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LOU064

CLOU064D12201 / NCT03944707

A randomized, patient- and investigator-blinded, placebo controlled study to assess the efficacy and safety of LOU064 in patients with inadequately controlled asthma

Statistical Analysis Plan (SAP)

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1 Introduction

1.1 Scope of document

The RAP documents contain detailed information to aid the production of Statistics & Programming input into the Clinical Study Report (CSR) for trial ***"CLOU064D12201".*** The Statistical analysis plan (SAP) describes the implementation of the statistical analysis planned in the protocol.

1.2 Study reference documentation

This SAP has been developed in accordance with clinical trial protocol amended version v01 (dated: 09 May 2019).

1.3 Study objectives

Objective(s)	**Endpoint(s)**
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• To determine the efficacy of LOU064 compared to placebo with respect to change from baseline in pre-dose FEV1 at Week 12	• Change from baseline in pre-dose FEV1 at Week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To characterize the pharmacokinetic profile of LOU064 in blood of asthma patients	• Concentrations of LOU064 in blood at steady state and calculation of respective PK parameters including but not limited to Cmax, Tmax, MRT, AUClast
• To determine the efficacy of LOU064 compared to placebo on changes in morning and evening peak expiratory flow rate (PEF) over the 12-week treatment period	• Change from baseline in PEF (AM and PM), as assessed by mean morning and mean evening PEF over 12 weeks of treatment (captured in eDiary)
• To evaluate the safety and tolerability of LOU064 in patients with inadequately controlled asthma	• All safety endpoints (including vital signs, ECG intervals, safety laboratory parameters, adverse events, and serious adverse events) through the End of Study/Early Termination Visit
• To determine the efficacy of LOU064 compared to placebo on daytime and nighttime asthma symptom scores over the 12-week treatment period	• Change from baseline in daytime and nighttime asthma symptom score over 12 weeks of treatment (captured in eDiary)
• To determine the efficacy of LOU064 compared to placebo on change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score over the 12-week treatment period	• Change from baseline in ACQ-5 score over 12 weeks of treatment (ACQ-assessment for the week preceding each planned visit up to End of Study)

• To determine the efficacy of LOU064 compared to placebo on total daily short-acting β-agonist (SABA) used over the 12-week treatment period	• Number of puffs of SABA taken per day over 12 weeks of treatment (captured in eDiary)

1.4 Study design and treatment

This is a non-confirmatory, multi-center, randomized, placebo-controlled, subject- and investigator-blinded, parallel-group study to evaluate the efficacy of LOU064 in patients with inadequately controlled asthma. This study will enroll approximately 75 subjects. However, in case of a higher dropout rate than assumed (10% over 12 weeks), and/or a higher variability of the primary endpoint in the planned first interim analyses than expected, up to 154 subjects may be randomized.
The study consists of:

- Screening Period of up to 2 weeks
- Run-in Period of minimum 3 weeks and maximum of 5 weeks
- Baseline visit
- 12-week Treatment Period
- Follow-up Period of approximately 3 weeks
- End of Study (EOS) visit approximately 3 weeks after the last study drug administration

The total duration for each subject in the study is approximately 20 weeks.

Figure 1-1 Study design

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Screening:
Subjects will be provided with an electronic peak expiratory flow (ePEF)/eDiary device in which they will record their PEF, daytime and nighttime asthma symptoms, and the use of rescue medication. Subjects will be instructed on eDiary completion and how to use the device for the assessment of peak flow. Subjects will perform PEF measurements twice daily (morning and evening) beginning the evening of the screening visit through the EOS visit. The investigator will check that the vaccination status of the subject is complete and there are no vaccinations planned during the study period.

Run in:
The run-in period has a minimum duration of three weeks (21 days) and may be extended by up to two weeks for a maximum of 5 weeks (35 days). If the time difference between the Screening and Run-in visits is less than two weeks, hematology, clinical chemistry, urinalysis and coagulation panel do not need to be tested again at the Run-in visit. All subjects will receive LOU064 matching placebo once daily in the morning for the duration of the run-in period. Subjects will be blinded to the identity of the treatment.

