to be maintained until Week 10.<br>b. Prednisone (stable doses ≤ 20 mg/day) or equivalent, budesonide MMX (stable doses ≤ 9 mg/day), or beclomethasone dipropionate (stable doses ≤ 5 mg/day), anticipating that these stable doses have to be maintained until Week 10<br>If these medications have recently been stopped, the treatment cessation must have occurred at least 2 weeks prior to screening |
| 8. | Patients who have been previously receiving anti-TNF-α therapy or vedolizumab or ustekinumab must have discontinued this therapy ≥ 8 weeks before the date of baseline endoscopy or ≥ 5 half-lives before the date of baseline endoscopy in case of investigational biologics agents |
| 9. | For patients with UC >8 years, results of a surveillance colonoscopy conducted within 2 years prior to screening are required to rule out dysplasia. This full colonoscopy might be done at screening instead of the procto-sigmoidoscopy to fulfill this requirement. |
| 10. | Either chest x-ray within 3 months prior to screening and/or a negative quantiFERON TB Gold In Tube test according to local guidelines and standard of care to exclude active or latent TB infection |

*Exclusion Criteria:*

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|---|---|
| 1. | Stoma, proctocolectomy, or subtotal colectomy |
| 2. | Physician judgment that patient is likely to require any surgery for UC during the study duration, or double-blind phase duration at least |
| 3. | Evidence of fulminant colitis, toxic megacolon, or perforation |
| 4. | Current or recent (within 4 weeks prior to screening) hospitalization for UC care and/or treatment with IV steroids |

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| 5. | The following laboratory results at screening:<br>a. Elevation at screening of aminotransferase (AST), alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN) or total bilirubin > 2 × ULN (unless due to Gilbert's disease) or evidence of chronic liver disease<br>b. Platelet count < 100,000/$mm^3$<br>c. Hemoglobin (Hgb) < 8.5 g/dL<br>d. Neutrophils < 1500/$mm^3$<br>e. Lymphocytes < 800/$mm^3$<br>f. Absolute white blood cell (WBC) count < 3000/$mm^3$ |
| 6. | Crohn's disease or indeterminate colitis or any other diagnosis not consisting with UC |
| 7. | History or evidence of incompletely resected colonic dysplasia or unconventional lesion at risk of colonic adenocarcinoma |
| 8. | Stool culture or other examination positive for enteric pathogen, including *Clostridium difficile* (*C. diff*) toxin. If positive, the patient should be treated and rescreening is allowed. |
| 9. | Men or women with childbearing potential not willing to use adequate birth control during the study. Adequate birth control includes surgical sterilization, intrauterine device, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy, double-barrier method (condom, diaphragm with spermicide), or abstinence during study and 30 days following the last follow-up visit. Women of childbearing potential will enter the study after a negative pregnancy test. |
| 10. | Breastfeeding |
| 11. | Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) from screening through the end of the study |
| 12. | Use of topical steroids and/or topical 5-aminosalicylic acid preparations within 2 weeks before the screening visit (all such medications should be withdrawn at least 2 weeks prior to the screening visit) |
| 13. | Use of antidiarrheals within 2 weeks before the screening visit (all such medications should be withdrawn at least 2 weeks prior to the screening visit) |
| 14. | Treatment with azathioprine, 6-MP, methotrexate (MTX), cyclosporin, tacrolimus, sirolimus, leflunomide and/or mycophenolate mofetil within 4 weeks before the screening visit (all such medications should be withdrawn at least 4 weeks prior to the screening visit) |
| 15. | Previous failure to more than 3 biologics including anti-TNF-$\alpha$ and/or anti-integrin and/or ustekinumab and/or any other biologics agents |
| 16. | Prior treatment with a JAK inhibitor |
| 17. | Clinically relevant cardiovascular, hepatic, neurologic, psychiatric, pulmonary, endocrine, or other major systemic disease that would put the patient at risk by participating in the study in the opinion of the investigator |
| 18. | A recognized hereditary, congenital, or acquired immunodeficiency disease including human immunodeficiency virus (HIV) infection and other cellular immunodeficiencies, hypogammaglobulinemia, or dysgammaglobulinemia |

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|---|---|
| 19. | Known active viral, bacterial, fungal, mycobacterial infection, or other infection or any major infection that required hospitalization or treatment with IV antibiotics or antifungal within 30 days of screening or that required treatment with oral antibiotics within 14 days of screening |
| 20. | History or known presence of chronic or recurrent infection (hepatitis B, C, HIV) |
| 21. | Any autoimmune disease, other than UC, with the exception of controlled Type I diabetes (hemoglobin A1c ≤8%) or treated hypothyroidism |
| 22. | Evidence of active malignancy |
| 23. | Live vaccine received within 4 weeks prior to screening |
| 24. | Previous treatment with lymphocyte-depleting agents such as alemtuzumab; alkylating agents such as cyclophosphamide or chlorambucil; total lymphoid irradiation; or selective B lymphocyte-depleting agents such as rituximab |
| 25. | Current or previous treatment with investigational therapy in another therapeutic clinical trial within 8 weeks or 5 half-lives before the date of baseline endoscopy |
| 26. | History of alcohol or drug abuse within 1 year of screening |
| 27 | Previous completion or withdrawal from this study. This criterion does not apply to participants undergoing rescreening procedures. |

**Number of Participants and Duration of Participation:**

The study will be conducted at approximately 75 to 90 centers in Europe. An estimated number of 150 patients was initially expected to be randomized, with 138 expected to complete the Induction Phase and around 100 expected to enter the OLE phase. After Futility Analysis, the sample size has been re-calculated in order to take into account the drop-out of the low dose as well as to target a percentage of patients with previous biologics exposure at 40% within the final analyzed population (i.e. placebo patients and OSE-127 high dose patients). Thus 32 additional patients, all of them being biologics experienced patients, will have to be included in order to reach this percentage.

The predicted number of patients who would be enrolled at each active investigational site is between 1 and 3. The total study is expected to last around 3 years from First Patient In to Last Patient Last Follow-up Visit.

The total study duration for an individual patient will be approximately up to 30 weeks (210 days) if the patient does not enter into the OLE or up to 58 weeks (406 days) if the patient participates in the OLE to include:

- Screening (up to 8 weeks/56 days)
- Randomization at Week 0 (1 day)
- Induction Phase (10 weeks, with treatment visits at Week 0, 2, and 6)
- Optional OLE Phase (24 weeks, with treatment visits at Weeks 10, 14,18, 22, 26, 30, and 34)
- Safety follow-up with no study drug administration from Week 10 to Week 22 (12 weeks / 84 days) or from Week 34 to Week 50 (16 weeks/112 days): i.e., last follow-up visit 16 weeks after the last infusion in both situations.

**Efficacy Assessments:**

Efficacy will be assessed using the modified Mayo Score for Assessment of Ulcerative Colitis (including stool frequency, rectal bleeding, and mucosal appearance at endoscopy [endoscopic sub-score]), clinical response, PROs (stool frequency and rectal bleeding), endoscopy, histology (including the Nancy Histological Index Score, the Geboes score and the RHI), measurements of CRP and fecal calprotectin, UCEIS, and the UC-100 score.

**PK/PD Assessments:**

Pharmacokinetics and PD will be assessed using PK and receptor occupancy (RO) (in a subgroup of 20 patients) [redacted]

**Safety Assessments:**

Safety will be assessed by adverse events (including SAEs), clinical laboratory assessments, vital signs, ECGs, physical examination, and immunogenicity assessments.

**Statistical Methods:**

Sample Size Calculation for Primary Endpoint:

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).

Rules for Interim Analysis:

Step 1: Conditional/Predictive Power Selection

The primary objective of Step 1 is to evaluate the primary efficacy endpoint (absolute variation of modified Mayo score between baseline and Week 10) and to decide if it will be considered uninteresting to pursue any further investigation. Our goal is to calculate the minimum sample size required under the caveat that the study would be terminated early if there was 95% confidence that the primary endpoint was less than the target value of interest (-1.5 difference for this study).

Interim futility analysis will be performed after the first 50 patients (i.e., 30% of the 150 planned patients) have completed the Induction Phase (availability of the primary endpoint at Week 10).

After testing the drug efficacy on n=50 patients in the Induction Phase, conditional/predictive power considering observed primary endpoint and an expected sample size of 50 patients per group will be calculated for each dose.

If the conditional power is < 20% and the predictive power is < 20% for both doses, the study will be discontinued for futility after 50 patients.

Step 2: Pursuit of the Trial for each dose:

If the trial goes on after the futility analysis (next inclusions of the remaining patients in the Induction Phase), a maximum of 50 patients will be studied in each group.

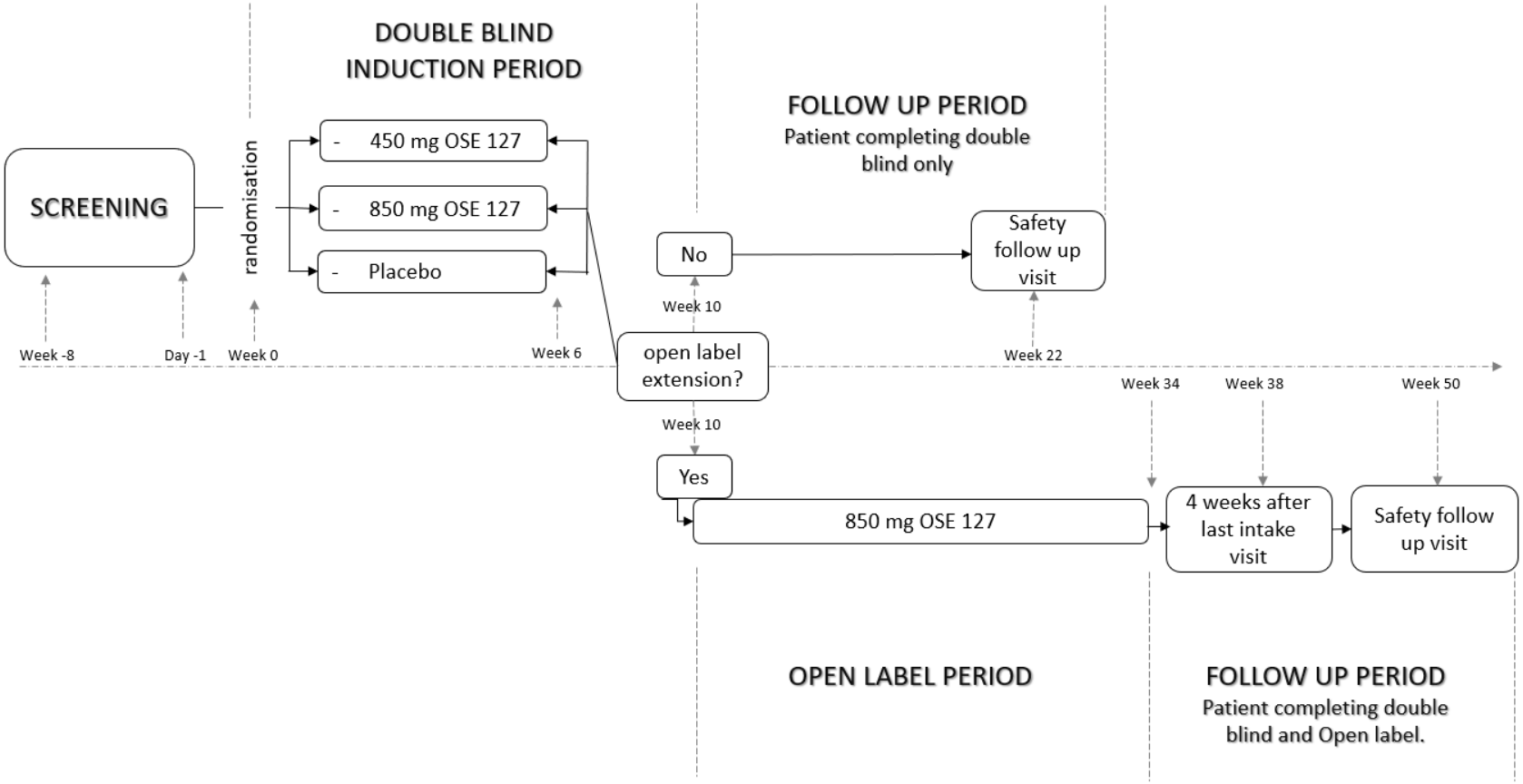
Final Analysis for Primary Endpoint:

The following statistical hypotheses are considered for the high dose:

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

The treatment difference will be assessed with an ANCOVA model which includes terms to adjust for the baseline Modified Mayo Score value, stratification factors, region, 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.

## 1.1 Schema


DOUBLE BLIND
INDUCTION PERIOD
FOLLOW UP PERIOD
Patient completing double blind only
SCREENING
randomisation
- 450 mg OSE 127
- 850 mg OSE 127
- Placebo
No
Safety follow up visit
Week 10
Week -8
Day -1
Week 0
Week 6
open label extension?
Week 22
Week 34
Week 38
Week 50
Week 10
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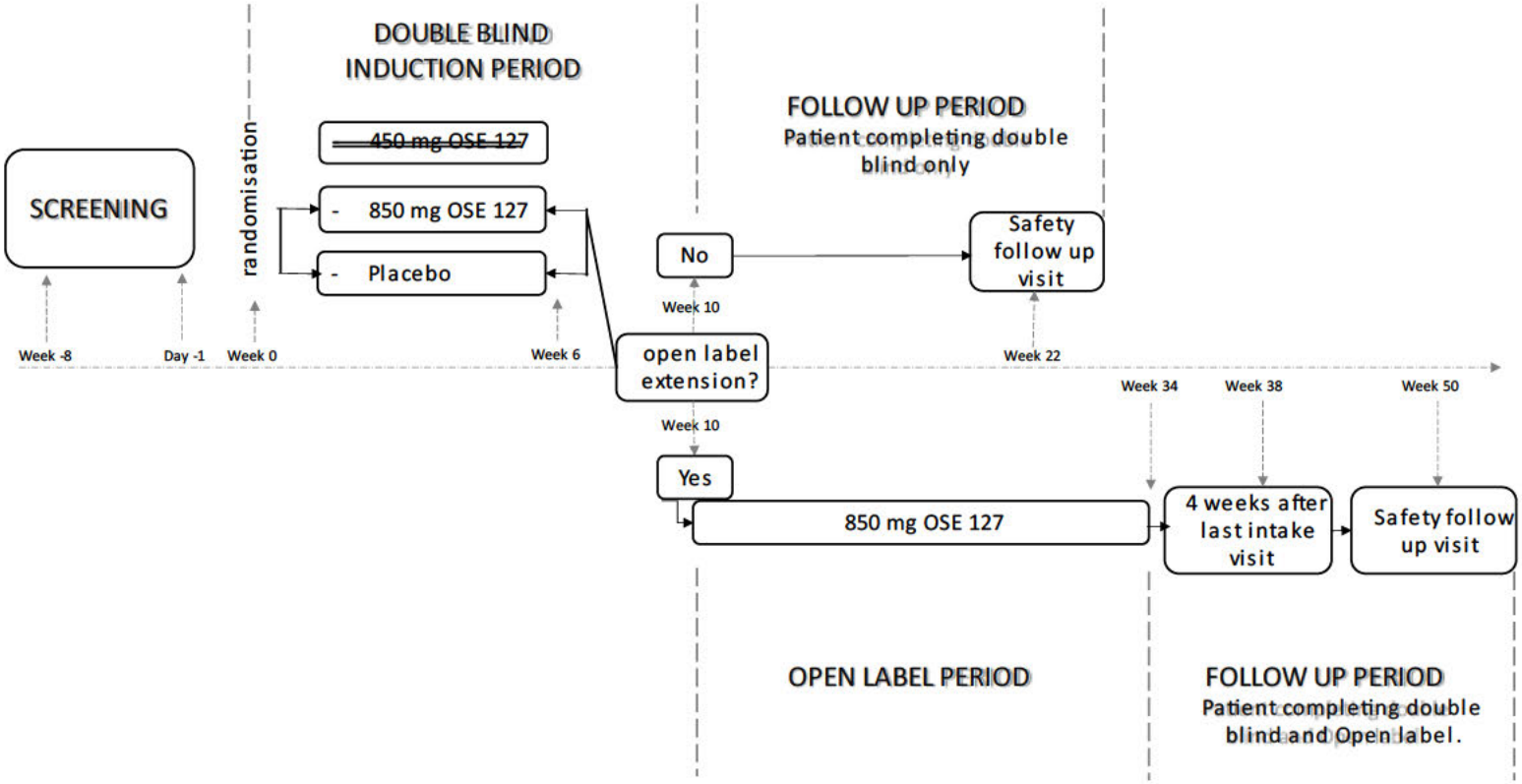
850 mg OSE 127
4 weeks after last intake visit
Safety follow up visit
OPEN LABEL PERIOD
FOLLOW UP PERIOD
Patient completing double blind and Open label.




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.

## 1.2 Schedule of Activities

### Table 1.1: Screening and Induction Double-blind Phase

| Study Procedures | Screening Visit | Visit 1 Week 0 [A] | Visit 2 Week 2 [A] | Visit 3 Week 6 [A] | Visit 4 Double-blind evaluation Week 10 | Follow-up / ET Visit Week 22 [B] |
|---|---|---|---|---|---|---|
| **Day** | **Maximum 56 days (8 weeks) prior to Day 1/W0** | **1** | **14 ± 4** | **42 ± 4** | **70 ± 4** | **154 ± 4** |
| **General Assessments** | | | | | | |
| Informed consent | X | | | | | |
| Inclusion/exclusion criteria | X | | | | | |
| Demographics | X | | | | | |
| Medical/surgical history | X | | | | | |
| Prior medication | X | | | | | |
| Physical examination | X [C] | X [D] | X [D] | X [D] | X [C] | X [D] |
| Vital signs [E] | X | X | X | X | X | X |
| Height | X | | | | | |
| Weight | X | X | X | X | X | X |
| 12-lead ECG | X | | | | X | X |
| Chest X-ray or quantiFERON TB Gold In Tube test [F] | X | | | | | |

| **Study Procedures** | **Screening Visit** | **Visit 1 Week 0** [A] | **Visit 2 Week 2** [A] | **Visit 3 Week 6** [A] | **Visit 4 Double-blind evaluation Week 10** | **Follow-up / ET Visit Week 22** [B] |
|---|---|---|---|---|---|---|
| **Day** | **Maximum 56 days (8 weeks) prior to Day 1/W0** | **1** | **14 ± 4** | **42 ± 4** | **70 ± 4** | **154 ± 4** |
| Collect stool for enteric pathogens culture and *C. diff* toxin assay [G] | X | | | | | |
| Collect the 2 clinical Mayo Sub-scores (rectal bleeding and frequency of stools) [H] | X | | | | | |
| Endoscopy [I] | X [J] | | | | X [K] | |
| Colon biopsy for UC histology confirmation [L] | X | | | | | |
| Colon biopsies for UC histologic scores | X | | | | X | |
| Colon biopsies for biomarkers | X | | | | X | |
| Send biopsy samples to local histopathology laboratory [M] | X | | | | X | |
| Send videos of endoscopy to Central Reading Platform | X | | | | X | |
| Randomization | | X | | | | |
| Concomitant medication | | X | X | X | X | X |
| Adverse events | | X | X | X | X | X |

| **Study Procedures** | **Screening Visit** | **Visit 1 Week 0** [A] | **Visit 2 Week 2** [A] | **Visit 3 Week 6** [A] | **Visit 4 Double-blind evaluation Week 10** | **Follow-up / ET Visit Week 22** [B] |
|---|---|---|---|---|---|---|
| **Day** | **Maximum 56 days (8 weeks) prior to Day 1/W0** | **1** | **14 ± 4** | **42 ± 4** | **70 ± 4** | **154 ± 4** |
| **Laboratory Assessments** | | | | | | |
| Pregnancy test (females of childbearing potential) [N] | X | X | X | X | X | X |
| Hematology, chemistry and urinalysis [O] | X | X | X | X | X | X |
| Serology tests for infections (HBV, HCV, HIV) [O] | X | | | | | |
| CRP in serum | | X | | | X | X |
| Stool collection – bowel pathogens [P] | X | | | | | |
| Stool collection – fecal biomarkers | | X | | | X | |
| Fecal calprotectin | | X | X | X | X | |
| ADAs [Q] | | X | | X | X | |
| **Study Drug Administration** | | | | | | |
| OSE-127 | | X | X | X | | |
| **PK/Receptor occupancy** | | | | | | |
| Draw blood [R] | | X | | X | X | |

| Study Procedures | Screening Visit | Visit 1 Week 0 [A] | Visit 2 Week 2 [A] | Visit 3 Week 6 [A] | Visit 4 Double-blind evaluation Week 10 | Follow-up / ET Visit Week 22 [B] |
|---|---|---|---|---|---|---|
| **Day** | **Maximum 56 days (8 weeks) prior to Day 1/W0** | **1** | **14 ± 4** | **42 ± 4** | **70 ± 4** | **154 ± 4** |
| **Efficacy Assessments** | | | | | | |
| Modified Mayo Clinic Score | X | | | | X | |
| Nancy Histological Index Score | X | | | | X | |
| Geboes Score | X | | | | X | |
| Robarts Histology Index | X | | | | X | |
| Distribute stool e-diary | X | | | | | |
| Check stool e-diary | | X | X | X | X | |
| [redacted] | | | | | | |

ADA=anti-drug antibody; *C. diff=Clostridium difficile*; CRP=C-reactive protein; eCRF=electronic case report form; PK=pharmacokinetics; TB=tuberculosis

Note: If a patient discontinues from the study prematurely, the activities listed at the Week 50 Follow-up visit will be performed.

