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LOU064

Protocol CLOU064A2201

A multicenter, randomized, double-blind, placebo-controlled Phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines

Document type:	Clinical Trial Protocol
EUDRACT number:	2018-000993-31
Version number:	00 (Original Protocol)
Clinical Trial Phase:	IIb
Release date:	08-Jan-2019

Clinical Trial Protocol Template Version 1.0 (01-Dec-2017)

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List of abbreviations

AAS	Angioedema Activity Score
AE	Adverse Event
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AUCinf	The area under the plasma (or serum or blood) concentration-time curve from time zero to infinity [mass x time / volume]
AUClast	The area under the plasma (or serum or blood) concentration-time curve from time zero to the time of the last quantifiable concentration [mass x time / volume]
AUCtau	The area under the plasma (or serum or blood) concentration-time curve from time zero to the end of the dosing interval tau [mass x time / volume]
AV block	Atrioventricular block
BCR	B Cell Receptor
b.i.d.	*bis in die* / twice a day
BP	Blood Pressure
BTK	Bruton's Tyrosine Kinase
BTK	Bruton's Tyrosine Kinase Inhibitor
BUN	Blood Urea Nitrogen
CK	Creatinine Kinase
CL/F	The apparent systemic (or total body) clearance from plasma (or serum or blood) following extravascular administration [volume / time]
Cmax	The observed maximum plasma (or serum or blood) concentration following drug administration [mass / volume]
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
CRA	Clinical Research Associate
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-Reactive Protein
CSR	Clinical study report
CSU	Chronic Spontaneous Urticaria
CU	Chronic Urticaria
CV	Coefficient of Variation
CYP	Cytochrome P
DBP	Diastolic Blood Pressure
DDE	Direct Data Entry

[redacted]

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]

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]

SOP	Standard Operating Procedure
SPT	Skin Prick Test
SUSAR	Suspected Unexpected Serious Adverse Reactions
TB	Tuberculosis
TBL	Total Bilirubin
T_{max}	The time to reach the maximum concentration after drug administration
$T_{1/2}$	The terminal elimination half-life [time]
UAS	Urticaria Activity Score
ULN	Upper Limit of Normal
ULOQ	Upper Limit Of Quantification
UPDD	Urticaria Patient Daily Diary
US	United States (of America)
UTI	Urinary Tract Infection
Vz/F	The apparent volume of distribution during the terminal elimination phase following extravascular administration [volume]
WBC	White Blood Cell(s)
WHO	World Health Organization
WoCBP	Women of Child-Bearing Potential
XLA	X-linked Aggamaglobulinemia

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Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (eg any background therapy).
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the subject in a time unit (eg 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained
eSource (DDE)	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource Platform/Applications reduce the use of paper capture source data during clinical visits. eSource combines source documents and case report forms (CRFs) into 1 application, allowing for the real time collection of clinical trial information to sponsors and other oversight authorities, as appropriate.
Healthy volunteer	A person with no known significant health problems who volunteers to be a study participant
Investigational drug/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study.
Other treatment	Treatment that may be needed/allowed during the conduct of the study (concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (eg Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis.

[redacted]

Personal data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples.
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned.
Randomization number	A unique identifier assigned to each randomized subject
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource.
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject.
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Variable	A measured value or assessed response that is determined from specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of study consent	Withdrawal of consent from the study occurs only when a subject does not want to participate in the study any longer, and does not allow any further collection of personal data

[redacted]