Baseline:
The run-in period will end with the Baseline visit, between Day -3 and Day 1, when randomization will take place. All baseline assessments must be completed and eligibility confirmed prior to randomization on Day 1. The Baseline visit can be performed on the same day as the Day 1 visit.

Treatment:
On Day 1 of the treatment period, after completion of all pre-dose assessments, eligible subjects will be randomized in a 3:2 ratio to receive either LOU064 or placebo
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Subjects will complete dosing on Day 85.

End of Study:
A study completion visit will occur approximately 3 weeks following the last dose of study drug.

2 First interpretable results (FIR)

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3 Interim analyses

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4 Statistical methods: Analysis sets

The screening set (‘all subjects’) includes all patients who signed informed consent.
The randomized set includes all patients who were randomized.
The safety set includes all patients who received at least one dose of study treatment.
The PK analysis set will include all patients with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that affect PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data. A subject with available PD data is a subject with at least one on-treatment spirometry assessment or with PD diary data (asthma scores, PEF)

for at least 14 days. Patients will be analyzed according to the study treatment received, unless otherwise specified. The analysis sets and protocol deviation codes are related as follows:

Table 4-1 Protocol deviation codes and analysis sets

Category Deviation code	Text description of deviation	Data exclusion
Subjects are excluded from all analyses (including safety) in case of these PDs:		Exclude subject completely from all analysis sets (including safety)
I1	*ICF not obtained*	
S1	*Subject did not take the study drug ever*	
Subjects are excluded from PD analysis in case of these PDs:		Exclude subject from PD analysis set
TRT03	*Treatment non-compliance (*)*	
Subjects are excluded from PK analysis in case of these PDs:		Exclude subject from PK analysis sets

(*) In case of this violation, the patient is still a member of the PD analysis set but efficacy data collected after the deviations are excluded from the PD analysis set. Namely for patient 1006010 efficacy data related to the last 4 weeks of the treatment period are excluded from the analysis set.

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5 Statistical methods for Pharmacokinetic (PK) parameters

PK analysis set will be used for the analysis of all pharmacokinetic parameters.
Timing of the blood sample collection for pharmacokinetic evaluation is outlined in the assessment schedule of protocol amended version v01 Table 8-1.

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5.1 Variables

The PK parameters which will be determined from the blood concentration time data include (but are not limited to): Cmax, Tmax, MRT, AUClast, AUC0-24h, $T_{1/2.}$ Pharmacokinetic parameters will be determined using WinNonlin Phoenix (version 8.0 or higher). PK parameters will be log-transformed.

5.2 Descriptive analyses

Pharmacokinetic parameters will be summarized using descriptive statistics including mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum and maximum, frequency (n, %) Commercially Confidential Information . An exception to this is Tmax where median, minimum and maximum will be presented. The descriptive summaries for PK parameters will be provided by treatment and visit/ sampling times.

5.3 Statistical model, assumptions and hypotheses

Not applicable.

6 Statistical methods for Pharmacodynamic (PD) parameters

6.1 Primary objective

The primary objective of this study is to determine the efficacy of LOU064 compared to placebo with respect to change from baseline in pre-dose FEV1 (L) at Week 12.

6.1.1 Variables

The primary analysis variable is the change from baseline in pre-dose FEV1 after 12 weeks of treatment with LOU064 at 100 mg q.d. or placebo.
The baseline pre-dose FEV1 is defined as the average of the FEV1 measurements performed 45 min and 15 min prior to dosing on Day 1. Only valid assessments will be considered. Invalid assessments are the ones not meeting the required wash-out from beta-agonists as indicated by the variable PHBMDN or with an unacceptable quality flag (variable REIRESFL). If one of the assessments is missing, then the non-missing pre-dose FEV1 will be considered as baseline. If both the assessments are missing the value collected at the baseline visit will be considered.
The pre-dose FEV1 measurements at week 2, week 4, week 8 and week 12 are handled in the same way.

6.1.2 Descriptive analyses

Summary statistics will be provided by treatment and visit both on absolute and changes from baseline values.

6.1.3 Statistical model, assumptions and hypotheses

The primary endpoint will be analyzed using a Bayesian repeated measures model with change from baseline in pre-dose FEV1 as response, adjusting for effects of treatment*visit interaction and baseline pre-dose FEV1.