A All assessments are to be completed before study drug administration

B For those patients who have not entered the open-label phase.

C Physical examination includes inspection of general appearance, eyes, ears, nose, throat, neck (including thyroid), lungs/thorax, heart/cardiovascular system, abdomen, nervous system, musculoskeletal system, extremities, skin and mucosae, lymph nodes and others, if applicable.

D Symptom driven physical examination.

E Vital signs include blood pressure, heart rate, respiration rate, and body temperature (collected as per usual practice). Vital signs will be taken every 30 minutes ± 10 minutes during the 1-hour infusion period and the 2-hour post-infusion period (7 times in total).

F If a patient does not have a chest x-ray or quantiFERON TB gold In Tube test within the last 3 months prior to screen, either may be done according to local guidelines or standard of care to exclude active or latent TB infection.

G This only needs to be collected in the absence of negative results from a recent examination (i.e., performed within 10 weeks prior to the first administration of study drug. Additional tests (e.g., ova + parasitic assessments) may be performed at the investigator's discretion. If the stool sample is positive for *C. diff* toxin or for serious pathogens, the patient should be treated and further rescreening is allowed (new test).

H Perform or schedule an endoscopy only if both rectal bleeding and frequency of stools are ≥ 1.

I Endoscopy to be conducted only if the 2 clinical Mayo Sub-scores – rectal bleeding and stools frequency- provided by the patient at the screening visit are both ≥1 (otherwise the patient is not eligible). **The timing between the screening endoscopy and the Visit 1/Week 0 must not exceed 14 days.**

J Endoscopy at screening needs only to be a sigmoidoscopy except if an extended assessment/colonoscopy is needed due to lack of a recent one (less than 2 years) for patients having suffering from UC for >8 years**.** The timing between the screening endoscopy and the Visit 1/Week 0 must not exceed 14 days **therefore the dates for scheduling both the full colonoscopy and the Visit1/Week 0 have to take into account the time that will be necessary locally in order to obtain the histopathological results before the 1st administration of the study drug.**

K Endoscopy at this time point needs only to be a recto-sigmoidoscopy in any case.

L Only in the lack of a histopathology report available in the patient's file confirming the diagnosis of UC. In such cases, a biopsy performed during the endoscopy at screening for a local histopathology assessment at screening may substitute this requirement.

M Send the biopsy samples to the local histopathology laboratory to get them included in the Formalin fixed paraffin embedded (FFPE) sample both at screening and Week 10 visits, and in addition in order to obtain histopathology confirmation of UC at screening visit only if needed according to Inclusion criterion 5.

N Serum at screening; serum or urine at other visits. Women who are surgically sterile or who are at least 1 year of menopause (confirmed by source documents and eCRF) will not have pregnancy testing.

O Hematology panel will include complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count (with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.

Chemistry panel will include total protein, albumin, glucose, total cholesterol, HDL and LDL cholesterol, triglycerides, total bilirubin (direct and indirect if total bilirubin values above 1.5 times the upper limit of normal), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl-transferase (GGT), sodium, potassium, chloride, creatinine, lactic dehydrogenase (LDH).CRP will be assessed at baseline, W10 and W22 only.

Urinalysis: A semi-quantitative dipstick evaluation for the following parameters will be performed: specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocytes, and nitrite. If the dipstick urinalysis is abnormal, a microscopic evaluation for (bacteria, casts, crystals, epithelial cells, RBC, and WBC) will be performed.

Serology: HBsAg, anti-HCV, anti-HIV.

P Stool studies for enteric pathogens must include a stool culture and *Clostridium Difficile* toxin assay. These tests must be performed during screening or must have been performed recently (as long as they were performed within 10 weeks prior to first study drug administration: i.e., V1/W0). Additional tests (e.g., ova and parasites) may be performed at the investigator's discretion.

Q Blood must be drawn pre-dosing.

R Blood will be drawn pre-dose and at the end of the infusion for PK analysis and only pre-dose for Receptor Occupancy analysis in a subset of 20 patients.

## Table 1.2: Open-label Extension Phase

| Study Procedures | Visit 4 OLE Week 10 | Visit 5 Week 14 | Visit 6 Week 18 | Visit 7 Week 22 | Visit 8 Week 26 | Visit 9 Week 30 | Visit 10 Week 34 | Visit 11 1st Follow-up visit Week 38 | Visit 12 Last Follow-up /ET Visit Week 50 |
|---|---|---|---|---|---|---|---|---|---|
| **Day** | 70 ± 4 | 98 ± 4[H] | 126 ± 4 [H] | 154 ± 4 [H] | 182 ± 4 [H] | 210 ± 4 [H] | 238 ± 4 [H] | 266 ± 4 [H] | 350± 4[H] |
| **General Assessments** | | | | | | | | | |
| Informed consent | | | | | | | | | |
| Physical examination | X [A, E] | X [A] | X [A] | X [A] | X [A] | X [A] | X [A] | X [B] | X [B] |
| Vital signs [C] | X [E] | X | X | X | X | X | X | X | X |
| Weight | X [E] | X | X | X | X | X | X | X | X |
| 12-lead ECG | | | | | | | X | X | X |
| Concomitant medication | X [E] | X | X | X | X | X | X | X | X |
| Adverse events | X [E] | X | X | X | X | X | X | X | X |
| **Laboratory Assessments** | | | | | | | | | |
| Pregnancy test (females of childbearing potential) [F] | X [E] | X | X | X | X | X | X | X | X |
| Hematology, chemistry and urinalysis [G] | X [E] | X | X | X | X | X | X | X | X |
| **Study Drug Administration** | | | | | | | | | |
| OSE-127 | X [D] | X | X | X | X | X | X | | |
| Collect PROs Mayo sub-scores | | X | X | X | X | X | X | X | X |

CRP=C-reactive protein; ET=early termination; PK=pharmacokinetics; TB=tuberculosis

A Symptom-directed physical examination.

B Physical examination includes eyes, ears, nose, throat, lungs/thorax, heart/cardiovascular system, abdomen, skin and mucosae, nervous system, lymph nodes, musculoskeletal system, and others, if applicable.

C Vital signs include blood pressure, heart rate, and body temperature. Vital signs will be taken every 30 minutes ± 10 minutes during the 1-hour infusion period and the 2-hour post-infusion period (7 times in total).

D Additional events to be performed at Visit 4 only for those patients who are entering the OLE phase

E These assessments have already been performed for all patients at Visit 4 (double blind evaluation part of the visit).

F Serum or urine. Women who are surgically sterile or who are at least 1 year of menopause (confirmed by source documents and eCRF) will not have pregnancy testing.

G Hematology panel will include complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), white blood cell (WBC) count (with differential: neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count.

Chemistry panel will include total protein, albumin, glucose, total cholesterol, HDL and LDL cholesterol, triglycerides, total bilirubin (direct and indirect if total bilirubin values above 1.5 times the upper limit of normal), alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl-transferase (GGT), sodium, potassium, chloride, creatinine, and lactic dehydrogenase (LDH).

Urinalysis: A semi-quantitative dipstick evaluation for the following parameters will be performed: specific gravity, pH, glucose, ketones, protein, blood, bilirubin, leukocytes, and nitrite. If the dipstick urinalysis is abnormal, a microscopic evaluation for (bacteria, casts, crystals, epithelial cells, RBC, and WBC) will be performed.

H During OLE, the interval between 2 administrations of OSE-127 high dose is of 4 weeks +/- 4 days. The date for each dispensation visit (as well as the date for the follow-up visits) has to be calculated as plus 4 weeks (±4 days) **from the previous dispensation visit date.**

# 2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

| Abbreviation | Definition |
|---|---|
| 6-MP | 6-mercaptopurine |
| ADA | Anti-drug antibodies |
| AE | Adverse event |
| AESI | Adverse event of special interest |
| ALT | Alanine aminotransferase |
| API | Active pharmaceutical ingredient |
| AST | Aspartate aminotransferase |
| AUC0-inf | Area under the concentration-time curve from time 0 extrapolated to infinity |
| AUClast | Area under the concentration-time curve from time 0 to the last observable concentration |
| AUCtau | Area under the concentration-time curve at steady state |
| BDRC | Blinded Data Review Committee |
| *C. diff* | *Clostridium difficile* |
| CI | Confidence interval |
| Cmax | Maximum plasma concentration |
| CRA | Clinical Research Associate |
| CRP | C-reactive protein |
| CTCAE | Common Terminology Criteria for Adverse Events |
| Ctrough | Serum concentration observed at the end of the dosing interval |
| DNA | Deoxyribonucleic acid |
| DSMB | Data Safety Monitoring Board |
| DSUR | Drug Safety Update Report |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eCRF | Electronic case report form |
| EDC | Electronic Data Capture (system) |
| ePRO | Electronic patient diary |
| ERIN | Event requiring an immediate notification |

| Abbreviation | Definition |
|---|---|
| ET | Early termination |
| EU | European Union |
| FFPE | Formalin fixed paraffin embedded |
| FA | Futility Analysis |
| FAS | Full Analysis Set |
| GCP | Good Clinical Practice |
| GGT | Gamma glutamyl-transferase |
| GLP | Good Laboratory Practice |
| HBsAg | Hepatitis B surface antigen |
| HBV | Hepatitis B virus |
| HCV | Hepatitis C virus |
| HDL | High-density lipoprotein |
| Hgb | Hemoglobin |
| HIV | Human immunodeficiency virus |
| IBD | Inflammatory bowel disease |
| ICF | Informed consent form |
| ICH | International Council for Harmonisation |
| IDMC | Independent Data Monitoring Committee |
| IFNγ | Interferon γ |
| Ig | Immunoglobulin |
| IL-7 | Interleukin-7 |
| IL-7R | Interleukin-7 receptor |
| IND | Investigational new drug (application) |
| IRB | Institutional Review Board |
| ISF | Investigator site file |
| ITT | Intent-to-Treat |
| IV | Intravenous |
| IWRS | Interactive web response system |
| LDH | Lactic dehydrogenase |
| LDL | Low-density lipoprotein |

| Abbreviation | Definition |
|---|---|
| LOCF | Last observation carried forward |
| mAb | Monoclonal antibody |
| MCH | Mean corpuscular hemoglobin |
| MCHC | Mean corpuscular hemoglobin concentration |
| MCV | Mean corpuscular volume |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MTX | Methotrexate |
| NA | Not applicable |
| NOAEL | No observed adverse effects level |
| NSAID | Non-steroidal anti-inflammatory drug |
| OLE | Open-label Extension |
| PBMC | Peripheral blood mononuclear cells |
| PD | Pharmacodynamic(s) |
| Ph. Eur. | European Pharmacopoeia |
| PK | Pharmacokinetic(s) |
| PRO2 | 2-item patient-reported outcome |
| PT | Prothrombin time |
| PTerm | Preferred Term |
| Qs | Sufficient quantity |
| RBC | Red blood cells |
| REP | Residual effect period |
| RHI | Robarts Histopathology Index |
| RNA | Ribonucleic acid |
| RO | Receptor occupancy |
| SAE | Serious adverse event |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SD | Standard deviation |
| SOC | System Organ Class |
| SUSAR | Suspected unexpected serious adverse reaction |

| Abbreviation | Definition |
|---|---|
| $t_{1/2}$ | Elimination half life |
| TB | Tuberculosis |
| TEAE | Treatment-emergent adverse event |
| Teff | Effector T cells |
| TMDD | Target mediated drug disposition |
| TNF-α | Tumor necrosis factor α |
| Tregs | Regulatory T cell |
| UC | Ulcerative colitis |
| UCEIS | Ulcerative Colitis Endoscopic Index of Severity |
| ULN | Upper limit of normal |
| USP | United States Pharmacopoeia |
| WBC | White blood cell |
| γ chain | Gamma chain |

# 3 INTRODUCTION

## 3.1 Global Overview of the Study

This is a prospective, international, multicenter, randomized (1:1:1) double-blind, placebo-controlled, phase 2 study designed 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 ulcerative colitis (UC).

The randomized, double-blind, placebo-controlled approach corresponds to a standard in this disease and is used to eliminate potential bias in reporting clinical efficacy and safety. The study has been powered to allow the detection of differences between efficacy of each dose of active treatment versus the placebo.

The study population (patients with moderate to severe UC who have failed or are intolerant to immunosuppressors, anti-tumor necrosis factor [TNF]-α, anti-integrin, ustekinumab and/or corticosteroids) was selected since it consists of patients who are in need of alternative new therapies to avoid the complications linked to the disease for as long time as possible, and in whom the safety profile of OSE-127 can be reliably assessed.

At Week 10, an open-label administration of OSE-127 for an additional 6 months will be offered to all patients regardless of their treatment allocation in the previous double-blind period. This will allow every patient, including those treated initially with the placebo, to be given the opportunity to receive the active treatment for a sufficient time.

## 3.2 Background

### *3.2.1 Ulcerative Colitis*

Ulcerative colitis is a chronic inflammatory condition causing mucosal inflammation of the rectum and the colon which is characterized by a relapsing and a remitting course. Ulcerative colitis is a lifelong disease observed mainly in Westernized countries and diagnosed mainly in young adults. The precise etiology is unknown. Ulcerative colitis arises from an interaction between genetic background and environmental factors, and medical therapy to cure the disease is not yet available.

Despite medical treatments acting on the clinical symptoms, the disease is characterized by a high symptom burden interfering with work, social, and leisure activities and may ultimately require surgery with a heavy burden in patient's life (i.e., removal of colon and rectum necessitating use of an ostomy bag). In addition, it has been demonstrated that UC was associated with an increased risk for intestinal dysplasia and cancer when compared to the general population (Herrinton 2012, Jess 2012, Itzkowitz 2004). This increased risk is mainly dependent of the persistent inflammation in the colon. (Itzkowitz 2004). The overall goal of treatment is to induce and to maintain clinical remission and mucosal healing. Treatment of UC consists of anti-inflammatory and immunosuppressive drugs, aiming at maximizing efficacy and minimizing side effects. The therapy is chosen based on the severity of the disease and the patient's response to previous therapy.

Typically, mild to moderate UC is treated with anti-inflammatory agents (5-amino-salicylates) administered by oral and/or rectal routes. For patients with mild to moderate UC who do not

respond to these therapies or for patients with moderate to severe UC, corticosteroids are used as second- or first-line therapy, respectively. Despite the effectiveness of corticosteroids in inducing remission in most patients, the multiple adverse effects of corticosteroids impede their long-term use. Moreover, after 1 year of treatment, approximatively 45% of patients who were initially responders become steroid-dependent or require surgery.

For patients unresponsive or intolerant to corticosteroids or who are steroid-dependent, other agents such as immunosuppressive agents (including azathioprine and cyclosporin), or biologics (such as anti-TNF-α), are used to induce and/or to maintain remission. More recently, biologics such as vedolizumab or ustekinumab have also been approved for treatment of patients with moderate to severe UC who fail conventional therapies and/or biologics. All these medications are limited in their ability to establish mucosal healing and clinical remission (Bressler 2015) and have significant safety limitations (Toruner 2008, Rutgeerts 2001, Sandborn WJ, Lichtenstein 2012). In addition to generally low remission rates across most therapies compared to placebo rates, 40% of the initial responders to biologics lose response over time and need to dose-escalate or discontinue biologics after 1 year of treatment (Oussalah 2009, Cote-Daigeneault 2015). Therefore, there is a population of patients with moderate to severe active UC who have previously failed to 1 or several types of drugs and who would need new therapeutic approaches.

### *3.2.2 Interleukin-7 and Interleukin-7 Receptor*

Interleukin (IL)-7 is a limiting and non-redundant cytokine that is mainly produced by epithelial and stromal cells. IL-7 is a critical survival factor for T lymphocytes and regulates T cell homeostasis, proliferation and survival (Mackall 2011, Lundstrom 2013) for both memory and naïve T cell subsets. IL-7 signals through the cell-surface interleukin-7 receptor (IL-7R), formed by the dimerization of the IL-7Rα and the common cytokine receptor gamma chain (γ-chain, CD132). IL-7 interacts with both domain D1 of the IL-7Rα (site-1) and domain D1 of the γ-chain subunit (site-2a) (Walsh 2012). Conventional mature T lymphocytes express high levels of IL-7R, except for naturally-occurring regulatory T cell (Tregs) that express low IL-7R. This specific expression pattern provides an opportunity for a selective targeting of pathogenic effectors while preserving regulatory immune mechanisms (Seddiki 2006, Liu 2006).

Upon activation, IL-7R delivers proliferative and anti-apoptotic signals. IL-7 induces mainly the JAK/STAT pathway but can also induce, depending on the physiological status of the cell, the PI3K or MAPK/ERK pathways, thereby delivering proliferative and anti-apoptotic signals as well as regulating expression of anti- and pro-apoptotic B-cell lymphoma 2 family members (Carette 2012).

### *3.2.3 Mechanism of Action of OSE-127 and Impact on IL-7R+ T cells*

OSE-127 is a humanized immunoglobulin (Ig) G4 monoclonal antibody (mAb) [redacted]. OSE-127 targets CD127, the α chain of the IL-7R and blocks access of IL-7 to the IL-7R.