Protocol summary

Protocol number	CLOU064A2201
Full Title	A multicenter, randomized, double-blind, placebo- controlled Phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adult chronic spontaneous urticaria patients inadequately controlled by H1-antihistamines
Brief title	A Phase 2b dose-finding study to investigate the efficacy, safety and tolerability of LOU064 in adult chronic spontaneous urticaria patients
Sponsor and Clinical Phase	Novartis IIb
Investigation type	Drug
Study type	Interventional.
Purpose and rationale	The purpose of this study is to evaluate the efficacy and safety of LOU064 in subjects suffering from CSU inadequately controlled by H1-antihistamines and to select a LOU064 dosing regimen for the subsequent Phase 3 program.
Primary Objective(s)	The primary objective of this study is to characterize the dose-response relationship of LOU064 administered once or twice daily in subjects with CSU with respect to change from baseline in UAS7 at Week 4
Secondary Objectives	To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline UAS7 at Week 12 To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline UAS7 over time To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of complete clinical response (UAS7= 0) over time To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of disease control (UAS7≤ 6) over time To evaluate the effect of LOU064 on angioedema (AAS7) with respect to the number of weeks with an AAS7= 0 response from baseline through Week 12 To evaluate the effect of LOU064 on disease-related quality of life with respect to achievement of a DLQI score of 0 or 1 at Week 4 and Week 12 To evaluate the effect of LOU064 on CSU-related quality of life with respect to change from baseline in DLQI at Week 4 and Week 12 To evaluate the pharmacokinetics (PK) of LOU064 resulting from oral dosing (PK sampling will be performed at Week 4 and Week 12) To evaluate safety and tolerability of LOU064 in subjects with CSU
Study design	This is a global Phase 2b multicenter, randomized, double-blind, placebo-controlled study. Study duration is 18 weeks (2 weeks screening period; 12 weeks treatment period; 4 weeks follow-up period). The study comprises the 7 following treatment arms: 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 Eligible subjects will be randomly assigned to the treatment arms in a 1:1:1:1:1:1:1 ratio.

[redacted]

Population	The study population will consist of approximately 308 female and male adult patients with at least moderately active chronic spontaneous urticaria inadequately controlled by second generation H1-antihistamines.
Key Inclusion criteria	Signed informed consent must be obtained prior to participation in the study. Male and female adult subjects aged ≥18 years of age. CSU diagnosis for ≥ 6 months prior to screening Diagnosis of CSU inadequately controlled by second generation H1-antihistamines as defined in the following: The presence of itch and hives for ≥6 consecutive weeks prior to screening in spite of use of non-sedating H1-antihistamines according to local treatment guidelines during this time period UAS7 score (range 0-42) ≥16 and HSS7 score (range 0-21) ≥ 8 during 7 days prior to randomization (Day 1) Presence of hives must have been documented within three months before randomization (either at screening and/or randomization; or documented in the subject`s medical history)
Key Exclusion criteria	Subjects having a clearly defined predominant or sole trigger of their chronic urticaria (chronic inducible urticaria) including urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary urticaria, or acquired/drug-induced urticaria Any other skin disease associated with chronic itching that might influence in the investigators opinion the study evaluations and results, eg atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis History or current diagnosis of ECG abnormalities indicating significant risk of safety for subjects participating in the study such as: • Concomitant clinically significant cardiac arrhythmias, eg sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker • History of familial long QT syndrome or known family history of Torsades de Pointes • Resting heart rate (physical exam or 12 lead ECG) < 60 bpm • Resting QTcF ≥450 msec (male) or ≥460 msec (female) at pretreatment [screening] or inability to determine the QTcF interval • Use of agents known to prolong the QT interval unless it can be permanently discontinued for the duration of study Significant bleeding risk or coagulation disorders Known or suspected history of an ongoing, chronic or recurrent infectious disease including but not limited to opportunistic infections (eg tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis), HIV, Hepatitis B/C
Study treatment	LOU064 capsules (dose strengths: 10 mg; 25 mg; 50 mg) Placebo capsules
Efficacy assessments	In this study, all efficacy measures are PROs: Urticaria Patients Daily Diary (UPDD), including

[redacted]

	Urticaria Activity Score (UAS) Angioedema Activity Score (AAS) Assessment of impact of CSU on sleep and daily activity Dermatology Life Quality Index (DLQI)
Pharmacokinetic (PK) assessments	Assessment of the concentration of LOU064 in blood up to four hours following oral administration and before administration at Week 4 and Week 12
Key safety assessments	Adverse event (AE) monitoring Physical examinations Vital signs Monitoring of laboratory markers in blood and urine ECG monitoring
Data analysis	The main purpose of this study is to characterize the dose-response relationship among LOU064 q.d. and b.i.d doses and placebo with respect to the change from baseline in UAS7 at Week 4, and select appropriate dose(s) to use in Phase 3 studies. [redacted] For secondary endpoints, 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.
Key words	Chronic spontaneous urticaria BTK inhibitor Urticaria activity score Angioedema activity score

