DIN	Drug-Induced Nephrotoxicity
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDC	Electronic Data Capture
ED_{50}	Dose at which 50% of Emax is achieved
EMA	European Medicines Agency
Emax	Maximum Change in Effect over Placebo
eSource	Electronic Source
EU	European Union
E_0	Expected Placebo Effect
FAS	Full Analysis Set
FcεR	Fc epsilon receptor
FcγR	Fc gamma receptor
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	hour
HBcAb	Antibodies against hepatitis B core antigen (anti-HBcAg antibodies)
HBsAb	Antibodies against hepatitis B surface antigen (anti-HBsAg antibodies)
HBsAg	Hepatitis B surface Antigen
HBV	Hepatitis B virus
HCP	Health Care Professional
HCV	Hepatitis C virus
HCVAb	Hepatitis C virus antibody
HDL	High-Density Lipoprotein
hERG	human Ether-*à-go-go* Related Gene
HIV	Human immunodeficiency Virus
HRQoL	Health-Related Quality of Life
HSS7	Weekly Hives Severity Score
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	Investigational Medical Product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

[redacted]

Objective(s)	Endpoint(s)
	○ Occurrence of treatment emergent serious adverse events during the study

[redacted]

3 Study design

This is a global Phase 2b multicenter, randomized, double-blind, parallel-group, placebo-controlled study investigating the safety, tolerability, and efficacy of six dosing groups of oral LOU064 in subjects with inadequately controlled CSU despite treatment with (second generation) H1-antihistamine treatment.

Throughout the study (i. e. Day -14 until Day 113), subjects must be on a stable treatment regimen with a second generation H1-antihistamine at a locally approved licensed posology ("background medication").

Subjects may take an additional second generation H1-antihistamine that is eliminated primarily via renal excretion (eg cetirizine, levocetirizine or bilastine) as rescue medication (see Section 6.2.3). The rescue H1-antihistamine must differ from the background H1-antihistamine

[redacted]

and may only be administered to treat unbearable symptoms (itch) of CSU on a day-to-day basis throughout the study (from Day -14 until Day 113).

All other CSU therapies (including H1-antihistamines at higher than approved doses) are prohibited (see Table 6-3 in Section 6.6.2).

An outline of the study design including three periods is presented in Figure 3-1, while a detailed visit and assessment schedule can be found in Table 8-1:

- Screening period (10-14 days prior to randomization): During the screening period, subjects who have provided informed consent will be assessed for study eligibility.
- Treatment period (Day 1 to Day 85): After screening, eligible subjects will be randomly assigned to one of the following treatment arms in a 1:1:1:1:1:1:1 ratio:
  - 10 mg LOU064 once daily
  - 35 mg LOU064 once daily
  - 100 mg LOU064 once daily
  - 10 mg LOU064 twice a day
  - 25 mg LOU064 twice a day
  - 100 mg LOU064 twice a day
  - Placebo

  [redacted]
- Follow-up period (Day 86 to Day 113): subjects are followed-up [redacted] to further assess safety.

An extension study is in development. Eligible subjects may roll-over into the extension study at Week 12 or at Week 16 (after completing all scheduled assessments planned at these visits), following roll-over criteria defined in the extension study protocol. The details of the study design and procedures of the extension, if implemented, will be described in a separate protocol.

[redacted]

4.2 Rationale for choice of background therapy

H1-antihistamines were chosen as background medication as it reflects the current treatment guidelines to add a second- or third-line therapy to H1-antihistamines in CSU patients who are not adequately controlled by H1-antihistamines (Zuberbier et al 2018).

4.3 Rationale for dose/regimen and duration of treatment

In this study, LOU064 will be used in three q.d. arms (10 mg; 35 mg; 100 mg) and three b.i.d. arms (10 mg; 25 mg; 100 mg) for 85 days (12 weeks). Treatment duration is covered by preclinical data and will allow the assessment of the effect size of LOU064 in CSU, the onset of action, and the early maintenance of the effect size plateau.

[redacted]

The proposed study design is expected to enable proper characterization of dose- and exposure-response relationships for once and twice daily dosing, and thus support determination of the

[redacted]

Table 8-1 Assessment schedule

Period		Treatment					Follow-up	
Visit	Screening	Randomization				End of Treatment/ PSW/Study Discontinuation	Study Completion	Unscheduled visit[14]
Day	-14	1	15	29	57	85	113	NA
Week	-2	0	2	4	8	12	16	NA
Obtain Informed Consent(s)	X							
Inclusion/exclusion criteria	X	X						
Demographic data	X							
Evidence of urticaria[1]	S	S						
Relevant medical history	X							
CSU History and prior urticaria treatment	X							
Cardiovascular History	X							
Physical Exam[2]	S	S	S	S	S	S	S	S
Vital signs	X	X	X	X	X	X	X	X
Height	X							
Weight	X					X	X	X
ECG	X[3a]	X[3b]	X[3a]	X[3c]	X[3a]	X[3c]	X[3a]	X
Dispense Subjects' eDiary	S							
Call the subject to check eDiary compliance[4]	S							
Prior and Concomitant medication	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Surgery and procedures	X	X	X	X	X	X	X	X
Re-screening	X							
Randomization		X						
Study drug dispensation		X		X	X			X
IRT transaction	X	X		X	X	X		X
Rescue medication dispensation and usage[5]	X	X	X	X	X	X	X	X
Subjects' eDiary review[6] – UPDD (incl. UAS) – AAS – Study medication compliance		S	S	S	S	S	S	S
Background medication dispensation and compliance assessment	X	X	X	X	X	X	X	X