OSE-127 presents the property to bind to a special epitope comprising both site-1 and site-2b of IL-7Rα. [redacted] differentiating OSE-127 from “site-1 only” anti-IL-7R mAbs that have been developed so far (Belarif 2018):

[redacted]

[redacted]

In summary, OSE-127 constitutes a rare opportunity to target effector T cells while sparing Tregs. [redacted]

### *3.2.4 Rationale for Clinical Development in Ulcerative Colitis*

IL-7 represents the fuel of auto-immune diseases (Dooms 2013) and a major challenge in the treatment of inflammatory diseases may be the presence of pathogenic memory T cells in the tissues, which are likely resistant to conventional immune modulator therapies. Consequently targeting IL-7R may be beneficial for inflammatory conditions (Dooms 2013, Shalapour 2012). Whilst colon is the major source of IL-7 outside lymphoid tissues in mice (Shalapour 2012), non-clinical and clinical data suggest a strong implication of IL-7R in inflammatory bowel diseases (IBD) and more specifically in UC. Of note, transgenic mice overexpressing IL-7 spontaneously develop chronic colitis with infiltration of IL-7Rα high colitogenic T cells in the gut mucosa which once isolated transferred colitis in immune-deficient mice, thereby demonstrating their pathogenicity (Wantanabe 1998, Yamazaki 2003, Okada 2005, Totsuka 2007, Buonocore 2010, Powell 2012, Willis 2012, Bernink 2013, Goldberg 2015).

In human, a recent transcriptional study of blood T cells from IBD patients showed a higher incidence of relapses as well as more aggressive disease course in patients with increased expression of genes involved in signaling initiated by both IL-7 and TCR ligation (Lee JC 2011). In addition, according to an analysis of up to 500 patients with IBD and 100 controls, key transcripts of the IL-7R pathway accumulate in inflamed colon tissues of severe IBD patients not responding to either immunosuppressive/corticosteroids, anti-TNF or anti-α4/β7 therapies. High expression of both IL-7R and IL-7R signaling signature in the colon before treatment were strongly associated with non-responsiveness to anti-TNF therapy. Experimentally, the importance of IL-7 in the maintenance of inflammation was confirmed using colon biopsies from UC patients: in an *ex vivo* 24-hour culture system, OSE-127 altered synthesis of interferon γ (IFNγ) by Teff. Accordingly, recent pharmacological data indicated that IL-7 receptor blockade by OSE-127 in vivo reduced human T cell homing to the gut and colonic inflammation in humanized mouse models (Belarif 2019).

The strategy of blocking IL-7R, which is different from current or future drugs used in UC may lead to a different and significant therapeutic benefit in UC patients. This strategy has

demonstrated its potent efficacy in preventing and/or curing ongoing diseases in several auto-immune and chronic inflammatory rodent models in colitis (Wantanabe 1998, Yamazaki 2003, Okada 2005, Totsuka 2007) as well as in type 1 diabetes (Peneranda 2012, Lee 2012), multiple sclerosis (Lee 2011, Lawson 2015), rheumatoid arthritis (Hartgring 2009, Hartgring 2010, Hartgring 2012), systemic lupus erythematosus (Gonzalez-Quintial 2011) and primary Sjögren's syndrome (Jin 2013).

Further details can be found in the Investigator's Brochure (version 2.0), which contains comprehensive information on the investigational product.

## 3.3 Risk-Benefit Assessment

### *3.3.1 Pharmacology and Pharmacodynamics Data of OSE-127 Exploring Benefits*

[redacted]

In summary, OSE-127 is a drug candidate with a novel and unique mechanism of action, its proof of concept has been confirmed in relevant [redacted] models [redacted]. Further details can be found in the Investigator's Brochure (version 2.0), which contains comprehensive information on the investigational product. This data supports the view that OSE-127 has the potential to improve the management of patients with auto-immune diseases where pathogenic IL-7R expressing T cells in tissues play a pivotal role, such as UC.

[redacted]

[redacted]

### *3.3.3 Clinical Data With Other Anti-ILRα Antagonist mAbs*

Two other anti -ILRα antagonist mAbs (GSK 26118960 [Glaxo Smith Kline] and PF 06342674 [Pfizer]), are directed against the same target as OSE-127 (i.e., IL-7Rα). But both antibodies are site-1 restricted mAbs and are describing a degree of "paradoxical agonist potential" assessed ex vivo (Kern 2016) and in human volunteers (Ellis 2018). Despite the partial agonist potential effect, they have been tested in several Phase 1 trials gathering around 150 healthy volunteers and patients without safety issues, neither short, nor long term clinically significant impact on T lymphocytes sub populations.

### *3.3.4 First in Human Study Conducted with OSE-127 Exploring Potential Risks*

A phase 1 study to evaluate the safety, tolerability, PK, PD, and immunogenicity of single and repeat ascending doses of OSE-127 has been conducted in Belgium and enrolled 63 healthy adult male and female volunteers. Among them, 45 patients were exposed to OSE-127 up to 10 mg/kg (single and double doses).

The study design was in line with the European Guidelines on Strategies to identify and mitigate risks for First-in-Human Clinical and early Clinical Trials with Investigational Medicinal Products (EMEA /CHMP/SWP/28367/07 Rev.1).

Clinical Safety

The administration of a single dose (0.002, 0.02, 0.2, 1, 4, or 10 mg/kg IV or 1 mg/kg SC) or 2 doses at 2-week interval (6 or 10 mg/kg) was safe and well tolerated. No serious adverse events

(SAEs) were reported. None of the patients prematurely discontinued their participation in the study for safety issue. All adverse events (AEs) were mild or moderate in intensity. No remarkable differences or dose-dependent trend could be observed between the different OSE-127 doses and placebo for AE incidence, for laboratory data, vital signs, or electrocardiogram (ECG) parameters over time, or for treatment-emergent laboratory, vital signs, or ECG abnormalities. Of note, no clinically significant lymphopenia and no cytokine release (IFNγ, IL12p70, IL4, IL5, IL6, IL8, TNFα) have been observed following OSE-127 administration.

Besides the absence of significant modification of total lymphocytes count, the percentages of lymphocyte subsets were not changed after the administration of OSE-127, in particular no modification was observed in the % of effector, central, effector-memory and naive cells neither in lymphocytes T CD8+ cells nor in lymphocytes T CD4+ cells.

Pharmacokinetics

In the single dose part of the study, no significant dose effect was observed on maximum plasma concentration ($C_{max}$; dose range: 1 mg/kg to 10 mg/kg). Despite a non-significant dose-proportionality of area under the concentration-time curve at steady state ($AUC_{tau}$), an increase of dose-normalized $AUC_{tau}$ was observed between 0.02 and 1 mg/kg while dose-normalized AUCtau seemed stable between 4 and 10 mg/kg. This behavior is expected for mAbs cleared by a Target Mediated Drug Disposition (TMDD) process. Half-life increased from 111 to 280 hours over the dose range of 1 mg/kg to 10 mg/kg. Relative bioavailability ($C_{max}$, area under the concentration-time curve from time 0 to the last observable concentration [$AUC_{last}$], and $AUC_{tau}$) was about 10-13% after SC administration compared to IV infusion of OSE-127.

After 2 IV infusions of OSE-127, approximate dose proportionality for $C_{max}$ and $AUC_{last}$ was observed from 6 to 10 mg/kg. The accumulation ratio was about 1.5 for AUCtau and about 1.25 for $C_{max}$. Half-life was approximately 300 and 390 hours after the second dose of OSE-127 at 6 and 10 mg/kg respectively.

Pharmacodynamics

Observed results have shown that receptor occupancy (RO) was above 95% quickly after the administration with CD127 receptors saturated at the first sampling time after the end of infusion from the dose of 0.02 mg/kg. Then, the duration of the maintenance over 95% RO was longer for higher doses and repeated administrations with a median time of CD127 RO > 95% lasting 4 h at 0.02 mg/kg, 96 h at 0.2 mg/kg, 336 h at 1 mg/kg, 672 h at 4 mg/kg, 1370 h at 10 mg/kg and 1370 h and 2450 h after repeated IV administrations (2 administrations 2 weeks apart) of 6 mg/kg and 10 mg/kg respectively.

Once the RO had started to decrease, the slope was steep as the %RO fell from > 95% to < 20% between 2 consecutive visits (2 weeks apart) or over 3 consecutive visits (4 weeks apart).

Immunogenicity (ADAs)

Anti-OSE127 Abs were detected after single (IV and SC) and multiple (IV) administration from a dose of 0.2 mg/kg and higher. The appearance of these ADAs was delayed with increasing and repeated doses, starting from 1 month after the first administration for the lower single doses to almost 3 months for the highest repeated dose. In the majority of positive subjects they were detected for the first time once the elimination of OSE-127 had been almost complete (e.g., for

70% of the single dose subjects once the concentration of OSE-127 in blood was below the LLOD of 31.3 ng/mL).No validated assay was available for the assessment of the neutralizing potential of these ADAs however, the comparison between patients with ADAs and patients without ADAs showed on average a similar clearance of the drug as well as similar RO values [redacted].

Further details can be found in the Investigator's Brochure (version 2.0), which contains comprehensive information on the study drug.

### *3.3.5 Potential Theoretical Risks Associated with OSE-127*

Since no safety issue has been identified so far with OSE-127, one should refer to potential risks associated with its mechanism of action as well as to theoretical common risks associated with products considered as “immunomodulators.” Table 3.1 summarizes these potential risks and the proposed strategies to mitigate/monitor them within this phase 2 trial in UC.

**Table 3.1: Summary of Potential Risks and Risk Mitigation/Monitoring Strategy**

| Potential Theoretical Risks | Rationale | Risk Mitigation/Monitoring Strategy |
|---|---|---|
| Infusion-related reactions | According to the literature and biology of IL-7 and IL-7R as well as to the current knowledge on OSE-127 based on in vitro, ex vivo and in vivo experiments in animals and in humans, a risk of cytokine release that could lead to acute reactions occurring during or after administration of OSE-127 is very unlikely. The First in Human Trial data has confirmed this very low risk with no observed clinical syndrome following IV administrations up to 10 mg/kg once or twice. No impact after administration of OSE-127 was observed on sera cytokine levels (TNF-α, IFN-γ, IL-12p70, IL-8, IL-6, IL-5, IL-4) after both single and double administrations of the product.<br><br>Hypersensitivity reactions could theoretically occur as for any drug and can manifest as fever, chills, urticaria, dyspnea, myalgia, and/or hypotension. No reactions of this type have been observed in the phase 1 trial in healthy volunteers.<br><br>As for other mAbs there could also be a risk of non-specific infusion-related reactions such as e.g. headache and nausea. occurring during infusions and within a period of a couple of hours post administration. | Infusions of OSE-127 will be delivered in an in-patient clinic within 60 minutes for both doses, with a 2-hour post-infusion surveillance. Clinical examination will be performed and vital signs will be checked before each infusion. Vital signs will be registered every 30 minutes during the infusion and during the 2-hour post-infusion surveillance period.<br><br>If any infusion-related reaction would occur, it will be managed by temporary interruption of the infusion, reduction of the infusion rate and symptom management at the discretion of the Investigator. |
| T cell lymphopenia and infections | Based on knowledge of IL-7/IL-7R functions, prolonged treatment with OSE-127 may in theory result in lymphopenia and depressed T-cell responses that could result in increased risk of infection.<br><br>These risks have not been seen [redacted] in the First in Human Trial where no clinically significant lymphopenia has been observed, with no modification in the % of lymphocytes subsets in particular no modification of effector, central, effector-memory and naive cells neither in lymphocytes T CD8+ cells nor in lymphocytes T CD4+ cells. | Absolute lymphocyte counts will be monitored at each visit and stopping criteria on lymphocyte counts will be employed.<br><br>To be included in the study, patients at screening will have to be tested negative at screening for Tuberculosis as well as for bowel pathogens including *Clostridium difficile* (*C. diff*) toxin. They will not be enrolled in case of known or recent active viral, bacterial, fungal, mycobacterial infection (any major infection that required hospitalization or treatment with IV antibiotics or antifungal within 30 days prior to screening or that required treatment with oral antibiotics within 14 days prior to screening) as well as in case of history or known presence of chronic or recurrent infection (hepatitis B, C, HIV). |

| Potential Theoretical Risks | Rationale | Risk Mitigation/Monitoring Strategy |
|---|---|---|
| | | In addition, the occurrence of infections will be closely monitored involving a DSMB that will meet regularly in order to assess AEs (after the first 9 patients having received 2 injections at first and then every next 20 patients). Of note after the last dosing of OSE-127 patients will enter a follow-up period for a duration of 4 months whether they have participated or not to the Open Label Extension Period. |
| Vaccination | Vaccination of patients during treatment with OSE-127 and prior to clearance of the antibody might in theory result in non-protective vaccinal antibody titers due to the pharmacologic activity of the antibody. Safety of the association of live vaccines and OSE-127 is unknown. | Patients with recent or concomitant live /attenuated vaccination (4 weeks prior to screening) will be excluded and for a period of 12 weeks after the last dose of OSE-127. |
| Anti-drug antibodies | The extrapolation of immunogenicity from healthy subjects to UC patients is unknown. ADAs may in theory result in immune system activation although no acute immune response has been observed in the ADAs positive volunteers during the First in Human Trial with OSE-127 [redacted]<br><br>Moreover there is no scientific rational that ADAs against an anti-IL7-RmAb could result in immune system activation on the contrary to other mAbs targeting at activation molecule e.g,.CD3, CD28 or CD40. The risk for ADAs against OSE-127 would be more about loss of efficacy due to disturbance of PK or the binding of ADAs to the active site of the anti-IL7R mAb. | Patients clinical safety will be closely monitored involving a DSMB that will meet regularly in order to assess AEs (after the first 9 patients having received 2 injections at first and then every next 20 patients). Of note after the last dosing of OSE-127 patients will enter a follow-up period for a duration of 4 months whether they have participated or not to the Open Label Extension Period. |

ADA=anti-drug antibodies; AE=adverse events; DSMB=Data Safety Monitoring Board; GLP=Good Laboratory Practice; HIV=human immunodeficiency virus; IL-7=interleukin 7; IL-7R=interleukin-7 receptor; IV=intravenous; UC=ulcerative colitis

### *3.3.6 Risk and Benefit Assessment: Conclusion*

Ulcerative colitis is a progressive, debilitating and potentially life-threatening inflammatory bowel disease There is an unmet medical need for disease-modifying therapies in this disease mainly for patients who are refractory or intolerant to previous treatments and who are therefore at increased risk of gastrointestinal malignancies and may ultimately require life-altering surgery (i.e., removal of colon and rectum, necessitating use of an ostomy bag).

The role of the IL-7/IL-7R pathway is established in the immunopathogenesis of UC and blocking IL7-R may improve some underlying immunologic abnormalities, which may result in clinical benefit.

OSE-127 is a humanized IgG4 mAb that targets CD127, the α chain of the IL-7R, and blocks access of IL-7 to the IL-7R. OSE-127 mAb is a full antagonist of CD127 and has demonstrated its ability to control IL7-induced T proliferation and survival as well to prevent pathogenic antigen-specific memory T cell responses and to block human T cell homing to the gut.

[redacted]

The first in human data has shown a good safety/tolerability profile of single and multiple OSE-127 doses in both male and female patients. No safety concern was reported from the non-clinical safety studies.

OSE-127 has never been used in patients with UC and at this stage, no statement can be made on its efficacy in treating this disease. Nevertheless, if OSE-127 has clinical efficacy, all patients participating in the present trial may experience this benefit since all of them will be offered to receive the active drug at Week 10 for an open label extension phase of 6 months.

### *3.3.7 Risks Associated with COVID-19*

Since patients may not be able to come to the investigational site for protocol-specified visits, alternative methods for safety assessments (e.g., phone contact, virtual visit, alternative location for assessment, including local labs) may be implemented when necessary and feasible. The investigator must discuss these options with the sponsor prior to their implementation.

Safety of the patients will remain a priority; patients will be included in the trial only if they meet the criteria established in the protocol.

It has been agreed with the DSMB that the following rules had to be applied for the management of those patients tested positive with or without any symptom consistent with COVID-19, depending on the period of occurrence:

- **Screening Period**: patient should not be randomized or initiated on study drug until resolution of symptoms or negative re-testing. Resumption of the screening process can be discussed afterwards with the study Medical Monitor on a case-by-case basis;

- **Induction Period**: the study drug has to be stopped and the patient withdrawn from the study
- **Open Label Extension**: treatment cessation will be discussed on a case-by-case basis with the study Medical Monitor taking into account the investigator's judgement on the potential benefit on UC observed with the study drug

# 4 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 ≥ 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<br>• Number and proportion of patients with endoscopic response or improvement at Week 10 defined by an endoscopic sub-score of Mayo ≤ 1 point.<br>• Mean change from baseline in the endoscopic activity measured at Week 10 by the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) |

| Objectives | Endpoints |
|---|---|
| • 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 |
| ***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<br>• Number and proportion of patients without acute histological inflammation at Week 10 defined by a Nancy Histological Index score of ≤ 1<br>• 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<br>o Endoscopic remission defined by an endoscopic Mayo sub-score = 0<br>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<br>• 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 |

| Objectives | Endpoints |
|---|---|
| | • Median change from baseline in fecal calprotectin at Weeks 2, 6, and 10<br>• 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 |
| • 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<br>• 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<br>• 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<br>• Correlation between efficacy outcomes and drug exposure |

# 5 OVERALL DESIGN AND PLAN OF THE STUDY

## 5.1 Overall Design

This is a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in patients with moderate to severe active UC.

The study includes 4 periods: screening, induction, optional extension, and follow-up.

Screening Phase: 8 weeks maximum

Following the screening period, eligible patients will be randomized and enter the 10-week placebo-controlled induction phase. The randomization will be stratified 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 had 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). Up to the 108 first inclusions, only 17 patients with previous exposure to biologics have been enrolled. Therefore, only patients with previous exposure to biologics and primary non response or secondary loss of response will be randomized from the 109$^{th}$ patient to the last randomized patient.

Induction Phase: Week 0 to Week 10

In the first step of the study (i.e. before the outcome of the pre-specified Futility Analysis; Global Protocol V1.0), patients were randomly assigned on Week 0 in a 1:1:1 ratio to receive 1 of the following regimens:

- Placebo intravenous (IV) infusion at Week 0, Week 2, and Week 6
- OSE127 Low Dose (450 mg) IV infusion at Week 0, Week 2, and Week 6
- OSE127 High Dose (850 mg) IV infusion at Week 0, Week 2, and Week 6

Following the pre-specified Futility Analysis and the recommendations issued by the IDMC, the randomization to the low dose of OSE-127 is cancelled since this dose has not reached the threshold for showing a potential effect versus placebo upon trial completion. Therefore within this amended protocol (Global Protocol V2.0), patients will be randomly assigned on Week 0 in a 1:1 ratio to receive 1 of the 2 following regimens:

- Placebo intravenous (IV) infusion at Week 0, Week 2, and Week 6
- OSE127 High Dose (850 mg) IV infusion at Week 0, Week 2, and Week 6

Infusions will be delivered in an in-patient clinic for 1 hour, with a 2-hour post-infusion surveillance. Clinical examination will be performed and vital signs will be checked before each infusion. Vital signs will be recorded every 30 minutes during the infusion and during the 2-hour post-infusion surveillance period.

At Week 10, all the patients will have a visit to record all the components of the primary and main secondary endpoints (see the study schema in Section 1.1).