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6.1.3.1 Model checking procedures

Diagnostic output from the PROC MCMC model will be reviewed and the model will be checked by assessing posterior distributions.

6.1.3.2 Graphical presentation of results

Posterior mean (SD) plots with 2-sided 80% credible intervals based on the fitted model and individual profiles will be produced by treatment and time.

6.2 Secondary objectives

6.2.1 Variables

Secondary efficacy variables supporting the secondary objectives are:

- Change from baseline in PEF (morning and evening) (eDiary, daily)
- Change from baseline in daytime and nighttime asthma symptom score (eDiary, daily)
- Change from baseline in ACQ-5 score (eDiary, per visit)
- Number of puffs of SABA taken per day (eDiary, daily)

PEF values taken from 02:00 to 13:59 are considered morning assessments, while values taken from 14:00 to 23:59 are considered evening assessments.
For each day daytime and nighttime symptom scores will be obtained as the mean score over the 4 items related to daytime and the 2 items associated to nocturnal period.
The number of puffs of SABA taken for day will be derived as the sum of morning and evening puff registered in that day (even if the morning assessment may record puffs taken

before the midnight of the previous day). If only the morning or the evening assessment is available the other assessment will be considered as = 0 puffs. If no assessment if available for one day the number of puffs taken for that day is set to missing.

For data recorded daily, the following periods are defined:

- Screening period= from the day of the screening visit to the day before the run-in visit. Data collected in this period won't be summarized.
- Run-in period = from the day after the run-in visit to the day before the first dosing (study day -1). This period will be considered for the definition of the baseline values.
- Treatment period = from day 2 to the day of the last administration. This period will be further divided in:
- Week1- Week 4 = from day 2 to day 29
- Week 5- 8 = from day 30 to day 57
- Week 9-12 = from day 58 to day 85.
- Week 13 and beyond= from day 86 to the last day of treatment (if applicable). Data collected in this period (if any) won't be summarized.
- Post treatment period = from the day after the last day of treatment till the end of study. Data collected in this period won't be summarized.

6.2.2 Descriptive analyses

Data will be summarized by treatment and time point (ACQ5) or interval (eDiary data).

6.2.3 Statistical model, assumptions and hypotheses

ACQ-5

This secondary endpoint will be analyzed using a similar methodology as followed for primary endpoint, with the exception that :

- ACQ- 5 baseline value (score collected at the baseline visit) will be used as a covariate instead of baseline FEV1
- Non-informative priors will be used for mean responses for each time point under LOU064/ placebo treatment.

Asthma symptom scores and PEF

The morning and evening PEF scores collected by e-peak flow/diary device will be analysed separately. For all daily collected measurements (morning and evening PEF, morning asthma symptoms score and evening asthma symptoms score) a similar methodology will be used as for the primary endpoint. However, the model will be fitted to the mean of 4-week intervals for each of these endpoints. The average score for each time interval is defined as the sum of daily scores divided by the number of days where eDiary records have been made on the respective score. The non-missing data within that interval will be used to calculate the mean value, as long as there are at least 16 days with non-missing eDiary data for the run-in period

and 14 days with non-missing data for post-baseline scores in a 4-week period. Otherwise, the value will be set as missing for that interval. These average scores will then be used in the model, which elsewise only differs from the primary models by the following two points:

- Baseline value of the secondary outcome will be used as covariate instead of baseline FEV1
- Non-informative priors will be used for mean responses for each time point under LOU064/placebo treatment.

SABA

For this secondary endpoint, the mean number of puffs of SABA taken in past 12 hours (morning/ evening) and overall will be calculated for each subject separately for run-in period (used as baseline value) for the 12 week-treatment period. Change from baseline in mean daily use of puffs of SABA over 12 weeks will be analyzed using a Bayesian regression model. The non-missing data within that interval will be used to calculate the mean value, as long as there are at least 16 days with non-missing eDiary data for the run-in period and 28 days with non-missing data for post-baseline period. The model will assess effects of treatment (LOU064/ placebo), baseline use of puffs of SABA per day, baseline pre-dose FEV1 and baseline daytime asthma symptom score.