[redacted]

Period		Treatment					Follow-up	
Visit	Screening	Randomization				End of Treatment/ PSW/Study Discontinuation	Study Completion	Unscheduled visit[14]
Day	-14	1	15	29	57	85	113	NA
Week	-2	0	2	4	8	12	16	NA
DLQI (Dermatology Life Quality Index)[7]		X		X		X		X
Urinalysis	X	X	X	X	X	X	X	X
Urine Pregnancy[8]		S		S	S	S	S	S
BLOOD SAMPLING:								
Hematology and Chemistry	X	X	X	X	X	X	X	X
Coagulation	X					X		X
[redacted]								
Total IgE		X		X		X	X	X
[redacted]								
HBV, HCV testing	X							X
FSH testing[9]	X							X
Serum pregnancy test[10]	X							X
PK sampling[11]				X		X		X
Assessment of how study medication was taken (with/without a meal)[12]				S		S		S
Roll-over criteria for extension study[13]						S	S	
Disposition (End of Treatment and Study disposition)	X							

S: recorded in the source documents only
X: recorded in the eCRF
[1] Before randomization, the presence of hives as sign of urticaria must have been documented. Hives can be documented during a study visit (screening/randomization); alternatively, presence of hives must have been documented in the medical history (not more than 3 months prior to the screening visit) or can be demonstrated using a photograph (not older than 3 months).
[2] Detailed description of physical exam: please refer to Table 8-8. A complete physical exam will be done at Screening. A short physical exam will be done at all subsequent visits
[3a] A single ECG measurement
[3b] Triplicate ECG measurement pre-dose
[3c] Triplicate ECG measurement pre-dose and triplicate ECG measurement 1h post-dose

[redacted]

Diary component	When assessed
• Number of hives [redacted]	

8.3.1.1.1 Weekly Hives Severity Score (HSS7)

The hives (wheals) severity score, defined by number of hives, will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (> 12 hives/12 hours; Table 8-3). A weekly score (HSS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 – 21.

Table 8-3 Hives Severity Score

Score	Hives (Wheals) (every 12 hours)
0	None
1	1-6 hives/12 hours
2	7-12/12 hours
3	> 12 hives/12 hours

8.3.1.1.2 Weekly Itch Severity Score (ISS7)

The severity of the itch will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (severe) (Table 8-4). A weekly score (ISS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 - 21.

Table 8-4 Itch Severity Score

Score	Pruritus (Itch) (every 12 hours)
0	None
1	Mild (minimal awareness, easily tolerated)
2	Moderate (definite awareness, bothersome but tolerable)
3	Severe (difficult to tolerate)

8.3.1.1.3 Weekly Urticaria Activity Score (UAS7)

The UAS7 is the sum of the HSS7 score and the ISS7 score. The possible range of the weekly UAS7 score is 0 – 42 (highest activity).

[redacted]

or (c) the presence of hives/wheals must have been documented in the medical record of the subject by a physician trained in the management of urticaria in the past 3 months.

8.3.4 Appropriateness of efficacy assessments

At the time the omalizumab studies were carried out, the treatment paradigm focused primarily on itch (ISS7) as a key symptom of CSU. Over the past several years the goal of therapy has evolved and the current target of therapy as described in the current CSU treatment guidelines (Zuberbier et al 2018) is to treat the disease until it is gone, i.e. complete control of the disease (UAS7= 0). Given the current emphasis on UAS7 in the medical community and as reflected in the CSU treatment guidelines, change from baseline in UAS7 will be used to characterize the dose-response relationship of LOU064 administered once or twice daily.

[redacted]

Data collected during this study will be used to provide information that will support selection of doses for further evaluation [redacted] which may be included in future studies.

8.4 Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to Section 10, Safety monitoring and reporting.

Main safety and tolerability assessments include:

- AEs and SAEs, including AEs leading to treatment discontinuation and events of interest such as infections, bleeding/bruising, QT-prolongation and myelomodulating effects (i.e. cytopenias)
- Physical examination
- Vital signs
- Laboratory evaluations
- ECG

Table 8-8 Physical Assessments

Assessment	Specification
Physical examination	A complete physical examination (performed at Screening) will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. A short physical exam (performed at all visits except Screening, see Table 8-1) will include the examination of general appearance, assessment of the skin for sign of urticaria and other skin lesions, and vital signs (blood pressure [SBP and DBP] and pulse).