Open-Label Extension Phase (OLE): Week 10 to Week 34

At Week 10 all the patients will be asked to participate in an open-label extension period and those willing to continue the study in accordance with the clinical investigator will receive additional infusions at Weeks 10, 14, 18, 22, 26, 30, and 34 at the high dose level of OSE-127 (i.e., 850 mg).

Study drug will be administered as described above during the Induction Phase.

Safety Follow up Phase: Week 10 to Week 22 or Week 34 to Week 50

If the patient does not participate in the OLE, the safety follow-up period during which no study treatment will be administered will start after Week 10 and will last 12 weeks after the end of the induction phase (Week 10 to Week 22 corresponding to 16 weeks after the last administration). In such case, 1 mandatory follow-up visit will be conducted at Week 22.

If the patient participates in the OLE Phase, the safety follow-up period will last 16 weeks after the last administration (Week 34 to Week 50) and 2 mandatory follow-up visits will be conducted at Week 38 and at Week 50.

An independent Data Safety Monitoring Board (DSMB) will be set up to primarily take care of the safety of the participating patients by reviewing the safety and tolerability data of the investigational drug on a regular basis.

The interim futility analysis planned as per global protocol V1.0 after 30% of the patients had completed the Induction Phase (see Section 10.9) has been achieved in December 2021. The DSMB members have acted as the Independent Data Monitoring Committee (IDMC) and have issued the recommendation to stop the low dose of OSE-127 since this dose had not reached the threshold for showing a potential effect versus placebo upon trial completion. As no safety issue has been reported at the time of the Futility Analysis (88 patients having received at least 2 infusions of the study drug), no other change in the study was recommended by the DSMB for safety reasons.

Efficacy will be assessed by modified Mayo Score for Assessment of Ulcerative Colitis (including stool frequency, rectal bleeding and mucosal appearance at endoscopy [endoscopic sub-score]), clinical response, PRO2 (stool frequency and rectal bleeding), endoscopy, histology (including the Nancy Histological Index Score, the Geboes score and the RHI), measurements of CRP and fecal calprotectin, UCEIS, and the UC-100 score.

Pharmacokinetics and PD will be assessed using PK and RO (in a subgroup of 20 patients)[redacted]

Safety will be assessed by AEs (including SAEs) clinical laboratory assessments, vital signs, ECGs, physical examination, and immunogenicity assessments.

## 5.2 Rationale for Study Design

The study population (patients with moderate to severe UC who have failed or are intolerant to immunosuppressive agents, anti-TNF-α, anti-integrin, ustekinumab and/or corticosteroids) was selected since this population consists of patients who are in need of alternative new therapies to avoid for as long time as possible the complications linked to the disease and in whom the safety profile of OSE-127 can be reliably assessed.

The double-blind, placebo-controlled design corresponds to a standard design in this disease and by avoiding potential bias in reporting clinical efficacy and safety will allow the detection of differences between each of the 2 doses of active treatment versus placebo.

The primary endpoint is the change in modified Mayo Score between baseline and Week 10 and the key secondary endpoint is the number and proportion of patients in clinical remission at Week 10. Both endpoints are assessing at the same time clinical symptoms as well as endoscopic findings in line with the Guideline on the development of new medicinal products for the treatment of Ulcerative Colitis CHMP/EWP/18463/2006 Rev.1 where it is said that a significant effect on both aspects of the disease is required at a population level. In line as well with this guideline which states that including the physician's global assessment sub-score of the Mayo Score is not of primary interest, the modified Mayo Score (i.e.; Total Mayo Score without the physician's global assessment) will be used for both endpoints, the former assessing this score as a continuous/quantitative variable (variation of MMS), the latter as a binary/qualitative variable (clinical remission: yes/no). Previous UC induction studies have evaluated initial endpoints at 8 to 12 weeks, and the present study proposes that Week 10 assessments for biologically naïve and experienced patients be used. Ten weeks is expected to be sufficient time for some degree of mucosal healing to occur and for clinical symptoms to improve. The use of endoscopy and histology maximizes objectivity in assessment of drug effect. Use of centrally read endoscopy will further reduce bias in assessment of endoscopic healing. At Week 10, an open-label administration of OSE-127 at Weeks 10, 14, 18, 22, 26, 30, and 34 will be offered to all patients regardless of their treatment allocation in the previous double-blind period. This will allow every patient, including those treated initially with the placebo, to be given the opportunity to receive the active treatment for a sufficient time. This administration will be done at the high dose level of OSE-127 (i.e., 850 mg).

### 5.3 Justification for Doses and Schedule of Administration

The selection of the dose levels was based on safety/tolerability, PK and RO data from the phase 1, single ascending dose part. [redacted].

[redacted]

[redacted]

[redacted]

In the proposed study design, UC patients will receive OSE-127 by IV infusions at Weeks 0, 2 and 6. Patients willing to continue the study will receive additional IV infusions of OSE-127 at Weeks 10, 14, 18, 22, 26, 30 and 34. [redacted]

## 5.4 End of Study Definition

End of Study is defined as the last patient's last visit in the study.

# 6 STUDY POPULATION

## 6.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible to participate in the study. It is expected that approximatively 10% of the enrolled patients will be > 64 years old.

| | |
|---|---|
| 1. | Provision of signed and dated informed consent document indicating that the patient has been informed of all the pertinent aspects of the trial prior to enrollment |
| 2. | Willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures |
| 3. | Willingness to refrain from live or attenuated vaccines during the study and for 12 weeks after last dose |
| 4. | Male or female 18 to 75 years of age, inclusive |
| 5. | Diagnosis of moderate to severe active UC* made at least 3 months before the screening visit. The diagnosis of UC must have been confirmed by endoscopy, with a minimal extent of 15 cm from anal margin and histology (i.e., histopathology report available in the patient's file); however, a biopsy for a local histopathology assessment at screening can substitute this requirement.<br>*Moderate to severe active UC is defined by a modified Mayo score between 4 and 9, inclusive. The modified Mayo score is defined by the addition of the rectal bleeding sub-score, the stool frequency sub-score, and the endoscopic sub-score. Thus, to be included, a patient must have the following:<br>a. a rectal bleeding score ≥ 1,<br>b. a stool frequency score ≥ 1 (sub-score calculated before bowel preparation), and<br>c. an endoscopic sub-score ≥ 2 |
| 6. | Previous or current biologic therapy for UC with **documented** history of a primary non clinical response to or a secondary loss of response to **at least:**<br>- **1** of the following agents used at a dose and regimens approved for the treatment of UC for sufficient time (including approved biosimilars):<br>• Anti-TNF-α agents<br>• Vedolizumab<br>• Ustekinumab<br>- **Or to 1 of the following investigational biologic agents (i.e. not yet approved in UC)** used at a therapeutical dose **(in such situations, pre-screening discussions with the Medical Monitor of the study will allow to define if the conditions of non-response are met):**<br>• Mirikizumab<br>• Rizankizumab<br>• Guselkumab<br>• Other biologic … |

| | |
|---|---|
| 7. | Patient currently receiving 1 or more of the following medication(s) for UC is eligible, provided that he/she has been receiving such treatment(s) for at least 4 weeks and with no change in dose or frequency in the 2 weeks prior to screening:<br>a. Oral aminosalicylates anticipating that the dose at screening has to be maintained until Week 10.<br>b. Prednisone (stable doses ≤ 20 mg/day) or equivalent, budesonide MMX (stable doses ≤ 9 mg/day), or beclomethasone dipropionate (stable doses ≤ 5 mg/day), anticipating that these stable doses have to be maintained until Week 10<br>If these medications have recently been stopped, the treatment cessation must have occurred at least 2 weeks prior to screening |
| 8. | Patients who have been previously receiving anti-TNF-α therapy or vedolizumab or ustekinumab must have discontinued this therapy ≥ 8 weeks before the date of baseline endoscopy or ≥ 5 half-lives before the date of baseline endoscopy in case of investigational biologics agents. |
| 9. | For patients with UC >8 years, results of a surveillance colonoscopy conducted within 2 years prior to screening are required to rule out dysplasia. This full colonoscopy might be done at screening instead of the procto-sigmoidoscopy to fulfill this requirement. |
| 10. | Either chest x-ray within the 3 months prior to screening and/or a negative quantiFERON TB Gold In Tube test according to local guidelines and standard of care to exclude active or latent TB infection |

## 6.2 Exclusion Criteria

Individuals who meet any of the following criteria are not eligible to participate in the study.

| | |
|---|---|
| 1. | Stoma, proctocolectomy, or subtotal colectomy |
| 2. | Physician judgment that patient is likely to require any surgery for UC during the study duration, or double-blind phase duration at least |
| 3. | Evidence of fulminant colitis, toxic megacolon, or perforation |
| 4. | Current or recent (within 4 weeks prior to screening) hospitalization for UC care and/or treatment with IV steroids |

| | |
|---|---|
| 5. | The following laboratory results at screening:<br>a. Elevation at screening of aspartate aminotransferase (AST), alanine aminotransferase (ALT) > 3 × the upper limit of normal (ULN) or total bilirubin > 2 × ULN (unless due to Gilbert's disease) or evidence of chronic liver disease<br>b. Platelet count < 100,000/$mm^3$<br>c. Hemoglobin (Hgb) < 8.5 g/dL<br>d. Neutrophils < 1500/$mm^3$<br>e. Lymphocytes < 800/$mm^3$<br>f. Absolute white blood cell (WBC) count < 3000/$mm^3$ |
| 6. | Crohn's disease or indeterminate colitis or any other diagnosis not consisting with UC |
| 7. | History or evidence of incompletely resected colonic dysplasia or unconventional lesion at risk of colonic adenocarcinoma |
| 8. | Stool culture or other examination positive for enteric pathogen, including *Clostridium difficile* (*C. diff*) toxin. If positive, the patient should be treated and rescreening is allowed. |
| 9. | Men or women with childbearing potential not willing to use adequate birth control during the study. Adequate birth control includes surgical sterilization, intrauterine device, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy, double-barrier method (condom, diaphragm with spermicide), or abstinence during study and **30** days following the last follow-up visit. Women of childbearing potential will enter the study after a negative pregnancy test. |
| 10. | Breastfeeding |
| 11. | Chronic use of nonsteroidal anti-inflammatory drugs (NSAIDs) from screening through the end of the study |
| 12. | Use of topical steroids and/or topical 5-aminosalicylic acid preparations within 2 weeks before the screening visit (all such medications should be withdrawn at least 2 weeks prior to the screening visit) |
| 13. | Use of antidiarrheals within 2 weeks before the screening visit (all such medications should be withdrawn at least 2 weeks prior to the screening visit) |
| 14. | Treatment with azathioprine, 6-MP, methotrexate (MTX), cyclosporin, tacrolimus, sirolimus, leflunomide and/or mycophenolate mofetil within 4 weeks before the screening visit (all such medications should be withdrawn at least 4 weeks prior to the screening visit) |
| 15. | Previous treatment with more than 3 biologics including anti-TNF-$\alpha$ and/or anti-integrin and/or ustekinumab and/or other biologics agents |
| 16. | Prior treatment with a JAK inhibitor |

| | |
|---|---|
| 17. | Clinically relevant cardiovascular, hepatic, neurologic, psychiatric, pulmonary, endocrine, or other major systemic disease that would put the patient at risk by participating in the study in the opinion of the investigator |
| 18. | A recognized hereditary, congenital, or acquired immunodeficiency disease including human immunodeficiency virus (HIV) infection and other cellular immunodeficiencies, hypogammaglobulinemia, or dysgammaglobulinemia |
| 19. | Known active viral, bacterial, fungal, mycobacterial infection, or other infection or any major infection that required hospitalization or treatment with IV antibiotics or antifungal within 30 days of screening or that required treatment with oral antibiotics within 14 days of screening |
| 20. | History or known presence of chronic or recurrent infection (hepatitis B, C, HIV) |
| 21. | Any autoimmune disease, other than UC, with the exception of controlled Type I diabetes (hemoglobin A1c ≤8%) or treated hypothyroidism |
| 22. | Evidence of active malignancy |
| 23. | Live vaccine received within 4 weeks prior to screening |
| 24. | Previous treatment with lymphocyte-depleting agents such as alemtuzumab; alkylating agents such as cyclophosphamide or chlorambucil; total lymphoid irradiation; or selective B lymphocyte-depleting agents such as rituximab |
| 25. | Current or previous treatment with investigational therapy in another therapeutic clinical trial within 8 weeks or 5 half-lives before the date of baseline endoscopy |
| 26. | History of alcohol or drug abuse within 1 year of screening |
| 27. | Previous completion or withdrawal from this study. This criterion does not apply to participants undergoing rescreening procedures. |

## 6.3 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

### *6.3.1 Patient Discontinuation of Study Drug*

OSE-127 will be reconstituted in a saline solution and administered by IV infusion in at least 60 min after dilution to the right concentration according to instructions provided in the Pharmacy Manual. If infusion related adverse reactions occur in one patient, the infusion flow rate will be decreased for this patient. If related adverse reactions continue, OSE-127 will be stopped for this individual patient.

### *6.3.2 Patient Discontinuation*

The participation of an individual patient may be discontinued prematurely for reasons such as:

- Withdrawal of written informed consent
- Required treatment with any medication known or suspected to interfere with the study drug, or increase of the dose of concomitant standard medications for UC treatment during the Induction study phase (up to Week 10)

- Adverse reactions during administration of the study drug
- Lack of study compliance
- Treatment unblinding
- Any other condition which in the opinion of the investigator and/or the Medical Monitor no longer permits safe participation in the study such as follows: (The Medical Monitor should be consulted prior to any patient's study drug discontinuation when medically feasible.)
    - Any opportunistic infection
    - Any serious infection that requires antimicrobial therapy or hospitalization, or any infection that meets SAE reporting criteria
    - Febrile neutropenia (temperature > 38.3°C or a sustained temperature of > 38°C for more than 1 hour) with absolute neutrophil count of < 1,000/$mm^3$
    - Symptomatic anemia (e.g., signs/symptoms including pallor, shortness of breath, new heart murmur, palpitations, lethargy, fatigue) with Hgb < 7.5 g/dL, or if transfusion is needed according to the investigator's judgement regardless of Hgb value
    - Evidence of active Hepatitis C Virus (HCV), Hepatitis B Virus (HBV), HIV or CoVid-19 (with or without symptoms) during the study

A patient may discontinue participation in the clinical study at his/her own request at any time without stating a reason.

The investigator can stop a patient's participation in the study at any time if continuation could lead to disadvantages for the patient which cannot be justified by the investigator.

The reason for withdrawal of the patient must be documented by the investigator together with all data collected until the day of premature study discontinuation including laboratory results and assessment of AEs.

Patients in in the double-blind phase who discontinue treatment before completion of induction will not be replaced.

### 6.4 Lifestyle Considerations

Men or women with childbearing potential must use adequate birth control during the study. Adequate birth control includes surgical sterilization, intrauterine device, oral contraceptive, contraceptive patch, long-acting injectable contraceptive, partner's vasectomy, double-barrier method (condom, diaphragm with spermicide), or abstinence during study and **30** days following the last follow-up visit. Women of childbearing potential will enter the study after a negative pregnancy test.

# 7 STUDY INTERVENTION

## 7.1 Identity

### *7.1.1 OSE-127*

OSE-127 is a humanized recombinant IgG4 mAb that specifically binds to human CD127 receptor, the α chain of the IL-7R (IL-7Rα). It is produced by recombinant expression technology in Chinese Hamster Ovarian cells line. The composition of OSE-127 is presented in Table 7.1.

OSE-127 is provided as a 50 mg/mL concentrate for solution in vials of 2 mL for IV infusion.

**Table 7.1: Composition and Concentration of OSE-127 Drug Product**

| Component | Concentration | Function | Reference to Standards |
|---|---|---|---|
| anti-CD127 mAb | 50 mg/mL | API | NA |
| L-Histidine | 20 mM | Buffering agent | Ph. Eur., USP |
| Acetic acid | Q.s pH 5.5 | pH adjustment | Ph. Eur., USP |
| Glycine | 50 mM | Stabilizing agent | Ph. Eur., USP |
| Polysorbate 20 | 0.02% (w/w) | Stabilizing agent | Ph. Eur., USP |
| Sorbitol | 180 mM | Stabilizing agent | Ph. Eur., USP |
| Water For injection | Qs | Solvent | Ph. Eur., USP |

API=active pharmaceutical ingredient; NA=not applicable, Ph. Eur=European Pharmacopoeia; Qs=sufficient quantity; USP=United States Pharmacopoeia.

### *7.1.2 Placebo*

Placebo is a standard saline solution for IV infusion.

## 7.2 Administration

OSE-127 will be reconstituted in a saline solution as per instructions provided in the Pharmacy Manual and administered by IV infusion in at least 60 min after dilution to the right concentration. In case infusion related adverse reactions occur, the infusion flow rate will be decreased.

Placebo (normal saline) similar in color and appearance to the active drug will be provided by the study site in an infusion bag identical to the bag used for the active drug and will be administered by IV infusion.

### *7.2.1 Induction Phase: Week 0 to Week 10*

At this stage (i.e. study resuming after the Futility Analysis outcome and the decision made to drop-out OSE-127 low dose arm), patients will be randomly assigned at Week 0 in a 1:1 ratio to receive 1 of the 2 following regimens:

- Placebo IV infusion at Week 0, Week 2, and Week 6

- OSE127 High Dose (850 mg) IV infusion at Week 0, Week 2, and Week 6

#### *7.2.2 Open Label Extension Phase (OLE): Week 10 to Week 34*

At Week 10 all the patients will be offered to participate in an OLE period and those willing to continue the study in accordance with the clinician investigator will receive additional infusions at Weeks 10, 14, 18, 22, 26, 30, and 34 at the high dose level of OSE-127 (i.e., 850 mg).

### 7.3 Packaging, Labelling and Storage

Study drug will be packaged and labeled by [redacted] according to all local legal and regulatory requirements. OSE-127 is filled at 2 mL extractable volume in 2R clear glass vials and individually packaged. The primary and secondary packaging together comply with the labelling requirements.

OSE-127 kits will be stored at depot and shipped at < -60°C on dry ice with 1 probe for temperature monitoring during transportation. Upon receipt at the local investigational site pharmacy, the study drug will be stored locally at 2°C- 8°C. Both storage temperatures and respective expiry dates will be mentioned on labels and will be managed by the Interactive Web Response System (IWRS) system.

### 7.4 Measures to Minimize Bias: Randomization and Blinding

#### *7.4.1 Randomization*

Patients will be randomized to placebo or OSE127 high dose (850 mg) in a 1:1 fashion. Treatment assignments will be obtained through an IWRS and disclosed to the investigational pharmacist or designee for dose preparation according to the Pharmacy Manual.

A stratification will be 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 will be randomized from the 109$^{th}$ patient to the last randomized patient.

Following process will be applied from patient's screening to study drug administration (Day 1):

- Screening visit: Inform Consent and Inclusion/Exclusion criteria
- Screening period: collection of all data related to Inclusion/Exclusion criteria will be performed by the site. Once all eligibility criteria are met, all data needed for randomization will be entered directly into the electronic case report form (eCRF) including confirmation by the investigator that all eligibility criteria are fulfilled and information about the stratification criteria. This information will be automatically

forwarded to the IWRS tool in order to proceed at randomization and for the IWRS system to allocate study drug treatment numbers and quantity of vials to the pharmacist in charge of preparing the drug before dispensation.

- Duration from the screening endoscopy to randomization and first treatment intake including study drug preparation and dispensation has to be a maximum of 14 days.