[redacted]

1 Introduction

1.1 Background

Chronic Spontaneous Urticaria (CSU) is defined as the spontaneous occurrence of itchy wheals (hives), angioedema or both lasting for at least 6 weeks (Zuberbier et al 2018). The classic description of urticaria is a wheal and flare with a pale elevated lesion and surrounding erythema, ranging in size from a few millimeters to a few centimeters across, usually occurring in groups and often coalescing to form large confluent lesions. CSU can be debilitating and is associated with intense itching and has a major impact on patient's well-being, suggested to be comparable to that of severe coronary artery disease (Greaves 2003). The symptoms of urticaria and urticarial-associated angioedema adversely affect daily activities and sleep (O'Donnell et al 1997). The burden of CSU on health-related quality of life (HRQoL) and work productivity is substantial (Maurer et al 2017).

Second generation H1-antihistamines are recommended as first line treatment for subjects with CSU but less than 40% of these subjects respond adequately (Guillén-Aguinaga et al 2016). While uptitration of second generation antihistamines is recommended by most CSU treatment guidelines as second line therapy (Zuberbier et al 2018), the efficacy of uptitrated H1-antihistamines in CSU has not been studied in larger clinical studies and hence uptitration is considered off-label. Omalizumab is a highly effective third line therapy for CSU subjects. However, less than 50% of subjects treated with Omalizumab reach a complete control of signs and symptoms of CSU (Kaplan et al 2016). Therefore, there is a high medical need for new treatment options for CSU subjects.

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase and member of the TEC kinase family. BTK is expressed in selected cells of the adaptive and innate immune system including B cells, macrophages, mast cells/basophils and thrombocytes. BTK is indispensable for signaling through the Fc epsilon receptor (FcεR1 for IgE) and the activating Fc gamma receptors (FcγR for IgG), as well as the B cell antigen receptor (BCR) and BTK inhibitors (BTKi) like ibrutinib are approved for the treatment of B cell malignancies (Hendriks et al 2014). Recently, it has been demonstrated that inhibition of BTK leads to inhibition of mast cell and basophil activation/degranulation in vitro and to reduced wheal sizes in skin prick tests with patients suffering from IgE-mediated allergies (Smiljkovic et al 2017; Regan et al 2017; Dispenza et al 2018). Thus, BTK inhibition is a promising therapeutic concept for the treatment of chronic urticaria.

LOU064 is a low molecular weight compound for oral administration that covalently binds and inhibits BTK with high selectivity. It has been shown to effectively inhibit basophil activation in healthy volunteers and CSU patients as measured by the inhibition of CD63 up-regulation. Additionally, LOU064 reduced wheal sizes in skin prick tests. The pre-clinical and clinical safety profile of LOU064 is favorable (for detailed information please refer to the Investigator`s Brochure (IB)). Thus, LOU064 may offer a novel therapeutic option for treating CSU.

1.1.1.1 Purpose

The purpose of this study is to evaluate the efficacy and safety of LOU064 in subjects suffering from CSU inadequately controlled by H1-antihistamines and to select a LOU064 dosing regimen for the subsequent Phase 3 program. Key efficacy evaluation criteria are the reduction

[redacted]

of signs (hives) and symptoms (itch) of CSU measured with the 7-day version of the Urticaria Activity Score (UAS7) and the improvement of health-related quality of life as measured by the Dermatology Life Quality Index (DLQI).