[redacted]

Assessment	Specification
	Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate eCRF that captures medical history. Significant findings made after signing the informed consent which meet the definition of an AE must be recorded as an AE.
Vital signs	Vital signs include BP and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured three times using an automated validated device, eg OMRON, with an appropriately sized cuff. The repeat sitting measurements will be made at 1 - 2 minute intervals and the mean of the three measurements will be used. In case the cuff sizes available are not large enough for the subject's arm circumference, a sphygmomanometer with an appropriately sized cuff may be used. Clinically notable vital signs are defined in Appendix 1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens detailed in this section (Table 8-9) unless noted otherwise. Details on the collections, shipment of samples and reporting of results by the central laboratory are provided to investigators in the laboratory manual.

Clinically notable laboratory findings are defined in Appendix 1.

Clinically significant abnormalities must be recorded on the relevant section of the eCRFs capturing medical history/current medical conditions/AEs.

Table 8-9 Laboratory assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin [only in case of clinically significant anemia, the following parameters will be assessed: Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV)], Platelets, Red blood cells (RBC), White blood cells (WBC) and Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline phosphatase (ALP), ALT, AST , Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine Kinase (CK), Creatinine, total Bilirubin (in case of clinically significant elevation: direct Bilirubin and indirect Bilirubin will be assessed) Only at baseline (Day 1) and Week 12: total Cholesterol, Low density Lipoprotein (LDL), High density Lipoprotein (HDL), Total Protein, Triglycerides, Blood Urea Nitrogen (BUN) or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting) Only at screening and baseline and when deemed necessary by the investigator: C-reactive Protein (CRP)
Urinalysis	Done on site: Macroscopic Panel (Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen)
Coagulation	Prothrombin time (PT)/International normalized ratio (INR), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)

[redacted]

Test Category	Test Name
Hepatitis markers	At Screening only: Hepatitis B surface antigen (HBsAg), anti-HBsAg antibodies (HBsAb), antibodies against Hepatitis B core antigen (HBcAb) and Hepatitis B-Deoxyribonucleic acid (HBV- DNA) as appropriate; Hepatitis C virus antibodies (HCVAb) and Hepatitis C-Ribonucleic acid (HCV-RNA) as appropriate
Additional tests	IgE, [redacted]; Follicle-stimulating hormone (FSH) (for female subjects with unclear fertility status), serum pregnancy test (for WoCBP)
Pregnancy Test	Urine pregnancy test for WoCBP

8.4.2 Electrocardiogram (ECG)

Standard 12-lead ECGs must be recorded after 10 minutes rest in the supine position according to the ECG investigator manual. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

Triplicate 12 lead ECGs are to be collected for central analysis as follows:

- Day 1: before administration of the first dose of study medication
- Week 4 and Week 12: before administration of study medication and 1h after administration of the study medication (study medication will be taken at the study site; ECG recording will be accompanied by taking samples for PK analysis (see Section 8.5.1).

Single 12 lead ECGs will be collected for central analysis at Screening, Week 2, Week 8 and Week 16.

For any ECGs with treatment emergent abnormalities, two additional ECGs must be performed to confirm the abnormal finding and copies forwarded to the central ECG laboratory for assessment. A monitoring or review process should be in place for clinically significant ECG findings throughout the study and especially at baseline before administration of study treatment.

In the event that a clinically significant ECG abnormality is identified at the site (eg severe arrhythmia, conduction abnormality of QTcF > 500 ms or QTcF prolongation> 60 ms), a copy of the assessment is sent to the core laboratory for expedited review if applicable, and the ECG is repeated (and a copy sent to the core laboratory) to confirm the diagnosis. If the subject is hemodynamically compromised, the investigator or a medically qualified person must initiate appropriate safety procedures without delay (for example cardioversion).

Clinically significant abnormalities must be recorded on the eCRF as either medical history/current medical conditions or AEs as appropriate.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above.

All pre-menopausal women who are not surgically sterile will have pregnancy testing at Screening (on serum), then at randomization (Day 1; BEFORE administration of the study

[redacted]

medication) and at Weeks 4, 8, 12 and 16 on urine. A positive urine test needs to be confirmed with serum test. If positive, the subject must be discontinued from study treatment.

Additional pregnancy testing might be performed if requested by local requirements.

Assessments of fertility

Medical documentation of oophorectomy, hysterectomy, or tubal ligation must be retained as source documents. Subsequent hormone level assessment to confirm the woman is not of child bearing potential must also be available as source documentation in the following cases:

1. surgical bilateral oophorectomy without a hysterectomy
2. reported 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile.

In the absence of the above medical documentation, FSH testing is required of any female subject, regardless of reported reproductive/menopausal status at screening/baseline.

8.4.4 Other safety evaluations

Not applicable.

8.4.5 Appropriateness of safety measurements

Given the mild inhibition of hERG channels and the fact that atrial fibrillation/atrial flutter are a known risk for ibrutinib and acalabrutinib, Novartis implements an intensive ECG monitoring strategy in this study to allow proper collection of ECG data together with PK sampling to detect and analyze any potential effect of LOU064 on cardiac function, in particular QTc prolongation. The laboratory evaluation plan will provide sufficient safety information for LOU064 in the target population.

8.5 Additional assessments

8.5.1 Pharmacokinetics

PK samples will be collected at the visits and time points defined in the assessment schedule. Instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment should be followed. Residual PK samples may be used to explore additional PK aspects such as metabolite formation or plasma protein binding of LOU064.