Because misallocations of study drug may have a detrimental effect on patients' safety and/or the study drug's efficacy and are a potential source of bias, utmost care should be taken to correctly dispense the study drugs as assigned.

### *7.4.2 Blinding*

During the Double-blind Phase, the study will be performed in a double-blind manner. All study drugs will be administered in identical bags and will be similar in color and appearance, thereby enabling double-blind conditions. An unblinded Pharmacist at each site will be responsible for reconstituting OSE-127 and providing OSE-127 high dose and placebo in similar bags.

The study blind should not be broken except in a medical emergency (where knowledge of the study drug received would affect the treatment of the emergency) or regulatory requirement (e.g., for SAEs or death [in Germany]). The blind must only be broken following discussion on a case-by-case basis, at the discretion of the Sponsor/Medical Monitor.

If the blind is broken, the date, time and reason must be recorded in the patient's eCRF, together with a note of a protocol violation, and any associated AE report.

The investigator will not be provided with randomization codes. The codes will be maintained within the IWRS which has the functionality to allow the investigator to break the blind for an individual patient. The investigator should notify the Sponsor/Medical Monitor prior to contacting IWRS and obtaining the identity of the treatment. All calls resulting in an unblinding event will be recorded and reported by the IWRS to the Medical Monitor and the Sponsor.

If an investigator, site personnel performing assessments, or patient, is unblinded, the patient must be withdrawn from the study and procedures accompanying withdrawal are to be performed. In cases where there are ethical reasons for the patient to remain in the study, the investigator must obtain specific approval from OSE-Immunotherapeutics for the patient to continue in the study.

## 7.5 Drug Accountability

The site Pharmacist is responsible for maintaining accurate study drug accountability records throughout the study.

The Sponsor's designated site monitor will periodically check the supplies of study drugs held by the pharmacist to ensure accountability and appropriate monitored storage conditions. Unused study drugs must be available for verification by the site monitor during on-site monitoring visits.

The site Pharmacist is responsible for destroying all unused study drug vials at the clinical site with the Sponsor's written permission (a certificate of destruction will be provided and filed in the Trial Master File). The site Pharmacist must verify that no remaining supplies are in the investigator's possession.

## 7.6 Compliance

OSE-127 and placebo will be administered by site staff.

Each dispensing of study drug will be documented in the eCRF.

## 7.7 Pre-study and Concomitant Therapy

For all randomized patients, pre-study therapies administered up to 6 weeks before the first dose of study drug must be recorded in the eCRF.

Any medication the patient takes other than the study drug is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage, and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

### *7.7.1 Medications Prior to Screening*

At screening, patients will be asked what medications they have taken during the last 8 weeks.

Those patients receiving the following medication(s) for UC at screening must have been treated for at least 4 weeks with these medication(s) and with no change in dose in the 2 weeks prior to screening. According to the investigator's opinion it must be expected that these medications will be maintained at the screening dose until W10:

- Oral amino-salicylates (mesalamine, sulfasalazine, olsalazine, balsalazide)
- Prednisone (doses ≤ 20 mg/day) or equivalent, budesonide MMX (doses ≤ 9 mg/day), or beclomethasone dipropionate (≤ 5 mg/day)

If these medications have just been discontinued recently, they must have been stopped for at least 2 weeks prior to the screening visit.

Those patients who have previously received azathioprine, 6-MP, or MTX must have discontinued therapy ≥ 4 weeks prior to the screening visit.

Those patients who have previously received anti-TNF-α therapy or vedolizumab or ustekinumab must have discontinued this therapy ≥ 8 weeks prior to the baseline endoscopy. Those who have previously received an investigational biologic agent must have discontinued this therapy ≥ 5 half-lives before the date of baseline endoscopy.

At each subsequent study visit, patients will be asked what concomitant medications they are currently taking.

### *7.7.2 Prohibited Medication*

The following treatments are prohibited during the study.

**Table 7.2: Prohibited Medications**

| Prohibited Medication Category | Prohibited Medications | Prohibited Period |
|---|---|---|
| Corticosteroids | Any corticosteroid with dose equivalent to > 20 mg/day of prednisone (Appendix A) | 2 weeks prior to screening until Week 10 is performed |

| Prohibited Medication Category | Prohibited Medications | Prohibited Period |
|---|---|---|
| | Budesonide MMX >9 mg/day<br>Betamethasone dipropionate >5 mg/day | |
| TNF-α antagonist | Infliximab, adalimumab, golimumab, certolizumab, or biosimilar agents | 8 weeks prior to the baseline endoscopy through the end of the study (including the OLE Phase) |
| Integrin antagonist | Vedolizumab natalizumab and etrolizumab or biosimilar agents | 8 weeks prior to the baseline endoscopy through the end of the study (including the OLE Phase) |
| Interleukin antagonist | Ustekinumab or other anti-IL-12/23 such as mirikizumab, rizankizumab, guselkumab… | 8 weeks prior to the baseline endoscopy through the end of the study (including the OLE Phase) |
| Rectal compounds | Rectal 5-ASA or rectal corticosteroids | 2 weeks prior to screening until Week 10 is performed |
| Antidiarrheal agents | Loperamide and diphenoxylate/atropine | 2 weeks prior to screening until Week 10 is performed |
| Immunosuppressive agents | Cyclosporine, thalidomide, tacrolimus, leflunomide, azathioprine, 6-MP, or MTX | 4 weeks prior to screening through the end of the study |
| JAK inhibitor | Any JAK inhibitor, | Any time before and through the end of the study |
| Investigational drugs | Any investigational agent | 8 weeks (or at least 5 half-lives) prior to the baseline endoscopy through the end of the study |
| Lymphocyte-depleting therapies | Alemtuzumab, alkylating agents such as cyclophosphamide or chlorambucil, total lymphoid irradiation, rituximab or any other lymphocyte B depleting therapy | Any time before and through the end of the study (including the OLE Phase) |
| Chronic nonsteroidal anti-inflammatory drugs (NSAIDs) [A] | Aspirin, ibuprofen, naproxen, diclofenac, indomethacin, COX-2 inhibitors | From screening until Week 10 is performed |
| Other biologic | Antibody based or other systemic biologics, e.g., denosumab, trastuzumab | May be allowed with the approval of the medical monitor |
| Vaccines | Any live/attenuated vaccine | 4 weeks prior to the screening until 12 weeks after the last dosing |

NSAID=non-steroidal anti-inflammatory drug; OLE=open-label extension

A Occasional use of NSAIDs for transient symptoms and daily use of aspirin up to 162.5 mg for the purpose of cardiovascular prophylaxis are permitted

### *7.8 Rescue Medication*

Not applicable.

### *7.9 Dose Modification*

Not applicable.

### 7.10 Treatment of Overdose

In case of an overdose of study drug, treatment should be suspended and the patient should receive appropriate medical treatment according to the clinical condition. Overdose should be immediately reported (see Section 8.3.1).

# 8 STUDY ASSESSMENTS AND PROCEDURES

## 8.1 Efficacy Assessments

Efficacy will be assessed by modified Mayo Score for Assessment of Ulcerative Colitis (including stool frequency, rectal bleeding, and mucosal appearance at endoscopy [endoscopic sub-score]), clinical response, PRO2 (stool frequency and rectal bleeding), endoscopy, histology (including the Nancy Histological Index Score, the Geboes score, and the RHI); measurements of CRP and fecal calprotectin, UCEIS, and UC-100 score.

### *8.1.1 Modified Mayo Score for Ulcerative Colitis*

The modified Mayo Score will be assessed at the time points outlined in the Schedules of Activities (Section 1.2).

The Mayo Score measures disease activity for UC (Schroeder 1987). The modified questionnaire has 3 domains (instead of the usual 4): 2 with questions answered by the patient (stool frequency and rectal bleeding) and 1 answered by an endoscopist (mucosal appearance at endoscopy). Each domain is graded from 0 to 3 (total score for modified Mayo Score ranges from 0 to 9). Higher scores indicate more disease activity.

**Table 8.1: Modified Mayo Score**

| 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

### *8.1.2 Endoscopy: Flexible Sigmoidoscopy*

A flexible proctosigmoidoscopy examination will be performed/scheduled at the screening visit and at Week 10 in order to establish the Mayo endoscopic sub-score.

As per Surveillance Guidelines for patients with UC (Eaden 2002, Harbord 2017), for patients who have had UC for >8 years and who have not had a colonoscopy procedure for cancer surveillance within 2 years prior to screening a full colonoscopy will be required at screening instead of flexible proctosigmoidoscopy patients to allow screening for dysplasia or to assess for the presence of adenomatous polyps. Any screening colonoscopy for malignancy should include surveillance biopsies consistent with local practice and will be analyzed locally. The investigator will have to ensure that any pre-cancerous polyp (confirmed by local histopathology) has been fully removed before the first administration of the study drug. In any case, at least 48 hours must elapse between a colonoscopy with polypectomy and the first administration of the study drug.

To ensure quality data and standardization, the same site endoscopist should perform the flexible sigmoidoscopies throughout the study wherever possible. Where this is not possible it should be clearly documented who performed each endoscopy procedure.

The endoscopic findings will be assessed at a central reading platform level by a central reader endoscopist who will review the videos of the endoscopies, blinded to the treatment and visit sequence of the recordings. Study videos will be scored separately using the Mayo Sub-score for all time points. The central reader's score at Screening and Week 10 will be entered directly into the eCRF.

Six biopsies from the area most affected by inflammation will be performed at screening and at Week 10. Two biopsies will be used to establish the Nancy score, the Geboes score and the RHI. These scores will be calculated by a central histopathologist (see Section 8.1.4). [redacted]

### *8.1.3 Mayo Clinical Sub-scores (Patient-reported Outcomes)*

Patients will record stool frequency and rectal bleeding on a daily basis using an electronic stool diary (ePRO). A sample of the question is provided in Appendix B.

#### *8.1.3.1 Patient Assessment of the 2 Clinical Sub-scores at Each Time Point*

Each patient serving as her/his own control in order to determine the degree of abnormality other/his stool frequency, at the screening visit she/he indicates the number of stools she/he had in a 24-hour period before the UC diagnosis or during a remission. The stool frequency sub-score will be determined based on the number of stools reported per 24 hours relative to the normal number of stools when not having a UC flare reported by the patient at the screening visit. A "stool" is defined as a trip to the toilet when the patient has either a bowel movement, or passes blood alone, blood and mucus, or mucus only.

The daily bleeding score represents the most severe category that describes the amount of blood for a given day. If a patient does not have a stool during a given day she/he has to enter a value of 'no blood seen' for that day.

#### *8.1.3.2 Collection of the 2 Clinical Sub-scores*

To ensure consistent diary recording, patients will be instructed to complete daily the electronic diary which will be transferred to the clinical database. At the beginning of screening period, the patients will be trained and will take their electronic diary at home to record data on their stool frequency and rectal bleeding. These values, when combined with the centrally read endoscopic assessment score, will determine the modified Mayo Score for eligibility. The ePRO must be

completed prior to the administration of any bowel preparation as part of the colonoscopy and/or flexible sigmoidoscopy procedure. In case it is completed after start of the bowel preparation, data from this day will be discarded and previous 3 days will be used for calculation.

All patient-facing materials, including the content of electronic daily diary, will be reviewed and approved by relevant Ethic Committees (ECs) if relevant for the country.

#### *8.1.3.3 Calculations for the 2 Clinical Sub-scores at Each Time Point*

The stool frequency and rectal bleeding data are based on the results from the most recent consecutive 3-day period within the 1 week before the visit. If a value is missing within the last 3 days, the next available value preceding the 3 days will be taken for calculation purposes. The average sub-score of the 3-day period (rounded to the nearest integer) will be used to determine the stool frequency and rectal bleeding sub-scores for the scheduled timepoints. Days on which the following conditions are met should be excluded from the calculation since these procedures could affect bowel frequency and/or blood content of the stool:

- The day(s) of the preparation for an endoscopy, if completed after preparation started
- The day of the endoscopy
- The 48 hours immediately following the endoscopy

Since antidiarrheals agents are prohibited from 2 weeks prior to screening and until Week 10, they are not supposed to interfere during the Induction phase of the trial. During the OLE Phase, the days on which such medications are taken should be excluded from the calculation of the 2 clinical sub-scores at the scheduled visits.

#### *8.1.3.4 Calculation of the Modified Mayo Score*

**For eligibility**

The modified Mayo score will be evaluated during the screening period, using patient diary entries collected in the ePRO device within the 3 days prior to randomization and the endoscopic sub-score established by the centralized reading platform on the flexible sigmoidoscopy conducted prior to randomization.

**For efficacy assessment at Week 10**

The modified Mayo Score will be evaluated as well at Week 10 using patient diary entries collected in the ePRO device within the 3 days prior to Week 10 visit and the endoscopic sub-score established by the centralized reading platform on the flexible sigmoidoscopy conducted at Week 10.

**For other time points**

The Clinical Mayo Score evaluating the Stool Frequency and the Rectal Bleeding at Week 0, 2, 6 will be calculated based on the 2 clinical sub-scores reported in the ePRO device by the patient.

Its evaluation throughout the OLE Phase before administration of the study drug and at the follow-up visits will be done by the investigator or his designee based on the 2 clinical sub-scores reported retroactively by the patient at the visits.

### *8.1.4 Histology*

Endoscopy to assess histology will be conducted at the time points outlined in the Schedules of Activities (Section 1.2).

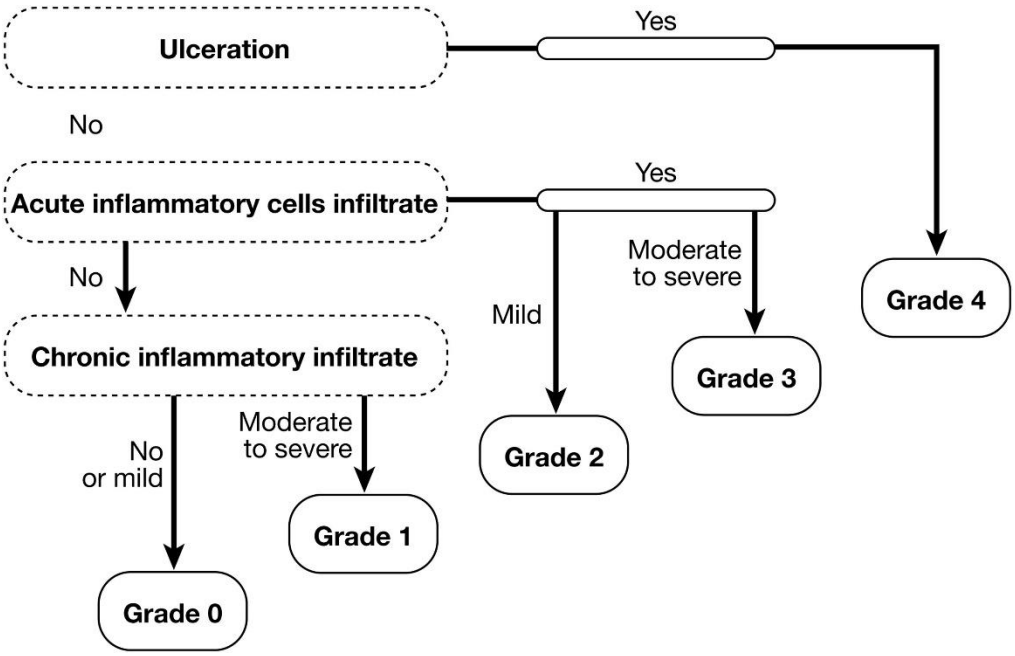
#### *8.1.4.1 Nancy Histological Index*

The Nancy Histological Index assesses 3 histological criteria:

1. The presence of mucosal ulceration
2. If ulceration is absent, assess the acute inflammatory cells infiltrate (defined as the presence of neutrophils or epithelial cells
3. If neutrophils are absent, assess chronic inflammatory infiltrate (defined as the presence of lymphocytes and/or plasmocytes and/or eosinophils (Marchal-Bressenot 2017).

Figure 1 presents the Nancy Histological Index scoring matrix.

**Figure 1: Nancy Histological Index**




Source: Marchal-Bressenot 2017

#### *8.1.4.2 Geboes Score*

The Geboes Score is a commonly used histologic index for UC and is composed of 7 categories (Geboes 2000). The categories have different grades to assess disease severity in UC as presented in Table 8.2. Higher scores indicate more severe disease.

## Table 8.2: Geboes Score

| Grade<br>Subgrade | Definition |
|---|---|
| Grade 0 | **Structural (architectural change)** |
| 0.0 | No abnormality |
| 0.1 | Mild abnormality |
| 0.2 | Mild or moderate diffuse or multifocal abnormalities |
| 0.3 | Severe diffuse or multifocal abnormalities |
| Grade 1 | **Chronic inflammatory infiltrate** |
| 1.0 | No increase |
| 1.1 | Mild but unequivocal increase |
| 1.2 | Moderate increase |
| 1.3 | Marked increase |
| Grade 2 | **Lamina propria neutrophils and eosinophils** |
| 2A | ***Eosinophils*** |
| 2A.0 | No increase |
| 2A.1 | Mild but unequivocal increase |
| 2A.2 | Moderate increase |
| 2A.3 | Marked increase |
| 2B | ***Neutrophils*** |
| 2B.0 | None |
| 2B.1 | Mild but unequivocal increase |
| 2B.2 | Moderate increase |
| 2B.3 | Marked increase |
| Grade 3 | **Neutrophils in epithelium** |
| 3.0 | None |
| 3.1 | < 5% crypts involved |
| 3.2 | < 50% crypts involved |
| 3.3 | > 50% crypts involved |
| Grade 4 | **Crypt destruction** |
| 4.0 | None |
| 4.1 | Probable – local excess of neutrophils in part of crypt |
| 4.2 | Probable – marked attenuation |
| 4.3 | Unequivocal crypt destruction |
| Grade 5 | **Erosion or ulceration** |
| 5.0 | No erosion, ulceration, or granulation tissue |

| Grade<br>Subgrade | Definition |
|---|---|
| 5.1 | Recovering epithelium + adjacent inflammation |
| 5.2 | Probable erosion – focally stripped |
| 5.3 | Unequivocal erosion |
| 5.4 | Ulcer or granulation tissue |

Source: Geboes 2000

### *8.1.4.3 Robarts Histopathology Index*

The RHI measures histological disease activity in UC in 4 areas: chronic inflammatory infiltrate, lamina propria neutrophils, neutrophils in epithelium, and erosion or ulceration (Mosli 2017). The RHI is presented in Table 8.3. Higher scores indicate more severe disease.

**Table 8.3: Robarts Histopathology Index**

| Descriptor | Score | Definition |
|---|---|---|
| Chronic inflammatory infiltrate | 0 | No increase |
| | 1 | Mild but unequivocal increase |
| | 2 | Moderate increase |
| | 3 | Marked increase |
| Lamina propria neutrophils | 0 | No increase |
| | 1 | Mild but unequivocal increase |
| | 2 | Moderate increase |
| | 3 | Marked increase |
| Neutrophils in epithelium | 0 | None |
| | 1 | < 5% crypts involved |
| | 2 | < 50% crypts involved |
| | 3 | > 50% crypts involved |
| Erosion or ulceration | 0 | No erosion, ulceration, or granulation tissue |
| | 1 | Recovering epithelium + adjacent inflammation |
| | 1 | Probably erosion – focally stripped |
| | 2 | Unequivocal erosion |
| | 3 | Ulcer or granulation tissue |

Source: Mosli 2017

### *8.1.5 C-reactive Protein and Fecal Calprotectin*

Blood and stool samples will be collected at the time points outlined in the Schedules of Activities (Section 1.2) to measure CRP (Vermeire 2006) and fecal calprotectin. (Schoepfer 2013).