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To characterize the dose-response relationship of LOU064 administered once or twice daily in subjects with CSU with respect to change from baseline in UAS7 at Week 4	• Change from baseline in UAS7 at Week 4
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in UAS7 at Week 12	• Change from baseline in UAS7 at Week 12
• To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in UAS7 over time	• Change from baseline in UAS7 over time
• To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of complete clinical response (UAS7= 0) over time	• Complete absence of hives and itch, assessed as UAS7= 0 response over time
• To evaluate the efficacy of LOU064 compared to placebo with respect to achievement of disease control (UAS7≤ 6) over time	• UAS7≤ 6 response over time
• To evaluate the effect of LOU064 on angioedema (AAS7) with respect to the number of weeks with an AAS7= 0 response from baseline through Week 12	• Cumulative number of weeks with an AAS7= 0 response between baseline and Week 12
• To evaluate the effect of LOU064 on disease-related quality of life with respect to achievement of a DLQI score of 0 or 1 at Week 4 and Week 12	• DLQI score of 0 or 1 at Week 4 and Week 12
• To evaluate the effect of LOU064 on CSU-related quality of life with respect to change from baseline in DLQI at Week 4 and Week 12	• Change from baseline in DLQI score at Week 4 and Week 12
• To evaluate the pharmacokinetics of LOU064 resulting from oral dosing at Week 4 and Week 12	• Concentrations of LOU064 in blood and calculation of respective PK parameters at Week 4 and Week 12
• To evaluate safety and tolerability of LOU064 in subjects with CSU	• Safety endpoints will include but not be limited to: o Occurrence of treatment emergent adverse events during the study

[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:

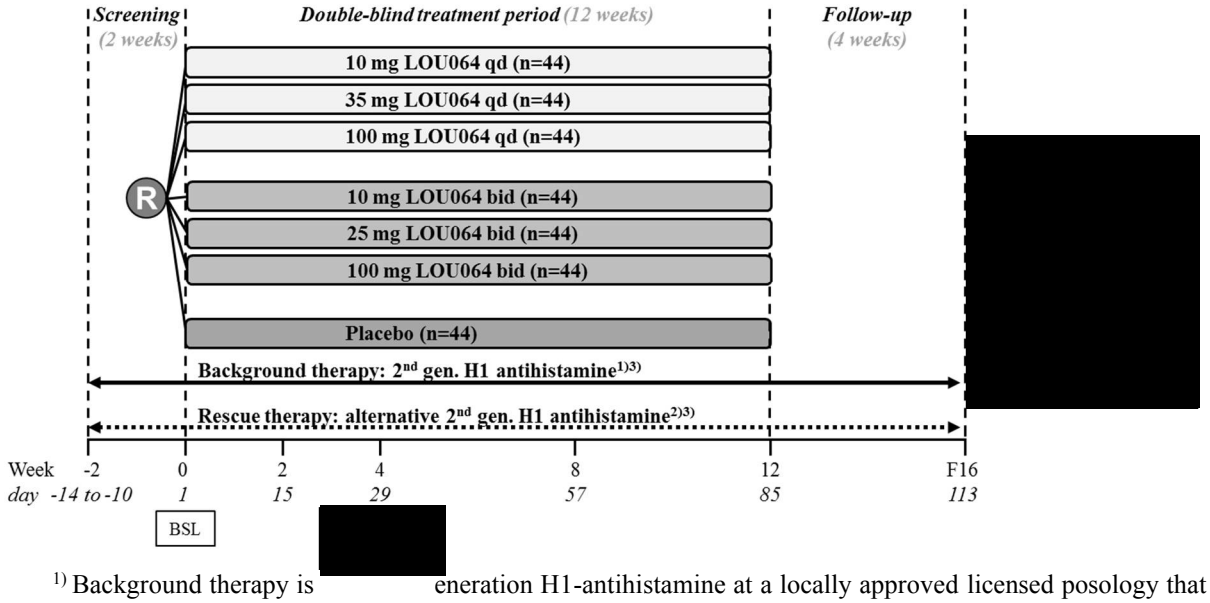
- Screening period (10-14 days prior to randomization): During the screening period, subjects who have provided informed consent will be assessed for study eligibility.
- Treatment period (Day 1 to Day 85): After screening, eligible subjects will be randomly assigned to one of the following treatment 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]

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]

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]

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]

malignancies, are less likely related to the pharmacology of inhibition of the BTK, but rather to the underlying indications being treated, for example, tumor lysis syndrome, second primary malignancies etc. Therefore, when comparing the safety risks between the approved BTKi (eg: ibrutinib and acalabrutinib) and LOU064, the relevance and importance of the study patient populations must be taken into consideration.