The PK sampling times selected were based on recent PK data as obtained from study CLOU064X2101. In particular due to the high blood clearance, a more dense sampling at early time points is required.

[redacted]

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol. The following PK parameters will be determined from the blood concentration time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): C_{max}, T_{max}, AUC_{last}, AUC_{tau}, $T_{1/2}$. Additional PK parameters may be added to further characterize the dose/exposure relationship or refine PK/PD analysis.

[redacted] Therefore and due to the limited sampling up to 4 hours these PK parameters may not be determined.

The PK of LOU064 will be characterized at Week 4 and Week 12 across all cohorts. The latter will provide a direct correlation of final safety and efficacy (PK/PD) readouts to exposure in term of AUC and C_{max}. Likewise the Week 4 readout will be a synchronized assessment with cardiovascular safety at the primary endpoint (Week 4). Proposed sampling schedule and rationale is given in Table 8-10. Detailed PK samples numbering and schedule is given in Appendix 6.

Table 8-10 PK sampling schedule

time	Sample	Comment
Day 1	no PK assessment	the initial exposure and first dose effect of LOU064 has been well characterized over a wide dose range in study CLOU064X2101
Week 4	[redacted]	Early Steady-state “full” PK profile baseline PK assessment which allows synchronization of parallel cardiovascular investigations which may be driven by initial high blood exposures (C_{max}) at the primary endpoint/interim analysis
Week 12 (last day, last dose)	[redacted]	Assess steady-state + intra-subject variability + putative time dependent effects on PK, PK/PD

[redacted]

[redacted]

9 Study discontinuation and completion

9.1 Discontinuation

9.1.1 Discontinuation of study treatment

Discontinuation of study treatment for a subject occurs when study treatment is stopped earlier than the protocol planned duration, and can be initiated by either the subject or the investigator.

Patients may voluntarily discontinue investigational treatment for any reason at any time.

The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being.

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the subject, eg required surgical interventions associated with a risk for clinically significant bleeding
- Following emergency unblinding
- Emergence of the following AEs:
    - AEs including hypersensitivity reactions, severe/serious infections (i.e., requiring specific intravenous/intramuscular anti-infectious therapy and/or hospitalization), thromboembolism, clinically significant spontaneous bleeding events and clinically significant ECG abnormalities (eg QT prolongation) for which continued exposure to the study drug would be detrimental
    - Abnormal liver laboratory results requiring discontinuation (see Appendix 2)
    - Abnormal renal laboratory results requiring discontinuation (see Appendix 3)
    - Platelets < 75 000/mm^3

[redacted]

Conditions that were already present at the time of informed consent should be recorded in medical history of the subject.

AEs (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

AE monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an AE is detected, it must be followed until its resolution or until it is judged to be permanent (eg continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the IB.

Abnormal laboratory values or test results constitute AEs only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in subjects with the underlying disease. See Appendix 1, Appendix 2 and Appendix 3 for alert ranges for laboratory and other test abnormalities.

10.1.2 Serious adverse events (SAEs)

An SAE is defined as any AE [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
  - social reasons and respite care in the absence of any deterioration in the subject's general condition

[redacted]

- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

- is medically significant, eg defined as an event that jeopardizes the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant". Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered SAE irrespective if a clinical event has occurred (see details in Section 10.1.5).

10.1.3 SAE reporting

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days following the last administration of study treatment must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

No pre-specified study endpoints are considered to be exempted from SAE reporting.

1. Screen Failures (eg a subject who is screened but is not treated or randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis/sponsor within 24-hours of learning of its occurrence.

2. Randomized OR Treated Subjects: SAEs collected between time subject signs ICF until 30 days after the subject has discontinued or stopped study treatment

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. A SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the IB or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO&PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

[redacted]

The primary objective of this study is to characterize the dose-response relationship among LOU064 q.d. and b.i.d. doses (10 mg, 35 mg, 100 mg q.d. and 10 mg, 25 mg, 100 mg b.i.d.) and placebo with respect to the change from baseline in UAS7 at Week 4, and to select an appropriate dose(s) to use in Phase 3 studies. [redacted]

12.4.1 Definition of primary endpoint(s)

The primary variable for the study is the change from baseline in UAS7 at Week 4. The UAS7 is the sum of the average daily UAS over 7 days. Note that the weekly score is derived by using the last 7 days prior to the visit.

[redacted]

[redacted]

12.4.3 Handling of missing values/censoring/discontinuations

Subjects who discontinue from study treatment early will be encouraged to stay in the study. All the available data collected will be used for the primary analysis.

[redacted]

Absence of angioedema (AAS7= 0)

The cumulative number of weeks with an AAS7= 0 response between baseline and Week 12 will be summarized by treatment group.