**C-reactive protein**

C-reactive protein is considered as an objective criterion of inflammatory activity. CRP rises early after the onset of inflammation and rapidly decreases after resolution of the inflammation (Vermeire 2004). It is induced by interleukin-6, TNF-α and other proinflammatory cytokines that are produced within the intestinal lamina propria (Vermeire 2006).

A serum sample for CRP measurement will be collected at baseline, Week 10 and Week 22 and will be analyzed locally by the site.

Blood samples (4 mL) providing a minimum of 2 mL for CRP analysis will be collected into appropriately labeled SST tubes containing serum separator at protocol-specified times. The actual times may change but the number of samples will remain the same. All efforts will be made to obtain the samples at the exact nominal time relative to dosing.

**Fecal Calprotectin**

Fecal calprotectin is a specific biomarker for intestinal inflammation that can easily be analyzed in stool samples and correlates well with endoscopic inflammation in UC (Schoepfer 2013).

A stool sample for this measurement will be collected during the induction period at Week 0, 2, 6 and 10.

Fecal samples (~20 g) will be collected into appropriately labeled stool collection containers, at protocol specified times (see schedule of activities) and will be frozen at approximately -20°C until shipped to the central laboratory. Samples will be analyzed by a central laboratory using a validated analytical method.

**Stool sample for culture**

A stool sample will be obtained at screening in order to rule out serious infection and should include evaluation for *C. diff* unless a negative result of culture performed recently is available (i.e., as long as these tests were performed within 10 weeks prior to the first administration of the study drug). Additional testing (*e.g.*, ova and parasites assessments) may be performed at the investigator's clinical appreciation.

If stool sample is positive for *C. diff* toxin or for serious pathogens the patient should be treated and further rescreening is allowed (new test).

[redacted]

### *8.1.7 Ulcerative Colitis Endoscopic Index of Severity*

The UCEIS is an endoscopic scoring system which includes assessment of vascular pattern, bleeding, and ulcers (Travis SPL 2012). The UCEIS will be assessed at the time points outlined in the Schedules of Activities (Section 1.2). The index is described in Table 8.4. Higher score indicate more severe disease.

**Table 8.4: Ulcerative Colitis Endoscopic Index of Severity Descriptors and Definitions**

| 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

### *8.1.8 UC-100 Score*

The UC-100 is a composite score consisting of scores from the modified Mayo stool frequency sub-score, the modified Mayo endoscopic sub-score, and the RHI. 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). The UC-100 composite score will be assessed at the time points outlined in the Schedules of Activities (Section 1.2)

## 8.2 Efficacy Endpoints

### *8.2.1 Clinical Remission*

Clinical remission is 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.

### *8.2.2 Clinical Response*

Clinical response will be assessed at Week 10 and 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.

### *8.2.3 Endoscopic Remission / Endoscopic Response*

Endoscopic remission is defined as:

- An endoscopic Mayo sub-score =0

Endoscopic response/improvement is defined as:

- An endoscopic sub-score of Mayo ≤ 1 point
- Improvement of endoscopic activity based on the UCEIS

### *8.2.4 Histologic Remission / Histologic Response*

- Histologic remission is defined as a Nancy Histological Index score of 0
- Absence of acute histological inflammation is defined as a Nancy Histological Index score of ≤ 1
- Improvement in histologic activity is measured by the score of Geboes and the RHI

### *8.2.5 Mucosal Healing*

Mucosal healing (endoscopic remission and histological remission) is defined as:

- An endoscopic Mayo sub-score = 0
- A Nancy Histological Index score of 0

## 8.3 Safety Assessments

Safety will be assessed by AEs (including SAEs), clinical laboratory assessments, vital signs, ECGs, physical examination, and immunogenicity assessments.

### *8.3.1 Adverse Events*

#### *8.3.1.1 Definitions*

**Adverse Event**

Per ICH, an AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with

the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Planned or elective surgical or invasive procedures for pre-existing conditions that have not worsened are not AEs. However, any complication that occurs during a planned or elective surgery is an AE. Conditions leading to unplanned surgical procedures may be AEs.

**Treatment-emergent Adverse Event**

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. An AE that occurs from the time the patient receives his/her first dose of study drug until his/her last study visit will be considered a treatment-emergent AE (TEAE) regardless of the assessed relationship to the administration of the study drug.

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.

For the recording of pregnancy and relevant laboratory data, see Section 8.3.1.2.

**Serious Adverse Event**

An SAE is any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening
- Requires hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is another medically important condition

**Death:** The death of a patient enrolled in a clinical study is per se not an event, but an outcome. Any AE resulting in a fatal outcome must be fully documented and reported, including situation for which the death occurred after treatment end, and regardless of the causality relationship between the death and the study drug. The cause of the death is usually the AE. If the cause cannot be determined, the case will be considered an unexplained death.

**Life-threatening:** Any AE that places the patient, in the view of the initial reporter (investigator), at immediate risk of death from the AE as it occurred, i.e. it does not include an AE that, had it occurred in a more severe form, might have caused death.

**Disability:** A substantial disruption of a person's ability to conduct normal life functions.

**Important medical event:** an important medical event that is not immediately life-threatening or will result in death or hospitalization, but which may jeopardize the patient or may require medical intervention to prevent 1 of the outcomes listed above, should be reported as “serious” as well. Medical and scientific judgment should be exercised in deciding whether a case is

serious. “Occurring at any dose” does not imply that the patient is receiving study drug at the time of the event.

**New facts:** New information which might alter the current benefit-risk assessment of the study drug or the trial; modify the use of the study drug, the conduct of the study, or documents related to the trial; or suspend, modify or terminate the clinical trial.

**Adverse Event of Special Interest**

An adverse event of special interest (AESI) is 1 of scientific and medical interest or concern regarding the study drug for which recording rules, special documentation such as hospital records and/or adjudication committee could be appropriate. It may be a serious or non-serious AE that may require further investigation in order to characterize and understand.

AESIs include:

- Allergy (local at the site of infusion and general) (Note: Humans administered foreign proteins are at risk of developing allergic reactions, including anaphylaxis)
- Infections (Note: IL 7 receptor inhibition may induce immunomodulation, so patients should be monitored clinically for manifestations of infectious disease, and, if necessary, appropriately treated [e.g., with antibiotics])
- Lymphopenia $<500 \times 10^{6/}$L.

Up to now, there is no safety concern with OSE-127 (See Investigator’s Brochure).

**Event Requiring an Immediate Notification (ERIN)**

An event must be notified immediately (i.e., without delay and within 24 hours at the latest) to the sponsor if it is:

- An SAE,
- An AESI, as defined above
- An overdose of the study drug even if asymptomatic,
- A pregnancy.

**Severity of Adverse Event**

Refers to the extent to which an AE affects the patient’s daily activities. Severity will be categorized according to the following criteria:

| | |
|---|---|
| **Mild:** | No interference with the patient’s daily activities and does not require mandatory corrective/symptomatic treatment |
| **Moderate:** | Moderate interference with the patient’s daily activities and/or requires minimal medical intervention or corrective treatment required |
| **Severe:** | Major and unacceptable interference with the patient’s daily activities and requires mandatory corrective/symptomatic treatment, possible hospitalization. |

The term "severity" is used to describe the intensity of an event. This is not the same as "serious". Seriousness, not severity, serves as the guide for defining regulatory reporting obligations. The highest severity grade attained should be reported, for AEs with divergent severities.

**Causality of Adverse Event**

The causal relationship of an SAE to the study drug will be rated as follows by the investigator:

| | |
|---|---|
| **Unrelated** | Clearly and incontrovertibly due only to extraneous causes, and does not meet criteria listed under unlikely, possible or probable |
| **Unlikely** | Does not follow a reasonable temporal sequence from administration of the study drug or is most likely related to another etiology than the trial drug such as the patient's clinical state, environmental factors or other therapies |
| **Possible** | Follows a reasonable temporal sequence from administration of the study drug, and/or a causal relationship cannot be excluded and remains likely |
| **Probable** | Good reason (such as clear-cut temporal association with improvement on cessation of the study drug or reduction in dose, or reappears upon (accidental) re-challenge, or follows a known pattern of response to the study drug) and sufficient documentation to assume a causal relationship |
| **Definitely** | There is sufficient argument supporting that the drug is causally involved, and there is no other cause reasonable to explain the event. It is more than probable that the event occurred due to the product. |

For the purpose of defining regulatory reporting obligation of suspected unexpected serious adverse reactions (SUSARs), the sponsor will rate the causal relation according to the following binary criteria:

| | |
|---|---|
| **No reasonable possibility** | Unrelated or unlikely related events |
| **Reasonable possibility** | Possibly, probably, or definitely related events |

**Outcome of the Event**

- Recovered/resolved
- Recovered/resolved with sequelae
- Recovering/resolving
- Not recovered/not resolved

- Fatal

**Action Taken with Regard to the Event**

- Action taken on study drug: dose not changed, study drug interrupted (temporally suspended), study drug withdrawn (permanently discontinued), not applicable (e.g., event is not a TEAE)
- Other actions taken: no action taken, corrective treatment for AE given, patient withdrawn from study

**Definition of Overdose**

This refers to any intake or administration of a quantity of study drug which is above the maximum dose recommended in the study protocol , independently of the occurrence of any AE.

The quantity should be considered per administration regarding the maximum dose recommended in the study protocol (850 mg) as well as per interval between 2 administrations (e.g. less than 2 weeks during the OLE phase).

*8.3.1.2 Recording Adverse Events*

**Period: Patient Enrolment to the First Administration of Study Drug:** Non-treatment emergent AEs will be recorded from the time when the patient is enrolled into the study (date of signature of the informed consent) until first administration of study drug.

**Period: First Administration of Study Drug to Patient's Last Study Visit:** Thereafter, all AEs are TEAEs (see Definitions, Section 8.3.1.1) and will be recorded until the final follow-up visit has been performed.

**Period After Last Study Visit** (*i.e.;* after Early Termination Visit or after the Last Safety Follow-up Visit scheduled as per protocol 16 weeks after the last administration of the study drug): Any SAE occurring after the patient's last study visit but considered by the investigator to be related to the study drug will be recorded and reported through the SAE form.

If an AE (serious or not) started during the study but did not end before the final follow-up visit, the investigator should make a reasonable effort to establish the outcome and the end date. An **additional Safety Follow-up Visit** should be scheduled **up to 2 weeks** after the final examination for those patients who experienced **not resolved related AEs** or laboratory parameters showing **not normalized clinically relevant changes** or **SAEs**. The assessments measured will be determined by the investigator and all data will be documented in the eCRF.

If this is not possible, the outcome recorded at the final follow-up visit will be assumed to be the final outcome.

If an event stops and later restarts, all the occurrences must be reported. Adverse events assessed as related to study drug by the investigator and all SAEs must be followed up until resolution.

Signs/symptoms should be documented if a definite diagnosis cannot be established. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE and/or SAE and not the individual signs/symptoms. If a diagnosis is accompanied by unusual symptoms, the diagnosis itself and the symptoms have to be reported separately.

#### *8.3.1.3 Responsibilities of the Investigator*

Adverse event data should be obtained through observation of the patient, from any information volunteered by the patient, or through patient questioning. The general type of question asked could be similar to: “Do you have any health problems?” or “Have you had any health problems since your last clinic visit?”

Adverse events are to be documented/recorded accurately and completely on the AE pages of the respective eCRF and in the patient’s source data.

All non-treatment and treatment-emergent AEs will be recorded.

This is true even if the study drug was not administered according to the study protocol.

For conditions leading to unplanned surgical procedures the underlying condition, should be documented as an AE, but not the procedure.

**Reporting SAEs, AESIs, Overdose**

For AEs that are "serious" (SAEs) as well as for AESIs, Overdose and Pregnancy, additional separate documentation is required using the SAE Forms.

The following variables will be recorded on the SAE Form and on the eCRFs provided in accordance to the eCRF completion guidelines:

- Description of the event, including its duration (date of onset and resolution),
- Whether the event constitutes a SAE or not (if yes, see event seriousness criteria in Section 8.3.1.1)
- Any action taken *(e.g., changes to study treatment, other treatment given and follow up tests*
- Outcome of the event
- Investigator’s assessment of causality *(the relationship to the study treatment[s] and study procedures)*
- Severity.

For all SAEs where important or relevant information is missing, active follow-up should be undertaken.

The assumption of a causal relationship between the study drug/study conduct and the AE is irrelevant to the obligation to record AEs and notifying ERINs to the Sponsor.

**For withdrawals due to AEs** the eCRF page "Study completion / Study termination Form" and a copy of the eCRF AE page needs to be completed.

**Overdose and AESI** need to be reported to the Sponsor’s Drug Safety Department following the process for SAE reporting (same form, same timelines).

If additional information is required by the Sponsor’s Drug Safety Department, then as a representative of the Sponsor, [redacted] must be granted access to the medical records.

**After patient's last study visit:**

The investigator records and forwards to the Sponsor’s Drug Safety Department all SAEs that she or he becomes aware of and she or he considers related to the study drug.

#### *8.3.1.4 Notifying of Serious Adverse Events*

If any SAE occurs, the investigator will take appropriate action immediately and will strive to identify the causes of the events.

SAEs will be notified by the Investigator to [redacted], acting on behalf of the Sponsor, as soon as possible, i.e. within 24 hours from first knowledge by e-mail or fax to:

[redacted]

[redacted] acknowledges the receipt of the SAE information by email to the investigational site within 1 working day. In the absence of email acknowledging the receipt or in case of issue in sending the fax or email, the investigator shall contact [redacted] by any means for ensuring the receipt of SAE information at the earliest opportunity.

Any follow-up information will be reported to [redacted] as soon as it becomes known, with the same process and timelines as described here above for initial reports. Photocopies of results, consultant report(s), a summary of the outcome of the reaction and the Investigator's opinion of study drug relationship to the SAE will accompany the SAE form if and when available, after pseudonymization of personal data. Prior to forwarding any personal data for safety reporting, the documents need to be coded in a way that keeps the patient's identity confidential (e.g., by using the patient's identification code, randomization number, etc.).The Sponsor will also perform an evaluation of the seriousness, causality and expectedness of all SAEs. All SAEs judged by either the Investigator or the Sponsor as having a reasonable suspected causal relationship to the study drug (i.e., probably or possibly related) will qualify as serious adverse reactions. If the Sponsor disagrees with the Investigator’s causality assessment, both the opinion of the Investigator and the Sponsor are provided with the report.

All reported SAEs will be included in the Sponsor’s safety database.

SUSARs are AEs which have a reasonable possibility to be related to the study drug and are both unexpected (i.e., the nature or severity is not expected from the information provided in the investigator’s Brochure) and serious. SUSARs are subject to expedited reporting to the Competent Authorities and Ethics Committees.

SUSARs will be notified to the Competent Authorities and to the relevant ECs by [redacted] immediately (ANSM)/within 7 (for fatal and life-threatening SUSARs) or 15 days (all other SUSARs), with follow-up information in the following 8 days. Expedited reporting will be performed taking into account local reporting regulation and specificities. If required, the investigator is responsible for informing local IECs/IRBs of safety reports in compliance with applicable regulatory requirements. Copies of all correspondence relating to reporting of any safety reports to the IEC/IRB should be maintained in the investigator site file (ISF) / Regulatory Binder.

Annual safety reporting to the Competent Authorities and the Ethics Committees will be in agreement with ICH guideline E2F “Note for guidance on development safety update reports (DSUR)”.

In addition, any other safety issue, such as any new fact including safety information which may alter the current benefit–risk assessment of the study drug or the concerned clinical trial, which may lead to changes in the use of the study drug, in the conduct of the clinical trial, or of its related documents including the study protocol, or which may lead to suspend or terminate this clinical trial or similar researches, which may alter the current benefit–risk assessment of the study drug will be reported by the Sponsor (or delegate) on an expedited basis to Health Authorities, Ethics Committees and the Investigators.

**Following-up AEs / SAEs**

At the patient's last study visit (including the Early Termination Visit), a Safety Follow-up Visit should be scheduled up to 2 weeks after the final examination only for those patients who experienced not resolved related AEs or laboratory parameters showing not normalized clinically relevant changes or SAEs. The assessments measured will be determined by the investigator. All data must be documented in the eCRF.

#### *8.3.1.5 Laboratory Values*

Laboratory values are also defined as AEs if they are outside the normal and if, in the opinion of the investigator, they represent a clinically relevant change versus pre-treatment values.

If abnormal laboratory values are signs of an AE (e.g., an infection) that has already been recorded, the respective abnormal laboratory value does not constitute a separate AE.

Wherever reasonable the reporting investigator will use the clinical term rather than the laboratory term (e.g., anemia versus low Hgb value).

### *8.3.2 Pregnancy*

Occurrence of pregnancy in a patient (or partner of a male patient) during a clinical study must be recorded.

Each pregnancy that starts during the study must be reported by the investigator to the Sponsor's Drug Safety Department within 24 hours of the investigator's knowledge of the pregnancy by using the SAE Form. The Sponsor's Drug Safety Department will then initiate a specific follow-up of the pregnancy and provide the site with Pregnancy Form, Any adverse outcome of the pregnancy must be recorded and notified on the pregnancy Form or SAE Form if this meets SAE reporting criteria. The investigator should make any reasonable effort to follow any pregnancy until birth of the child.

### *8.3.3 Laboratory Parameters*

The tests listed in Table 8.5 will be conducted on samples collected and analyzed by standard laboratory procedures at the time points outlined in the Schedules of Activities (Section 1.2). Tests that are not done must be reported as such on the eCRFs.

**Table 8.5: Laboratory Parameters**

| | | |
|---|---|---|
| **Hematology (local laboratory)** | | |
| Hemoglobin<br>Hematocrit<br>Mean corpuscular hemoglobin (MCH)<br>Mean corpuscular hemoglobin concentration (MCHC)<br>Mean corpuscular volume (MCV) | Erythrocytes<br>Thrombocytes<br>Leukocytes | Differential white blood cell count including neutrophils, lymphocytes, monocytes, eosinophils, basophils. |
| **Chemistry (local laboratory)** | | |
| Creatinine<br>Total bilirubin (direct and indirect if total bilirubin values are above 1.5 times the upper limit of normal)<br>C-reactive protein | Alkaline phosphatase<br>Aspartate aminotransferase<br>Alanine aminotransferase<br>Gamma glutamyl transpeptidase<br>Glucose | Total protein<br>Albumin<br>Sodium<br>Potassium<br>Chloride<br>Cholesterol (total, HDL, LDL)<br>Triglycerides<br>Lactate dehydrogenase |
| **Urine (local laboratory)** | | |
| Glucose<br>Nitrate<br>pH | Hemoglobin or RBC<br>Leukocytes<br>Specific gravity | Protein<br>Ketones |
| **Other Tests**<br>1. At screening, HBV, HCV and HIV infection should be excluded via local laboratory. Mandatory tests include:<br>• HBsAg for HBV;<br>• Anti-HCV antibodies for HCV;<br>• Anti-HIV antibodies.<br>In case of positive HBsAg and/or anti-HCV, patient can be excluded from further screening activities, or confirmatory tests can be arranged (anti-HBs, anti-HBc, HBV DNA, HCV RNA) and decision on patient's eligibility will be made based on results of confirmatory tests and discussion with Medical Monitor. In case of positive anti-HIV, patient will be excluded from screening.<br>2. Stool collection to test for bowel pathogens (local laboratory)<br>3. Stool collection to test for fecal calprotectin [redacted] (central laboratory)<br>4. Pregnancy test in women of childbearing potential (local laboratory) | | |

DNA=deoxyribonucleic acid; HBsAg=hepatitis B surface antigen; HBV=hepatitis B virus; HCV=hepatitis C virus; HDL = high-density lipoprotein; HIV=human immunodeficiency virus; LDL = low-density lipoprotein; RNA=ribonucleic acid

### *8.3.4 Vital Signs*

Vital signs will be measured and recorded at the time points outlined in the Schedules of Activities (Section 1.2). The following measurements must be performed: systolic/diastolic

blood pressure, heart rate, respiration rate and temperature collected as per usual practice. Vital signs will be measured after the patient has been in the supine position for at least 5 minutes. All measurements will be recorded on the vital signs eCRF. Abnormal test results may be repeated at the discretion of the investigator and must be reported on the corresponding eCRF.