- *Infections:* BTK is an important signaling node downstream of cell surface receptors and expressed in several immune cells of the adaptive and innate system, including B cells, macrophages and mast cells/basophils. Therefore, LOU064 has the potential to increase the risk of infections. Patients with X-linked agammaglobulinemia (XLA) – a genetic defect associated with a lack of BTK – suffer from recurrent bacterial and enteroviral infections which may be associated with neutropenia (Kumar et al 2006). However, in XLA BTK-deficiency leads to impaired B cell and plasma cell development and in turn to a close to complete absence of immunoglobulins. In adult patients, BTK inhibition primarily interferes with B cell activation but not plasma cell function and is therefore not associated with a marked decrease of immunoglobulins (Hendriks et al 2014; Sun et al 2015; Nutt et al 2015). Administration of ibrutinib and acalabrutinib is associated with a risk of infection in patients suffering from B cell malignancies (see Summary of Product Characteristics (SmPC) for ibrutinib and acalabrutinib). All patients participating in LOU064 clinical studies will be monitored closely for signs and symptoms of infections while in the study. Patients with a known history of chronic recurrent or active ongoing infections will be excluded from the study (refer to Section 5.2 for details).
- *Impaired platelet function:* BTK is a signaling kinase in one of several platelet activation pathways. In the prescribing information for both ibrutinib and acalabrutinib, bleeding/bruising events are very common and affecting approximately 50% of patients with hematologic malignancies. Warnings on hemorrhagic events including deaths have also been described (see SmPC for ibrutinib and acalabrutinib). Compared to other drugs in the same class, LOU064 demonstrated a higher selectivity for BTK vs. other TEC kinases. Thus, bleeding may be less a safety concern when compared to ibrutinib and acalabrutinib. Patients receiving LOU064 must be closely monitored for any signs and symptoms of bleeding while in the study. Subjects with a known history of bleeding disorder, subjects taking medication that is known to increase the bleeding risk (other than acetylsalicylic acid), and subjects with an increased thromboembolic risk must be excluded from the study (see details in Section 5.2).
- *Myelomodulation*: The role of BTK inhibition in myelomodulation is not fully understood. Treatment emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients with hematologic malignancies treated with ibrutinib and acalabrutinb (see SmPC for ibrutinib and acalabrutinib). Therefore, patients must be closely monitored for signs and symptoms of cytopenia while in the study, and those with a history of hematological disorders or with markedly altered hematologic parameters at baseline must be excluded from the study (see details in Section 5.2).
- *Risk of cardiovascular origin*: LOU064 is an *in vitro* inhibitor of the hERG channel protein, without affecting other ion channels. [redacted]

[redacted] For ibrutinib, atrial fibrillation was described for 3% to 6% of subjects across multiple trials which might be associated with Na-channel inhibition (see SmPC for ibrutinib). For acalabrutinib, both atrial fibrillation and atrial flutter of any grade were reported in 3% of patients (see SmPC for acalabrutinib). Therefore, an intensive ECG monitoring strategy be implemented in this study (see Section 8.4.2). In addition, patients with a known history or current diagnosis of ECG abnormalities indicating significant risk of safety will be excluded from the study (see details in Section 5.2).

- *Drug-drug interactions*: [redacted] Concomitant administration with moderate or strong CYP3A4 inhibitors or inducers may possibly cause substantial changes in LOU064 drug exposure, and must be avoided while in the study.
- *Reproductive toxicity*: LOU064 is not genotoxic or mutagenic in *in vitro* or *in vivo* studies. [redacted] For ibrutinib and acalabrutinib, embryofetal toxicity in animals is reported (see SmPCs). Highly effective methods of contraception must be practiced.

Women of child bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the subject will not reliably comply, they should not enter or continue in the study.