It will be derived based on AAS eDiary. A weekly AAS7 score will be derived by adding up the daily scores of the 7 days preceding the visit, and ranges from 0 to 105. If the AAS7 assessment is missing, it will be considered as a non-response for the cumulative number of weeks that subjects achieve AAS7= 0 response calculation. The cumulative number of weeks achieving AAS7= 0 response between baseline and Week 12 will be [redacted]

DLQI

Seven scores will be derived from the DLQI: the score of each of the six dimensions as well as the total score of the DLQI will be calculated based on the developers' rules. For each of these seven scores the change from baseline and percentage change from baseline will also be derived. Summary statistics will be calculated for the absolute values as well as for the change and percentage change broken down by visit and treatment group.

Summary tables of the number of subjects with DLQI score of 0 or 1 will be presented by treatment group and visit.

12.5.2 Safety endpoints

All safety endpoints (i.e. AEs, laboratory data, vital signs, and ECG as well as potential risks defined in the safety profiling plan) will be summarized by treatment for all subjects of the safety set. All data will be included in the analysis regardless of rescue medication use.

Adverse events

All information obtained on adverse events will be displayed by treatment group and subject.

The number (and percentage) of subjects with treatment emergent AEs (events started after the first dose of study treatment or events present prior to the first dose of study treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term
- by treatment, primary system organ class, preferred term and maximum severity
- by treatment, Standardized MedDRA Query (SMQ) and preferred term

All AEs with onset in the follow-up period will be considered as treatment emergent. A subject with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Summaries will also be presented for AEs by severity and for study treatment related AEs.

If a subject reported more than one AE with the same preferred term, the AE with the greatest severity will be presented. If a subject reported more than one AE within the same primary system organ class, the subject will be counted only once with the greatest severity at the system organ class level, where applicable. All AEs with onset in the follow-up period will also be summarized separately.

[redacted]

Separate summaries will be provided for study medication related AEs, deaths, SAEs, and other significant AEs leading to discontinuation.

All AEs including the non-treatment emergent AEs will be listed.

Laboratory data

The summary of laboratory evaluations will be presented for two groups of laboratory tests (hematology and serum chemistry). Descriptive summary statistics for the change from baseline to each study visit will be presented. These descriptive summaries will be presented by test group, laboratory test and treatment group. Change from baseline will only be summarized for subjects with both baseline and post baseline values.

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged.

Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized. For each parameter, the maximum change from baseline will be analyzed analogously.

Vital signs

Analysis of the 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. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

All vital signs data will be listed by treatment group, subject, and visit/time and if ranges are available, abnormalities will be flagged.

ECG

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

PR, QRS, QT, QTcF, and RR intervals will be obtained from 12-lead ECGs for each subject during the study. Frequency tables will be produced for the number and percentage of subjects with notable QT and QTcF intervals and with noteworthy PR, QRS and Heart Rate interval or changes from baseline.

[redacted]

12.5.3 Pharmacokinetics

LOU064 blood concentration data will be listed by treatment, subject, and visit/sampling time point. Descriptive summary statistics for PK concentration will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

[redacted]

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	-Discontinue the study treatment immediately -Hospitalize if clinically appropriate -Establish causality -Record the AE and contributing factors (eg concomitant medication, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (subject is asymptomatic)	-Repeat LFT within the next week -If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	-Repeat LFT within 48 hours -If elevation persists, establish causality -Record the AE and contributing factors (eg, conmeds, med hx, lab) in the appropriate eCRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	-Repeat LFT within 48 hours -If elevation persists, discontinue the study drug immediately -Hospitalize if clinically appropriate -Establish causality -Record the AE and contributing factors (eg concomitant medication, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (eg, reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (subject is asymptomatic)	-Repeat LFT within the next week -If elevation is confirmed, initiate close observation of the subject	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	-Discontinue the study treatment immediately -Hospitalize the subject -Establish causality -Record the AE and contributing factors (eg concomitant medication, medical history, laboratory values) in the appropriate eCRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	-Consider study treatment interruption or discontinuation -Hospitalization if clinically appropriate -Establish causality -Record the AE and contributing factors (eg concomitant medication, medical history, laboratory values) in the appropriate eCRF	Investigator discretion

[a] Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN
[b] (General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
[c] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage – related conditions; non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms.

Based on investigator's discretion, investigation(s) for contributing factors for the liver event can include: serology tests, imaging and pathology assessments, hepatologist's consultancy, obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

[redacted]

Whenever a renal event is identified, a detailed patient history and examination are indicated to identify and potentially eliminate risk factors that may have initiated or contributed to the event:

- Blood pressure assessment (after 5-minute rest, with an appropriate cuff size)
- Signs and symptoms like fever, headache, shortness of breath, back or abdominal pain, dysuria or hematuria, dependent or periorbital edema
- Changes in blood pressure, body weight, fluid intake, voiding pattern, or urine output
- Concomitant events or procedures such as trauma, surgical procedures, cardiac or hepatic failure, contrast media or other known nephrotoxin administration, or other diseases or causes, eg, dehydration due to delirium, tumor lysis

Table 16-4 Renal event follow-up

FOLLOW-UP OF RENAL EVENTS
Assess, document and record in CRF • Urine dipstick and sediment microscopy evidence of Drug-Induced Nephrotoxicity (DIN): crystals, red blood cells (dysmorphic/glomerular vs. non-dysmorphic/non-glomerular), white blood cells, tubular epithelial cells • Blood pressure and body weight • Serum creatinine, BUN, electrolytes (sodium, potassium, phosphate, calcium), bicarbonate and uric acid • Urine output
Review and record possible contributing factors to the renal event (co-medications, other co-morbid conditions) and additional diagnostic procedures (MRI etc.) in the CRF
Monitor patient regularly (frequency at investigator's discretion) until • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

[redacted]

16.4 Appendix 4: Prohibited medications

The lists provided in the table below are non-exhaustive. In case of any doubt, the corresponding SmPC should be checked.