Display of model results (holds for all endpoints)

In a similar manner as followed for primary endpoint (Section 6.1), for each of the secondary endpoints, the posterior probabilities of 'true' effect of LOU064 over placebo will be derived from the fitted model. The posterior probabilities will be compared to the prespecified criteria mentioned in Section 6.1 at interim/ final stage as a guide for PoC evaluation of treatment effect on the endpoint.

6.2.3.1 Model checking procedures

Diagnostic output from the PROC MCMC model will be reviewed and the model will be checked by assessing posterior distributions.

6.2.3.2 Graphical presentation of results

For PEF, Asthma symptom score and ACQ-5 the adjusted posterior mean estimates over 12 weeks with 2-sided 80% credible limits will be plotted for each of the treatment over time. Individual profiles will be produced by treatment.

6.3 Exploratory objectives

7 Statistical methods for safety and tolerability data

7.1 Variables

Adverse events, vital signs (blood pressure, pulse rate, body temperature), ECG intervals, laboratory measurements, as well as subject demographics, baseline characteristics, and treatment information.

7.2 Descriptive analyses

Subject demographics and other baseline characteristics

All data for background and demographic variables will be listed by treatment group and subject. Age will be summarized as a continuous variable as well as a categorical data (18-64,>= 65). Summary statistics will be provided by treatment group.
Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.
The following baseline characteristics will be also summarized by treatment:

- Smoking status (never / former / current)
- Number of asthma exacerbations in the last 12 months (considering the following categories: 0, 1, 2, >2)
- FEV1 pre-dose (L and % predicted)
- Reversibility (ml and in % vs pre bronchodilator). In case of multiple attempts the last one before day 1 will be considered). A reversibility test will be considered valid even if performed without the wash-out from beta agonists (variable PHBMDN), provided that no quality issue is raised (variable REIRESFL)
- ACQ5 score
- Assessment of atopic status (skin prick test and RAST)
- IgE at screening or at end of study visit (if both available the screening assessment will be considered)
- Eosinophils at day 1
- CRP
- Impact of COVID-19 pandemic. This will be assessed reporting frequencies and percentages of subjects randomized and completing the study before the pandemic, randomized before but completing the study during the pandemic and randomized

during the pandemic. The start of the pandemic is defined = 01MAR2020. A visit occurred on 01mar2020 is classified as during the pandemic.

Specifically for the assessment of atopic status the following data will be provided:

- Number of subjects performing skin prick test for at least one allergen
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- Number of subjects performing RAST test (for at least one allergen)
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Percentages will be derived vs the total number of pts tested for each test.

Finally, frequencies and percentages (on the total number of patients in the safety sets) of pts falling in the following 3 categories will be provided:

- Atopic (positive to skin prick test or RAST test)
- Non atopic (patients with data available for skin prick test or RAST without any positive result)
- Not Evaluable (without any Skin Prick test or RAST data)

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.
A summary of protocol deviations by treatment group will be provided too, as well as a distribution of the patients by country and site.

Treatment

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.
The duration of study treatment exposure is calculated as:

Treatment exposure (in weeks) = 52*(Last date of study drug administration – First date of study drug administration + 1)/365.25

Treatment exposure will be descriptively summarized by treatment using n, mean, standard deviation, median, minimum, and maximum.

Vital signs

Analysis of vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign, treatment group and visit/time. Change from baseline will only be summarized for subjects with both baseline and post-baseline values.

ECG evaluations

Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

Laboratory data listing will be provided presenting all parameters in a subject with any abnormal values. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

Adverse events

All information obtained on adverse events will be displayed by treatment and subject.
The number and percentage of subjects with adverse events will be tabulated by system organ class (SOC) and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system and treatment.
For the legal requirements of ClinicalTrials.gov and EudraCT, two required tables on <on-treatment/treatment emergent> adverse events which are not serious adverse events with an incidence greater than 5% and on <on-treatment/treatment emergent> serious adverse events and SAEs suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.
If for the same patient, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

For occurrence, the presence of at least one SAE / SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.
The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

Other safety evaluations

Not applicable.

Immunogenicity

Not applicable.

7.3 Graphical presentation

Boxplots to visualize trends in longitudinal safety data (vitals, ECG, lab parameter) will be created.

8 Statistical methods for biomarker data

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