In summary, CSU patients with inadequate response to H1-antihistamines and other available treatment options participating in this clinical trial may benefit from treatment with LOU064 due to its impact on mast cell and basophil activation. Additionally, this study will help improve the scientific understanding of LOU064 in the management of CSU and offer the potential of developing an innovative drug that could potentially improve the quality of life for CSU patients beyond the conventional treatment modalities currently available to them. Potential risks are mitigated by compliance with inclusion/exclusion criteria, study procedures, close clinical monitoring and study drug discontinuation rules. As with investigational drugs in general, not

[redacted]

all safety risks are known. Patients and investigators participating in this study will be informed should important new safety information become available.

5 Population

The study population will consist of adult patients with at least moderately active CSU inadequately controlled by second generation H1-antihistamines.

Randomization will be stratified by prior exposure to anti-IgE biologics (including omalizumab and ligelizumab) and by geographical region; [redacted]

The goal is to randomize approximately 44 subjects per arm (i.e. a total of 308 subjects) in approximately 90 centers worldwide. With an estimated screening failure rate of 30%, approximately 440 subjects will be screened.

Subjects who drop out after they have been randomized will not be replaced.

5.1 Inclusion criteria

Subjects eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Male and female adult subjects aged ≥18 years of age
3. CSU diagnosis for ≥ 6 months prior to screening
4. Diagnosis of CSU inadequately controlled by second generation H1-antihistamines at the time of randomization as defined in the following:
   - The presence of itch and hives for ≥6 consecutive weeks prior to screening in spite of use of non-sedating H1-antihistamines according to local treatment guidelines during this time period
   - UAS7 score (range 0-42) ≥16 and HSS7 score (range 0-21) ≥ 8 during 7 days prior to randomization (Day 1)
5. Presence of hives must have been documented within three months before randomization (either at screening and/or at randomization; or documented in the subject`s medical history)
6. Willing and able to complete an Urticaria Participant Daily eDiary (UPDD) for the duration of the study and adhere to the study protocol
7. Subjects must not have had any missing eDiary entries in the 7 days prior to randomization (Day 1)

[redacted]

5.2 Exclusion criteria

Subjects meeting any of the following criteria are not eligible for inclusion in this study:

1. Use of other investigational drugs within 5 half-lives of Screening, or within 30 days (for small molecules) prior to Screening or until the expected pharmacodynamic (PD) effect has returned to baseline (for biologics), whichever is longer; or longer if required by local regulations.
2. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes
3. Subjects having a clearly defined predominant or sole trigger of their chronic urticaria (chronic inducible urticaria) including urticaria factitia (symptomatic dermographism), cold-, heat-, solar-, pressure-, delayed pressure-, aquagenic-, cholinergic-, or contact-urticaria
4. Other diseases with symptoms of urticaria or angioedema, including but not limited to urticaria vasculitis, urticaria pigmentosa, erythema multiforme, mastocytosis, hereditary urticaria, or acquired/drug-induced urticaria
5. Any other skin disease associated with chronic itching that might influence in the investigators opinion the study evaluations and results, eg. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis
6. History or current diagnosis of ECG abnormalities indicating significant risk of safety for subjects participating in the study such as:
   - Concomitant clinically significant cardiac arrhythmias, eg sustained ventricular tachycardia, and clinically significant second or third degree AV block without a pacemaker
   - History of familial long QT syndrome or known family history of Torsades de Pointes
   - Resting heart rate (physical exam or 12 lead ECG) < 60 bpm
   - Resting QTcF ≥450 msec (male) or ≥460 msec (female) at pretreatment (screening) or inability to determine the QTcF interval
   - Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of study
7. Subjects taking medications prohibited by the protocol (see Section 6.2.2, Table 6-3).
8. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or in situ cervical cancer), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
9. Pregnant or nursing (lactating) women
10. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using highly effective methods of contraception while taking study treatment and for 7 days after stopping study medication. Highly effective contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject). Periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

[redacted]

- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.
- Male sterilization (at least 6 months prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject.
- Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS), or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

In case of use of oral contraception, women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

11. Sexually active males unwilling to use a condom during intercourse while taking study treatment and for 7 days after stopping study treatment. 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 must not donate sperm for the time period specified above.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form (ICF).