Table 16-5 Moderate and strong inhibitors of CYP3A4

Strong inhibitors of CYP3A4	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib, indinavir, indinavir/ritonavir, itraconazole, ketoconazole, LCL161, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, saquinavir/ritonavir, telaprevir, telithromycin, tipranavir/ritonavir,troleandomycin, Viekira pack, voriconazole
Moderate inhibitors of CYP3A4	ACT-178882, amprenavir, aprepitant, atazanavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporine, darunavir, diltiazem, dronedarone, erythromycin, faldaprevir, ferula asafetida resin (*herbal product*), FK1706, fluconazole, imatinib, isavuconazole, netupitant, nilotinib, schisandra, sphenanthera, tofisopam, verapamil

Table 16-6 Moderate and strong inducers of CYP3A4

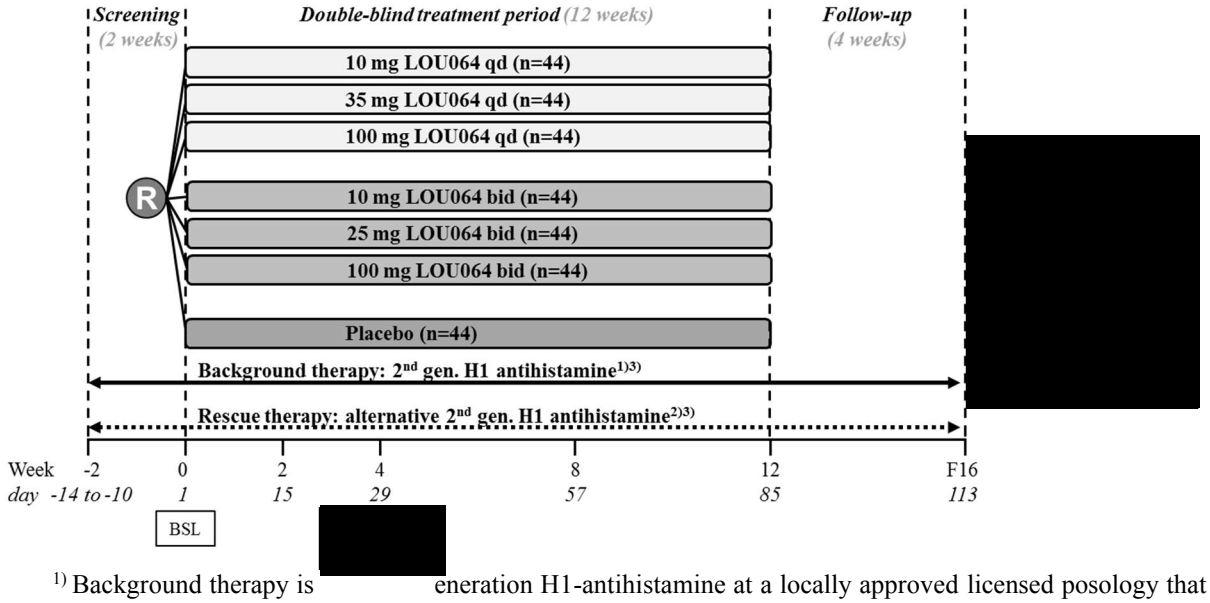
Strong inducers of CYP3A4	avasimibe, carbamazepine, enzalutamide, ifampin, mitotane, phenobarbital, phenytoin, rifabutin, St. John's wort (herbal product)
Moderate inducers of CYP3A4	bosentan, efavirenz, etravirine, lersivirine, lopinavir, modafinil, nafcillin, ritonavir/tipranavir, semagacestat, talviraline, thioridazine

[redacted]

ISS7	Weekly Itch Severity Score
IUD	Intrauterine device
IUS	Intrauterine system
i.v.	intravenous
LC-MS/MS	Liquid Chromatography–Mass Spectrometry
LDH	lactate dehydrogenase
LDL	Low-Density Lipoprotein
LFT	Liver function test
LLOQ	lower limit of quantification
MAD	Multiple Ascending Dose
MAR	Missing At Random
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
[redacted]	[redacted]
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
[redacted]	[redacted]
MRI	Magnetic Resonance Imaging
ng	Nanogram(s)
NOAC	Novel Oral Anti Coagulant
NOAEL	No-Observed Adverse Event Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
PCR	Protein-creatinine ratio
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
PRO	Patient Reported Outcomes
PT	prothrombin time
PTT	Partial Thromboplastin Time
q.d.	*quaque die* / once a day
QMS	Quality Management System
QoL	Quality of Life
QTcF	QT interval corrected by Fridericia's formula
RBC	Red Blood Cell(s)
RNA	Ribonucleic Acid
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SC	Steering Committee
sCr	serum Creatinine
SD	Standard Deviation
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query

[redacted]

Figure 3-1 Study Design



[redacted]

[1)] Background therapy is [redacted] eneration H1-antihistamine at a locally approved licensed posology that must be administered every day with a stable treatment regimen throughout the study (from Day -14 until Day 113).