When vital signs, ECGs, and/or blood sample collection occur at the same time, vital signs should be performed before ECGs and/or blood sample collection.

#### *8.3.5 Electrocardiograms*

During the study, 12-lead ECGs will be performed at the time points outlined in the Schedules of Activities (Section 1.2).

The patient must be in a supine position in a rested and calm state for at least 5 minutes before ECG assessment is conducted. If the patient is unable to be in the supine position, the patient should be in the most recumbent position possible. All ECGs should be performed in a standardized method, in triplicate, and approximately 30 seconds apart, prior to blood draws or other invasive procedures. Each ECG must include the following measurements: QRS, QT, corrected QT, RR, and PR intervals.

The investigator or designated site physician will review and sign all ECGs. Results must be summarized in writing and classified as normal; abnormal; abnormal, clinically relevant; or abnormal, not clinically relevant. Once signed, the original ECG tracing will be retained with the patient's source documents. At the request of the Sponsor, a copy of the original ECG will be made available.

#### *8.3.6 Physical Examinations*

The investigator or qualified designee will perform a complete physical examination (genitourinary examination not required) at screening and then symptom-driven physical examinations at the time points outlined in the Schedules of Activities (Section 1.2). Pre-dose abnormal findings will be reported on the medical history eCRF. Any adverse change from the baseline physical examination (day 0 examination) will be documented on the AE eCRF. Height will be measured at screening only.

A full physical examination will include inspection of general appearance, eyes, ears, nose, throat, neck (including thyroid), lungs/thorax, heart/cardiovascular system, abdomen, nervous system, musculoskeletal system, extremities, skin and mucosae, lymph nodes and others, if applicable.

#### *8.3.7 Additional Safety Assessments*

##### *8.3.7.1 Tests for Tuberculosis*

If a patient does not have a chest x-ray or a negative quantiFERON TB Gold In Tube test within the last 3 months prior to screening, 1 or the other will be done according to local guidelines and standard of care to exclude active or latent TB infection.

### 8.4 Other Parameters

Laboratory analyses for PK, RO and ADAs data will be carried out by a bioanalytical laboratory under the responsibility of the Sponsor, following the principles of GLP regulations of the OECD and using validated bioanalytical methods. Validation data and details of the analytical procedure will be gathered in an analytical report that will be attached to or referred to in the

Clinical Study Report upon completion of the study. The randomization list will be sent to the bioanalytical center in order to select the samples to be analyzed.

### *8.4.1 PK and Receptor Occupancy*

Blood will be drawn in a subset of 20 patients at the time points outlined in the Schedule of Activities (Section 1.2) for PK and RO analysis (3 mL/time-point and 1 mL/time-point respectively for PK and RO).

Individual patient serum OSE-127 concentrations will be used to derive and calculate PK parameters as appropriate: $C_{max}$ and time to $C_{max}$), trough serum concentration observed at the end of the dosing interval ($C_{trough}$), elimination half-life ($t_{½}$). For each PK and RO sample, the theoretical and exact dates and times at which the study drug is lastly administered should be reported in the eCRF in addition to the exact dates and times of serum sample collection.

### *8.4.2 Anti-drug Antibodies*

Blood (3 mL/time-point) will be drawn in all patients at the time points outlined in the Schedule of Activities (Section 1.2) in order to determine the incidence of anti-OSE-127 antibodies detection.

[redacted]

# 9 STUDY CONDUCT

## 9.1 Observations by Visit – Double-blind Phase

### *9.1.1 Screening Visit and Screening Period (Maximum 8 Weeks Prior to Day 1/Week 0)*

The following procedures are to be completed at this visit **ensuring that the screening endoscopy is performed within 2 weeks before the Week 0/Baseline visit.**

- Provide informed consent and request Inform Consent Form (ICF) signature
- Record demographic data including sex and age
- Record medical/surgical history (including any risk factors)
- Record previous and current medications
- Verify eligibility (inclusion/exclusion criteria)
- Complete full physical examination (including height and weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Perform 12-lead ECG
- If a patient does not have a chest x-ray or a negative quantiFERON TB Gold In Tube test within the last 3 months prior to screening (to exclude active or latent TB infection) 1 or the other will be done according to local guidelines and standard of care
- Viral testing: HBV, HCV and HIV infection should be excluded via local laboratory. Mandatory tests include:
  - Hepatitis B surface antigen (HBsAg) for HBV
  - Anti-HCV antibodies for HCV
  - Anti-HIV antibodies
    In case of positive HBsAg and/or anti-HCV, the patient can be excluded from further screening activities, or confirmatory tests can be arranged (anti-HBs, anti-HBc, HBV DNA, HCV RNA) and decision on patient's eligibility will be made based on results of confirmatory tests and discussion with Medical Monitor. In case of positive anti-HIV, patient will be excluded from screening.
- Draw blood for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Collect stool for enteric pathogens culture and *C. diff* toxin assay in the absence of available negative results from such an examination performed recently (i.e., as long as these tests were performed within 10 weeks prior to the first administration of the study drug). Additional tests (e.g., ova + parasitic assessments) may be performed at the investigator's clinical appreciation. If stool sample is positive for *C. diff* toxin or for serious pathogens the patient should be treated and further rescreening is allowed (new test)

- Collect the 2 clinical Mayo Sub-scores -rectal bleeding and frequency of stools- provided by the patient and **only if both are ≥1** (otherwise the patient is not eligible), perform or schedule an endoscopy for the following day(s) after bowel preparation
- Send the videos of the endoscopy to the Central Reading Platform
- Send the biopsy samples to local histopathology laboratory in order to get them included in formalin fixed paraffin embedded (FFPE) sample and, only if applicable according to inclusion criterion 5, in order to get histopathology confirmation of UC
- If a full colonoscopy has been performed according to inclusion criterion 9, send to local histopathology laboratory the biopsies performed for cancer surveillance in order to get histopathology analyses
- Distribute electronic diary to the patients and provide training on this tool for a daily collection of the 2 clinical Mayo sub-scores

### *9.1.2 Randomization*

- Calculate the modified Mayo Score based on the endoscopic sub-score provided in the eCRF by the Central Reading Platform and the 2 clinical sub-scores reported in the ePRO by the patient within the 3 days preceding the randomization (see Section 8.1.3.4); if modified Mayo Score is between 4 and 9, inclusive, indicate the 2 following variables for stratification: previous exposure to biologics (yes/no) and concomitant use of steroids (yes/no)

### *9.1.3 Week 0 (Visit 1; Day 1)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Check stool e-diary
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology, chemistry, serum CRP, and ADA tests
- Collect urine for urinalysis
- Collect stool
- Draw blood for PK pre- and post-infusion (subset of 20 patients)
- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

### *9.1.4 Week 2 (Visit 2; Day 14 ± 4)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Check stool e-diary
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Collect stool
- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

### *9.1.5 Week 6 (Visit 3; Day 42 ± 4)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Check stool e-diary
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology, chemistry, and ADA tests
- Collect urine for urinalysis
- Collect stool
- Draw blood for PK pre- and post-infusion (subset of 20 patients)
- Draw sample for RO pre-infusion (subset of 20 patients)
- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

### *9.1.6 Week 10 (Visit 4; Day 70 ± 4)*

The following procedures are to be completed at this visit:

- Complete full physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Perform 12-lead ECG
- Draw blood for serum pregnancy test in women of childbearing potential
- Draw blood for hematology, chemistry, serum CRP, and ADA tests
- Collect urine for urinalysis
- Collect stool
- Draw blood for PK pre- and post-infusion (subset of 20 patients)
- Draw sample for RO pre-infusion (subset of 20 patients)
- Perform endoscopy (in any case, even if the patient is going to enter the OLE, the endoscopy must be performed **before** the administration of the study drug at W10)
- Send the biopsy samples to local histopathology laboratory in order to get them included in FFPE sample
- Send the videos of the endoscopy to the Central Reading Platform
- Review concomitant medications
- Record AEs
- Check stool e-diary and retrieve the ePRO from patient if appropriate

### *9.1.7 Week 22 (Follow-up Visit for Patients not Entering Open-label Extension; Day 154 ± 4;)*

The following procedures are to be completed at this visit:

- Complete full physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Perform 12-lead ECG
- Review concomitant medications
- Record AEs
- Draw blood for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests, serum CRP
- Collect urine for urinalysis

## 9.2 Observations by Visit – Open-label Extension

### *9.2.1 Week 10 (OLE Part of the Visit 4; Day 70 ± 4)*

The following procedures have already been completed at this Visit 4 for all the patients, whether they are entering or not into the OLE:

- Complete full physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Perform endoscopy and send the biopsy samples to central lab

The following procedures have to be completed at this visit only for those patients who are entering into the Open-Label Extension (they can be performed within the few days following the W10 assessment visit if needed on a logistical standpoint but in any case **must not** be done before the W10 endoscopy):

- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

### *9.2.2 Week 14 (Visit 5; Day 98 ± 4 ; in any case, the date for V5 dispensation visit has to be calculated as plus 4 weeks (±4 days) from V4 dispensation visit)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

### *9.2.3 Week 18 (Visit 6; Day 126 ± 4. in any case, the date for V6 dispensation visit has to be calculated as plus 4 weeks (±4 days) from V5 dispensation visit)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

### *9.2.4 Week 22 (Visit 7; Day 154 ± 4. in any case, the date for V7 dispensation visit has to be calculated as plus 4 weeks (±4 days) from V6 dispensation visit)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

#### *9.2.5 Week 26 (Visit 8; Day 182 ± 4; in any case, the date for V8 dispensation visit has to be calculated as plus 4 weeks (±4 days) from V7 dispensation visit)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

#### *9.2.6 Week 30 (Visit 9; Day 210 ± 4; in any case, the date for V9 dispensation visit has to be calculated as plus 4 weeks (±4 days) from V8 dispensation visit)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Administer study drug
- Record vital signs every 30 minutes ± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

#### *9.2.7 Week 34 (Visit 10; Day 240 ± 4 ; in any case, the date for V10 dispensation visit has to be calculated as plus 4 weeks (±4 days) from V9 dispensation visit)*

The following procedures are to be completed at this visit:

- Symptom-directed physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Perform 12-lead ECG
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis
- Administer study drug
- Record vital signs every 30 minutes± 10 minutes during the infusion and during the 2-hour post-infusion surveillance period

#### *9.2.8 Week 38 (Visit 11; First Safety Follow-up Visit for Patients Who Participated to the OLE Phase; Day 266 ± 4; the date for this visit has to be calculated as plus 4 weeks (±4 days) from V10 dispensation visit)*

The following procedures are to be completed at this visit:

- Complete full physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Perform 12-lead ECG
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis

#### *9.2.9 Week 50 (Visit 12; Last Safety Follow-up Visit for Patients Who Participated to the OLE Phase; Day 350 ± 4; the date for this visit has to be calculated as plus 4 weeks (±4 days) from V11 visit)*

The following procedures are to be completed at this visit:

- Complete full physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)

- Perform 12-lead ECG
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis

### 9.3 Early Termination Visit

The following procedures are to be completed at this visit:

- Complete full physical examination (including weight)
- Measure and record vital signs (blood pressure, heart rate, respiration rate, and temperature)
- Perform 12-lead ECG
- Review concomitant medications
- Record AEs
- Collect the 2 PROs Mayo clinical sub-scores
- Draw blood or collect urine for serum pregnancy test in women of childbearing potential
- Draw blood for hematology and chemistry tests
- Collect urine for urinalysis

# 10 STATISTICAL METHODS

## 10.1 Disposition of Patients

The following patient data will be tabulated:

- The number of patients in each analysis set
- Dates of first signed informed consent, last visit and last contact (overall only)
- The number and percentage of patients who completed or discontinued the study during the Induction phase as documented on the study termination page and the number and percentage of patients for each Induction discontinuation reason
- The number and percentage of patients who entered, completed or discontinued the study during the OLE phase and the number and percentage of patients for each OLE discontinuation reason

All information collected in the eCRF regarding allocation, code breaking, study discontinuation and information on Induction and OLE phases will be listed.

## 10.2 Protocol Deviations

Protocol deviations will be categorized into minor and major deviations and validated by a Blinded Data Review Committee (BDRC) before database lock. The number and percentage of patients with major protocol deviations will be tabulated, overall and per class of deviation.

All available information concerning major protocol deviations, violations on eligibility criteria and patients not treated will be listed.

## 10.3 Analysis Populations

There will be 4 patient populations in this study for analyses: , the Full Analysis Set (FAS), the per-protocol population, the safety population, and the PK/RO population.

**The Full Analysis Set (FAS)**

All randomized patients with moderate to severe active ulcerative colitis who have failed or are intolerant to previous treatment and who received any amount of blinded study drug.

**Per-protocol 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 outcome significantly. All decisions to exclude patients for the per-protocol population dataset will be made prior to the unblinding of the study. Analyses using the per-protocol population may be provided as a sensitivity analysis.

**Safety Population**

The safety population is defined as all patients who received any amount of study drug.

**Population for PK/RO Analyses**

The PK/RO evaluable population is defined as those patients who are part of the sub-study on PK/RO, who receive at least 1 dose of study drug and have sufficient blood sampling to allow for PK/Receptor Occupancy evaluation.

## 10.4 General Considerations

A formal Statistical Analysis Plan (SAP) will be developed and finalized by the sponsor, prior to unblinding of treatment assignment. This plan will define the population for analysis, outline all data handling conventions, and specify all statistical methods to be used for safety and efficacy data analysis. Deviations from the statistical analyses outlined in this protocol will be indicated in this plan; any further modifications will be noted in the final clinical study report.

Summary statistics will be presented for continuous variables, by way of n, n missing, mean, standard deviation (SD), median, minimum and maximum and by way of group n missing frequencies and percentages for categories of categorical variables. Percentages will be calculated using the total patients per group.

Descriptive statistics for parameters of interest will be provided by treatment group and overall. All results will be presented to 1 decimal place

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.

From a statistical point of view, this study will not be comparative between the 2 doses of OSE127, so comparison of confidence intervals (CIs) between the 2 doses will be exploratory.

If patients have Mayo score data at baseline but missing for Week 10, then data will be imputed using a multiple imputation approach (last-observation-carried-forward (LOCF) will be performed as a sensitivity analysis). Further details on any sensitivity analyses (multiple imputation, tipping point analysis, etc.) and data handling details regarding issues such as missing data will be discussed in the SAP.

## 10.5 Demographics, Baseline Characteristics and Concomitant Medications

Demographic analyses will be carried out using the FAS population as main analysis population.

Demographic and baseline characteristics will be summarized using frequency distributions and summary statistics based on the primary efficacy data set for each treatment group and for all patients combined.

## 10.6 Treatment Compliance

For each study drug administration, the start and end date (times) and the total dose will be recorded. The total volume of OSE-127 or placebo administered in mL will be recorded at each visit.

Exposure to study drug will be summarized by group for the safety population as described below. The cumulative dose, dose intensity and treatment duration will be presented.

The total number of infusions received will be summarized both by descriptive statistics and by presenting the number and percentage of patients in each category.

Study drug administration details will be summarized by descriptive statistics and will include, percentage of infusion delayed and reason for delay, average number of days delayed, infusion duration and percentage of infusion with duration not respected or stopped temporarily.

- Cumulative dose (mg) = sum of all doses received during induction period will be calculated with the following data available during cycle.
- Dose intensity is defined as:
  - total actual doses taken (=cumulative dose) / total planned doses * 100%
  with total planned doses = prescribed doses (at randomization)
- Relative Duration (%) = [ Duration (week) / Planned Duration] * 100
- Planned duration is 6 weeks for induction period.

## 10.7 Efficacy Analyses

Efficacy analyses will be carried out using the FASpopulation as main analysis population. Efficacy analysis will be also repeated for per protocol populations.

Primary endpoint analysis:

The following statistical hypotheses are considered :

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

The treatment difference will be assessed with an ANCOVA model which includes terms to adjust for the baseline Modified Mayo Score value, stratification factors, region, 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. Multiple imputation will be described in the SAP.

Mayo Scores Analyses:

Modified Mayo score will be listed and summarized as continuous data. Changes from baseline will be summarized across time for each dose. Week 10 changes from baseline will be plotted and summarized by dose to visually assess dose-related changes and analyzed as primary analysis. Thus, changes from baseline will be analyzed using an analysis of covariance model with treatment, baseline score, stratification criteria at randomization as factors and region. Estimates of the treatment differences in response function and associated 95% CIs for OSE-127 high dose (850 mg) against placebo will be calculated. Should any of the assumptions underlying the model fail to hold, an alternative analysis will be used and fully documented. Longitudinal mixed effects modeling approach will be considered when appropriate. This model will include additional terms for week and a treatment-by-week interaction. Patient effects will be considered random in this model. Due to likely small numbers, center effects will not be fitted in the model.

**Modified Mayo Sub-Scores Analyses**

The 3 components or sub-scores of the Modified Mayo Score are:

- Stool frequency (0-3)
- Rectal bleeding (0-3)

- Findings on endoscopy (0-3)

These will be listed and summarized as ordered categorical data. Changes from baseline will be summarized in frequency tables to assess improvement, no change or worsening of disease as measured by the 3 sub-scores. The data will be examined and, if appropriate, these categorical response variables analyzed using a proportional odds model or alternative logistic regression approach.

**Clinical Remission or Clinical Response Analysis**

Responders will be analyzed using a logistic model with treatment, baseline score and 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% CIs for OSE-127 High Dose (850 mg) against placebo will be calculated from the model. These results will be back-transformed to give point estimates of the difference in proportions and associated 95% CIs.

**Patient-reported Outcomes (PRO2: Rectal Bleeding and Soft Stools)**

The diary records daily stool counts, and rectal bleeding scores used in the calculation of efficacy endpoints. This data will be listed only. Further presentation or analysis of this daily data may be made. Any additional analyses will be described and fully documented.

**Endoscopic Improvement / Remission - Histologic Improvement/ Remission - Mucosal Healing - 50% Reduction Versus Baseline of Fecal Calprotectin**

Same logistic model will be used for these responders' criteria.

**Change from Baseline in CRP and Fecal Calprotectin**

The CRP and fecal calprotectin will be presented on a log-transformed scale. Serum concentrations of CRP will be listed and summarized by time post-dose for each dose. Mean changes from baseline will be plotted and summarized across time. Week 10 changes from baseline will be plotted and summarized by dose to visually assess dose-related changes.

**Pharmacokinetic Variables**

The PK analysis set will be used for PK analyses. All the PK data will be collected for population PK/PD analysis. The population PK/PD analysis will be performed with the support of a separate PK data analysis plan.

**Pharmacodynamic Data**

Summary statistics will be presented by dose and day for measurements of RO as well as for measured PD biomarkers.

**Pharmacokinetic/Pharmacodynamic Relation Analysis**

Exploratory PK/PD relationship for CD127 RO and other relevant PD markers will be performed by graphical presentation of individual PK concentration/parameters versus PD measurements.

**Immunogenicity**

Systemic presence (serum) of ADA and its influence on PK and PD will be evaluated.

## 10.8 Safety Analyses

The safety analysis will be carried out on the safety population by treatment group on the Week 0 to Week 10 period for all patients, on the Week 0 to Week 24 period for patients who do not participate to the OLE phase and on the Week 0 to Week 50 period for patients who will take part in the OLE phase. Safety analyses will be descriptive in nature.

**Adverse Events**

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). All AEs with an onset between start of treatment and end of the residual effect period (REP), a period of 16 weeks after the last dose of trial medication, will be assigned to the on-treatment period for evaluation (i.e. treatment-emergent).

Statistical analysis and reporting of AEs will concentrate on TEAEs, i.e., all AEs occurring between start of treatment and end of the residual effect period. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'.

Summary of AEs (number and % of patients) and summarized by System Organ Class (SOC) and Preferred Term (PTerm) will be tabulated by group and overall for patients with:

- At least 1 TEAE
- At least 1 related TEAE all grades
- At least 1 AESI all grades TEAE
- At least 1 serious TEAE
- At least 1 serious TEAE related to the study treatment
- At least 1 severe TEAE
- At least 1 severe TEAE related to the study treatment
- TEAE leading to treatment discontinuation
- Related TEAE leading to treatment discontinuation
- TEAE leading to death
- Related TEAE leading to death

Adverse events will be summarized by presenting the number and percentage of patients having at least 1 AE, overall and by treatment group. Data will be presented by SOC and PTerm and maximum Common Terminology Criteria for Adverse Events (CTCAE) grade. A patient with multiple occurrences of an AE will be counted only once in the AE category. A patient with multiple grades for an AE will be summarized under the maximum CTCAE grade recorded for the event.

Similar analyses will be done for ERINs.

Written narratives will be produced for all SAEs and AESIs.

Adverse events/SAEs occurring after signing the ICF but before starting study treatment, including those observed in patients included but never treated with the study drug, will be listed separately from those occurring after treatment start.

**Laboratory Abnormalities**

The summaries will include all laboratory assessments collected no later than 16 weeks after treatment discontinuation. 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 and will have a severity grade calculated using appropriate common terminology criteria for AEs (CTCAE, version 5.0). A listing of laboratory values will be provided by laboratory parameter, by patient. A separate listing will display notable laboratory abnormalities (at least a grade 2 and shift from baseline of at least 1 grade). The frequency of these notable laboratory abnormalities will be displayed by parameter. The shift tables using CTCAE grades to compare baseline to the worst post-baseline value will be produced for all relevant safety measures as described in the SAP. Note that for parameters with 2 directions abnormalities (hypo/hyper), 2 tables will be presented.

**Other Safety Data**

Other safety data (e.g., vital signs, ECG) will be listed, notable values will be flagged, and any other information collected will be listed as appropriate. Any statistical procedures performed in order to explore the data will be used only to highlight any interesting comparisons that may warrant further consideration.

### 10.9 Interim Analyses

**Step 1: Conditional/Predictive Power Selection**

The primary objective of Step 1 is to evaluate the primary efficacy endpoint (absolute variation of Modified Mayo score between baseline and Week 10) and to decide if it will be considered uninteresting to pursue any further investigation. Our goal is to calculate the minimum sample size required under the caveat that the study would be terminated early if there was 95% confidence that the primary endpoint was less than the target value of interest (-1.5 difference for this study).

Interim futility analysis will be performed after 50 patients (total) have completed the Induction Phase; 33% of the 150 planned patients.

After testing the drug on n=50 patients in the first stage (Induction Phase), conditional/predictive power considering observed primary endpoint and an expected sample size of 50 patients per group will be calculated for each dose.

The choice of the dose for the Step 2 will be done depending of following information:

- Overall safety of each dose and risk-benefit analysis
- Conditional and predictive power

If the conditional power is <20% and the predictive power is <20% for both doses, the study will be discontinued for futility after 50 patients.

### Step 2: Pursuit of the Trial for Each Dose

If the trial goes on to the second stage (next inclusions of the remaining patients in the Induction Phase), a maximum of 50 patients will be studied in each group.

## 10.10 Determination of Sample Size

Sample size calculation describes only the comparison between OSE127 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 having had 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 (40% out of the 104 patients that will constitute the 2 remaining arms for final analysis).

## 10.11 Subgroups Analysis

All the analyses described from Section 10.5 to Section 10.8 will be repeated in the specific population of patients who had previously received biologics treatment.

## 10.12 Multiplicity

To further maintain the overall Type I error rate at 5%, the key secondary assessment will also be performed sequentially. The first key secondary endpoint (Clinical Remission) will be tested only if the primary comparison is significant, and the next key secondary endpoint will be tested only if the previous key secondary endpoint is significant. The order of the key secondary objectives will be specified in the SAP before database lock.

# 11 DATA MANAGEMENT

## 11.1 Data Collection

### *11.1.1 Electronic Case Report Form*

An electronic data capture (EDC) system will be used for the study. An ePRO will be developed as a specific module for patient questionnaires.

The eCRF will be developed and validated in order to be compliant with the requirements of ICH E6, Guideline for GCP. The eCRF will be provided by [redacted] and will be used to collect the data required by the study protocol. Data will be data entered by the site staff.

To ensure confidentiality, security of the data and compliance with the requirements of ICH E6, personal logins and passwords will be used. This process allows the restriction of system access to authorized personnel only. The list of authorized personnel will be documented. The system will ensure a traceability of any data modified, the date of modification, the reason for modification and identification of the corresponding user via the audit-trail. Data entry will be performed by investigators or their staff designated after a specific eCRF training. Then data will be extracted from eCRF to the study database. Each confirmation or correction of data must be performed by authorized site staff on the eCRF with the reason of correction.

After completion and cleaning process of data and before database lock, each eCRF will be signed by the investigator using electronic signature function available on the eCRF (entering login and password). This action will ensure that the investigator confirm the accuracy, completeness, legibility of the data collected on the eCRF.

The trained investigator site staff will enter the data required by the protocol into the eCRFs from source documents (e.g., medical records and study-specific data capture tools as needed) directly into the study database on a central server. All information in the eCRFs must be traceable to these source documents. Data recorded directly into the eCRFs will be defined before study start and the eCRFs will be considered the source data. Clinical Research Associates (CRAs) and a Data Manager will review eCRFs entered by investigational staff for completeness and accuracy. Automatic quality programs check for data discrepancies in the eCRFs and the resulting queries will be notified to the investigational site using an electronic data query process within the EDCs system. Designated investigator site staff are required to respond to queries and make any necessary changes to the data. Details of the data correction process will be specified in the Data Management Plan.

A validated, electronic database will be employed from the EDC system. An audit trail of all changes to this database, including the date, reason for the data change and who made the change, will be maintained within the same database. The audit trail will be part of the archived data at the end of the study.

The complete data management process (data capture, data entry, data validation, checks on plausibility, query handling, data editing after entry, coding, data base closure, etc.) will be defined in advance within a data handling plan/ data management plan together with a description of the personnel responsible for data entry.

## 11.2 Data Correction

Automatic and manual queries will be defined according to the data validation plan. These queries will be generated by [redacted] and sent through the EDC system for clarification. Corrections will be entered directly into the system. This procedure will be repeated until all queries are resolved. All query forms will be linked to the eCRF in the EDC system.

## 11.3 Data Handling

The final data will be transferred to the SAS-system for data analyses in accordance with the SAP. The MedDRA dictionary will be used for coding of medical history, AEs and concomitant diseases. Concomitant medication will be coded using the World Health Organization Drug Dictionary **A**natomical **T**herapeutic **C**hemical code.

### *11.3.1 Deviations from the Protocol*

Deviations from the protocol will be judged during the study and/or when an individual patient's eCRF is completed (monitored).

Before unblinding the data, a BDRC will classify protocol deviations (major/minor) for statistical analysis.

## 11.4 Data Quality Assurance

The Sponsor or designee will conduct a site visit to verify the qualifications of each investigator, inspect the site facilities, and inform the investigator of responsibilities and the procedures for ensuring adequate and correct documentation.

The investigator is required to prepare and maintain adequate and accurate case histories designed to record all observations and other data pertinent to the study for each study participant. All information recorded on the eCRFs for this study must be consistent with the patients' source documentation (i.e., medical records).

# 12 QUALITY CONTROL AND QUALITY ASSURANCE

## 12.1 Study Initiation Activities

The investigator(s) are informed about study objectives and methods, the inclusion and exclusion criteria, the time-schedule, and study procedures at a Pre-Study Visit by the CRA (if necessary), an investigators' meeting, and during the Site Initiation Visit by the CRA.

## 12.2 Training of Site Staff

The investigator will ensure that everyone assisting with the clinical study is adequately informed about the protocol, the investigational product(s), and their study-related duties and functions. Furthermore, the investigator will maintain a list of qualified persons to whom the investigator has delegated study-related duties.

## 12.3 Documentation and Filing

### *12.3.1 eCRF System*

All data recorded according to this study protocol must be documented in an eCRF. The investigator and persons authorized by the investigator will be instructed about how to complete the eCRF. Entries in the eCRF must only be made by the investigator or persons authorized by the investigator. A list of all persons who are allowed to make entries in the eCRF must be available in each study site.

The investigator must verify that all data entries in the eCRF are accurate and correct. Entries will be checked against appropriate source documentation by the monitor.

### *12.3.2 List of Patients (Patient Identification Log)*

The investigator will keep a confidential list of names of all patients participating in the study, so that the patients' records can be identified if necessary.

In addition, the investigator will keep a list of all patients screened on a screening log to document identification of patients who entered pre-study screening. If someone is not eligible to participate in the study, a reason must be provided.

### *12.3.3 Source Data*

Per ICH, source data are defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents which comprise clinical documentation, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, patient files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical study).

### *12.3.4 Investigator Site File / Regulatory Binder*

Before site initiation [redacted] will provide an ISF/ Regulatory Binder to each site. The ISF will include essential documents as defined by the ICH GCP guideline and applicable local requirements.

The investigator will be responsible for the update and maintenance of the ISF, which will be reviewed periodically by the CRAs. These documents will be reviewed during an audit by the Sponsor or an inspection by the Regulatory Authorities.

All study-related documents are to be archived and stored according to legal requirements.

Prior to destruction of study-related documents, the investigator will contact the Sponsor for approval and conformation.

## 12.4 Monitoring

The CRA is responsible for checking the quality of data and ensuring that the investigative site is adhering to the study protocol. Additionally, the monitor CRA that the site is following the legal and ethical requirements as stated in local laws and the principles of GCP.

The interval between monitoring visits will depend on the recruitment rate and the complexity of the study.

Source data verification is an essential part of the monitoring process and the investigator must grant direct access to the patient's source data.

The extent and nature of monitoring will be described in detail in the Monitoring Plan.

## 12.5 Audits and Inspections

Audits will be performed according to the corresponding audit program. The Sponsor's Quality Assurance Department or designee may visit the investigative site to audit the performance of the study, as well as all study documents. Audits may also be performed by contract auditors who will be instructed about the timing and extent of the audits. In the event of an audit at the investigational site, the monitor will usually accompany the auditor(s).

Inspections by Regulatory Authority representatives and ECs/IRBs are possible at any time, even after the end of study. The investigator is to notify the Sponsor immediately of any such inspection. The investigator and institution will permit study-related monitoring, audits, reviews by the EC/IRB and/or Regulatory Authorities and will allow direct access to source data and source documents for monitoring, audits, and inspections. Source data verification is performed in accordance with data protection regulations and guidelines and all information reviewed will be kept confidential.

The patients will be informed in writing that representatives of the Sponsor, EC, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

# 13 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

## 13.1 Good Clinical Practice

The procedures set out in this study protocol are designed to ensure that the Sponsor and investigator abide by the principles of the GCP guidelines of the ICH, and of the Declaration of Helsinki. The study also will be carried out in keeping with local legal requirements.

## 13.2 Informed Consent

Before each patient is admitted to the study, informed consent will be obtained (or his/her legally authorized representative) according to the regulatory and legal requirements of the participating country *(*i.e., the Declaration of Helsinki, ICH GCP, applicable laws in the European Union and other applicable local regulations). This consent form must be dated and retained by the investigator as part of the study records. The investigator will not undertake any investigation specifically required only for the clinical study until valid consent has been obtained. The terms of the consent and when it was obtained must also be documented in the eCRF.

The explicit wish of a minor, or mentally incapacitated adult, who is capable of forming an opinion and assessing the study information, to refuse participation in or to be withdrawn from the study at any time will be considered by the investigator.

## 13.3 Protocol Approval and Amendment

Before the start of the study, the study protocol and/or other relevant documents will be approved by the EC/IRB/Competent Authorities, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, receive approval from the appropriate personnel, and receive IRB/EC/Competent Authority approval prior to implementation (if appropriate).

Administrative changes (not affecting the patient benefit/risk ratio) may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

## 13.4 Archiving Study Records

According to ICH guidelines, essential documents should be retained:

- For at least 15 years after completion or discontinuation of the trial, or
- For at least 2 years after the granting of the last marketing authorization in the European Community and when there are no pending or contemplated marketing applications in the European Community, or
- For at least 2 years after formal discontinuation of clinical development of the investigational product.

However, these documents should be retained for a longer period if required by the applicable legal requirements.

## 13.5 Data Safety Monitoring Board

An independent DSMB has been set up to primarily take care of the safety of the participating patients by reviewing the safety and tolerability data of the investigational drug on a regular basis. The DSMB met first after the 9 first patients had received 2 infusions of the study drug and then met again after every group of 20 patients having received 2 treatment infusions up to 88 patients having received at least 2 infusions at the time of the Futility Analysis including 55 patients who had already rolled over to OLE receiving high dose of OSE-127 in an open manner. In the absence of safety signals no change on the conduct of the study has been recommended by the DSMB following these successive meetings. Information about the DSMB is provided in a separate charter.

The DSMB accepted later on to take over the additional responsibility of analyzing the results of the pre-specified interim Futility Analysis and as such the DSMB members acted as well as the Independent Data Monitoring Committee (IDMC) for this interim analysis. The DSMB charter was amended (addendum 1) in order to include the information about the IDMC.

## 13.6 Premature Termination of the Study

If the investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients if the study continues, the study may be terminated after appropriate consultation between the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such a finding.

Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study;
- Failure to enroll patients at an acceptable rate;
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.

If the study is prematurely discontinued, the on-going patients should be seen as soon as possible and the same assessments as described in Section 9.1.7 should be performed.

In case of study suspension (temporary halt), the study may resume once concerns about safety, protocol compliance and data quality are addressed and satisfy the Sponsor, the IRB/IEC and Competent Authorities.

## 13.7 Confidentiality and Data Protection

All study findings, documents and records identifying directly or indirectly the patient will be kept confidential. The investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor (e.g., in order to answer a request from a competent authorities).

Personal data from patients will be pseudonymized by the allocation of a participant code. Only this participant code will be used to identify the patient throughout the study e.g.; on eCRFs and other study documents. If the patient's name or other directly identifying data appears on any other document (e.g., the signed informed consent, medical exam reports, etc.) it/they must be redacted before a copy of the document is supplied to the Sponsor. Data will be processed in

accordance all applicable laws relating to privacy (including without limitation the regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (“GDPR”).

## 13.8 Liability and Insurance

The Sponsor will take out reasonable third-party liability insurance cover in accordance with all local legal requirements. The civil liability of the investigator, the persons instructed by him and the hospital, practice or institute in which they are employed and the liability of the Sponsor with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study are governed by the applicable law.

The Sponsor will arrange for patients participating in this study to be insured against financial loss due to personal injury caused by the pharmaceutical products being tested or by medical steps taken in the course of the study.

## 13.9 Publication Policy

By signing the study protocol, the investigator agrees with the use of results of the study for the purposes of national and international registration, publication and information for medical and pharmaceutical professionals, without allowing the direct or indirect identification of concerned patients. If necessary, the authorities will be notified of the investigator's name, address, qualifications and extent of involvement.

An investigator shall not publish any data (poster, abstract, paper, etc.) without having consulted with the Sponsor in advance.

# 14 REFERENCE LIST

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# 15 APPENDICES

## 15.1 Appendix A: Prednisone Equivalents

| Corticosteroid Drug Name | Approximate Equivalent Dose (mg) to 5 mg Prednisolone | Conversion Factor to Prednisolone |
|---|---|---|
| **Short-Acting ($T_{1/2}$ 8-12 h)** | | |
| Cortisone | 25 mg | 0.2 |
| Hydrocortisone | 20 mg | 0.25 |
| **Intermediate-Acting ($T_{1/2}$ 18-36 h)** | | |
| Methylprednisolone | 4 mg | 1.25 |
| Prednisone | 5 mg | 1.0 |
| Triamcinolone | 4 mg | 1.25 |
| **Long-Acting ($T_{1/2}$ 36-54 h)** | | |
| Betamethasone | 0.6-0.75 mg | 7.5 |
| Dexamethasone | 0.75 mg | 6.67 |

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## 15.2 Appendix B: Patient Diary

### Mayo clinical score visit XX

**You are going to evaluate every day the frequency of your stool as well as the degree of your rectal bleeding.**

**Please, make these evaluations every day at the same moment of the day *(e.g.; every evening before going to sleep or every morning at wake-up)* and assess these 2 parameters within the previous 24-hour period.**

> ***Note*** *that symptoms on the day of an oral bowel preparation, the day of an endoscopy, and the day following an endoscopy* ***should be excluded in any symptom score calculation*** *to avoid diarrhea and/or rectal bleeding from the bowel preparation or the endoscopy or the biopsy*

### A - Stool frequency

Count the number of stools that you passed within the last 24 hours **in addition to your "usual number"**, knowing that:

- One stool is defined as a "trip" to the toilets when you had either a bowel movement, or passed blood alone, or blood and mucus, or mucus only.
- The usual number of stools for you is the one that you usually had before your diagnosis of UC or the one that you usually had during a period of remission of your disease (you should have provided this number to your doctor at the 1st visit for this study).

Tick the corresponding score below:

| Parameter | Number of stools within the previous 24 hours | Score |
|---|---|---|
| **Stool frequency per day** | • Normal number of stools | 0 point |
| | • 1-2 stools more than normal | 1 point |
| | • 3-4 stools more than normal | 2 points |
| | • ≥ 5 stools more than normal | 3 points |

### B - Rectal bleeding

Count the number of cases within the last 24 hours when you have seen rectal blood

**(indicate the most severe bleeding of the day)**.

Tick the corresponding score below:

| Parameter | Number of bleeding | Score |
|---|---|---|
| **Rectal bleeding** *(indicate the most severe bleeding of the day)* | • No blood seen | 0 point |
| | • Streaks of blood with stool less than half the time | 1 point |
| | • Obvious blood with stool most of the time / half of the time or more | 2 points |
| | • Blood alone passes | 3 points |