[2)] Rescue therapy is a second generation H1-antihistamine at a locally approved licensed posology that is eliminated primarily via renal excretion (eg cetirizine, levocetirizine or bilastine). The rescue H1-antihistamine must differ from the background H1-antihistamine and may only be given to treat unbearable symptoms (itch) of CSU on a day-to-day basis throughout the study (from Day -14 until Day 113).

[3)] H1-antihistamines used for background therapy and rescue therapy must not be changed throughout the study.

4 Rationale

4.1 Rationale for study design

This randomized, double-blind, parallel-group, placebo-controlled design supports dose-range finding and assessment of efficacy as well as safety of LOU064 in subjects with CSU inadequately controlled by H1-antihistamines. The balanced allocation of subjects to placebo and 6 treatment arms receiving LOU064 at doses from 10 to 100 mg either once or twice daily aims to establish an accurate dose-response model for the two dosing intervals allowing the selection of the treatment regimen with the best benefit-risk profile for patients in the confirmatory phase of the development program with LOU064 (also see Section 4.3).

The screening period will allow the assessment of eligibility of subjects and the determination of baseline disease activity. The assessment of the primary endpoint will be at Week 4 as LOU064 is expected to have a fast onset of action. A 12-week treatment period was chosen to investigate the maintenance of the expected effect size plateau and to allow historic comparison to other treatment options for CSU, eg omalizumab. A 4-weeks follow-up will enable the assessment of sustained treatment response or CSU relapse after withdrawal of LOU064.

[redacted]

optimal dosing regimen for LOU064 for confirmation into Phase 3. For detailed description of pre-clinical and clinical study results please refer to the IB.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

Placebo was chosen as comparator to adjust for the known pronounced placebo effect in CSU patients. The use of placebo in this patient population is considered to be appropriate since patients will additionally receive a background therapy with H1-antihistamines (see Section 6.1.2).

[redacted]

4.6 Benefits and risks

To date, no CSU patients have been treated with LOU064, and no reports about treatment of CSU patients with other BTK inhibitors have been published. However, chronic urticaria is a mast cell and basophil driven disease (Ferrer et al 2015) and LOU064 as well as other BTK inhibitors have been shown to effectively inhibit mast cell and basophil activation:

- BTK inhibition interferes with the up-regulation of the activation markers CD63 and CD203c (LOU064 IB).
- LOU064 and ibrutinib, an approved BTK inhibitor used to treat B cell malignancies, have been shown to effectively reduce wheal sizes in skin prick tests (Regan et al 2017; Dispenza et al 2018; LOU064 IB). SPT inhibition was shown to be a reliable clinical proxy for measuring the effectiveness of a compound to treat CSU (Arm et al 2014).

BTK inhibition may offer a new therapeutic principle for treating CSU that differs significantly from H1-antihistamines and anti-IgE biologics. BTK inhibition with LOU064 may therefore offer treatment options for patients with contraindications against or having an inadequate response to approved treatment options for CSU including biologics. These patients with a high unmet medical need will be part of the eligible patient population for this study.

[redacted] No serious or severe AE have been associated with the administration of LOU064, the majority of observed AEs were singular events and there was no relationship between LOU064 doses and AEs or the number of all observed AEs. A summary of AEs and of the pre-clinical safety data can be found in the IB.

Based on a thorough review of safety information currently available in the literature together with an assessment of safety data obtained from both clinical and preclinical experience with LOU064, the following safety topics are considered as potential risks for LOU064 and require close monitoring in the proposed study. Of important note, many safety risks identified for ibrutinib and acalabrutinib, two BTK inhibitors approved for the treatment of B cell

[redacted]

[4] To be performed in screening period between day -14 and randomization
[5] Rescue medication usage will be assessed by reviewing the patient's eDiary answer to UPDD question 5
[6] UPDD: Urticaria Patient Daily Diary; UAS: Urticaria Activity Score; AAS: Angioedema Activity Score
[7] DLQI is completed in the patient's eDiary during site visit
[8] Only performed in women of childbearing potential. Serum pregnancy test done by central lab to confirm positive urine pregnancy test
[9] Only for female subjects with unclear fertility status
[10] Only performed in women of childbearing potential
[11] Detailed PK sampling schedule is provided in Table 8-10
[12] At the PK visits, the subject should be asked how the study medication was usually (≥80%) taken in the preceding week: with (interval between 1 hour before and 2 hours after the meal) or without a meal. This information should be recorded in the source documents.
[13] Evaluate roll-over criteria as defined in extension study protocol if implemented
[14] Unscheduled visit: the assessment(s) performed at an unscheduled visit are at the investigator's discretion

8.1 Screening

Screening and re-screening

Subjects will have a screening period of 10 to 14 days to establish eligibility for the study.

If for any reason a subject is a screen failure, the subject may be re-screened. Re-screening is only allowed once. There is no restriction on how much time must pass from the date of screen failure to the date of re-screening.

IF a subject re-screens for the study, then the subject must sign a new ICF and be issued a new subject number prior to any screening assessment being conducted for the subject under the new screening subject number. The investigator/qualified site staff will record if the subject was re-screened on the re-screening eCRF and any applicable screening numbers the subject was issued prior to the current screening number.

The date of the new informed consent signature must be entered on the informed consent eCRF to correspond to the new screening subject number. For re-screening, all screening assessments must be performed per protocol.

Information to be collected on screening failures

Subjects who sign an ICF and subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure subjects. No other data will be entered into the clinical database for subjects who are screen failures, unless the subject experienced a SAE during the screening Phase (see SAE section for reporting details). If the subject fails to be randomized, the IRT must be notified within 2 days of the screen fail that the subject was not randomized.

[redacted]

[redacted]

[redacted]

- Any other laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
- Patient received a live virus vaccination during the study

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the subject's premature discontinuation of study treatment and record this information.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see withdraw of informed consent section). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (eg telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section. This contact should preferably be done according to the study visit schedule.

If the subject cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the subject, or with a person pre-designated by the subject. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- new/concomitant treatments
- AEs/SAEs

The investigator must also contact the IRT to register the subject's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of assigned treatment code section (6.6.2).

9.1.2 Withdrawal of informed consent

Subjects may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a subject:

- Does not want to participate in the study anymore, and
- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (eg telephone, e-mail, letter) to understand the primary reason for the subject's decision to withdraw his/her consent and record this information.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the subject are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study withdrawal. A final evaluation at the time of the subject's study withdrawal should be made as detailed in the assessment table.

[redacted]

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

To ensure subject safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. A minimum of 3 months of the newborn must be followed up.

Pregnancy should be recorded and reported by the investigator to the Novartis CMO&PS. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, subject or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Novartis Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes, even if not associated with a SAE

[redacted]

[redacted]

12.5 Analysis of secondary endpoints

All analyses will be based on the FAS if not specified otherwise. For handling of missing data refer to Section 12.4.3.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Summary tables will be presented by treatment group and visit (as applicable) using descriptive statistics, which include absolute and relative frequencies for categorical variables and arithmetic mean, standard deviation, minimum, maximum, median and first and third quartile for continuous variables. For the secondary analysis of UAS7, complete clinical response, controlled disease and AAS7= 0, pairwise comparisons of each LOU064 doses to placebo will be performed. No adjustment for multiple comparisons will be done due to the exploratory nature of this study.

UAS7

Summary statistics of the absolute and percent change from baseline in UAS7 will be presented by treatment group and visit in the Treatment and Follow-up periods.

Complete clinical response

The complete clinical response, i.e. absence of hives and itch, is defined as subjects achieving UAS7= 0.

The number of subjects with UAS7= 0 will be summarized by treatment group and visit in the Treatment and Follow-up periods.

[redacted]

Controlled disease (UAS7≤ 6)

The number of subjects with UAS7≤ 6 will be summarized by treatment group and visit in the Treatment and Follow-up periods.

[redacted]

[redacted]

Summary statistics will include mean (arithmetic and geometric), standard deviation (SD), coefficient of variation (CV) (arithmetic and geometric), median, minimum and maximum. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations.

PK parameters will be listed by treatment and subject. Descriptive summary statistics for PK parameters will be provided by treatment. An exception to this is T_{max} where median, minimum and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUC_{last}	The AUC from time zero to the last measurable concentration sampling time (t_{last}) (ng x h/mL)
AUC_{inf}	The AUC from time zero to infinity (ng x h/mL)
AUC_{tau}	The AUC calculated to the end of a dosing interval (tau) at steady-state (ng x h/mL)
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng/mL)
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h)
Lambda_z	Smallest (slowest) disposition (hybrid) rate constant (1/h) may also be used for terminal elimination rate constant (1/h)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (h). Use qualifier for other half-lives
CL/F	The total body clearance of drug from the plasma (L/h)
Vz/F	The apparent volume of distribution during terminal phase (associated with λz) (L)

The PK profile of LOU064 will be characterized but not limited to the PK parameters listed above. [redacted]

16.3 Appendix 3: Specific renal alert criteria and actions and event follow-up

Table 16-3 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50 % [1]	• Consider causes and possible interventions • Repeat assessment within 24-48h if possible • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected • Consider patient hospitalization and specialized treatment
New onset dipstick proteinuria ≥ 3+ When urine proteins are measured as a follow-up of positive urine dipstick measurements: Protein-creatinine ratio (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	<u>Assess & document</u> • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[1] Corresponds to KDIGO criteria for Acute Kidney Injury

Additional specialized assessments are available to assess renal function or renal pathology. (Note: in exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the Renal Safety Group to potentially identify project-wide patterns of nephrotoxicity.)

[redacted]