12. Major surgery within 8 weeks prior to screening or surgery planned prior to end of study (16 weeks after randomization)
13. History of live attenuated vaccine within 6 weeks prior to randomization or requirement to receive these vaccinations at any time during study drug treatment
14. Evidence of clinically significant cardiac, neurologic, psychiatric, pulmonary, renal, hepatic, endocrine, metabolic, hematological disorders or gastrointestinal disease that, in the investigator's opinion, would compromise the safety of the participant, interfere with the interpretation of the study results or otherwise preclude participant participation.
15. Uncontrolled disease states, such as asthma, or inflammatory bowel disease, where flares are commonly treated with oral or parenteral corticosteroids
16. Hematology parameters at screening:
    Hemoglobin: < 10 g/dl
    Platelets: < 100 000/mm^3
    White blood cells: <3 000/mm^3
    Neutrophils: < 1 500/mm^3

[redacted]

17. Significant bleeding risk or coagulation disorders
18. History of gastrointestinal bleeding, eg in association with use of Nonsteroidal Anti-Inflammatory Drug (NSAID)
19. Requirement for anti-platelet or anticoagulant medication (for example, warfarin, or clopidogrel or Novel Oral Anti-Coagulant - NOAC) other than acetylsalicylic acid (up to 100 mg/d)
20. History or presence of thrombotic or thromboembolic event, or increased risk for thrombotic or thromboembolic event
21. History or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate Aminotransferase (AST)/ Alanine Aminotransferase (ALT) levels or International Normalized Ratio (INR) of more than 1.5x upper limit of normal (ULN) at screening
22. History of renal disease or creatinine level above 1.5x ULN at screening
23. Known or suspected history of an ongoing, chronic or recurrent infectious disease including but not limited to opportunistic infections (eg tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis), HIV, Hepatitis B/C.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible subjects.

6 Treatment

6.1 Study treatment

There will be 3 dispensing visits: Randomization, Week 4 and Week 8.

6.1.1 Investigational and control drugs

Novartis Global Clinical Supply (GCS) will provide the following IMP supplies in appropriately blinded labeled bottles (Table 6-1).

Table 6-1 Investigational and control drug

Investigational/Control Drug (Name and Strength)	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
LOU064 10 mg	Capsule	Oral use	Double-blind supply; bottles	Sponsor global
LOU064 25 mg	Capsule	Oral use	Double-blind supply; bottles	Sponsor global
LOU064 50 mg	Capsule	Oral use	Double-blind supply; bottles	Sponsor global
LOU064 placebo	Capsule	Oral use	Double-blind supply; bottles	Sponsor global

[redacted]

6.1.2 Additional study treatments

No other additional treatment beyond investigational treatment (LOU064 and placebo) is requested for this trial. Subjects will take background medication (second generation H1-antihistamines at (locally) approved licensed doses) with a stable regimen during the study (Section 6.2.1) . For rescue medication, see Section 6.2.3.

6.1.3 Treatment arms/group

Subjects will be assigned at Day 1 to one of the following 7 treatment arms (Table 6-2) in a ratio of 1:1:1:1:1:1:1. Each subject will take 2 capsules in the morning and 2 capsules in the evening at home (except for Week 4 and Week 12 morning dose, which are to be taken on site during the site visit), for a total of 4 capsules daily. Depending on the treatment arm, these capsules will contain LOU064 at different dose strengths or placebo. The patient must take one capsule from each morning bottle (identified with a sun symbol) in the morning and one capsule from each evening bottle (identified with a moon symbol) in the evening.

Table 6-2 Treatment regimen per arm

Number of capsules per intake per treatment arm		Arm A: 10 mg LOU064 qd	Arm B: 35 mg LOU064 qd	Arm C: 100 mg LOU064 qd	Arm D: 10 mg LOU064 bid	Arm E: 25 mg LOU064 bid	Arm F: 100 mg LOU064 bid	Arm G: Placebo
Morning dose	10 mg LOU064	1	1	0	1	0	0	0
	25 mg LOU064	0	1	0	0	1	0	0
	50 mg LOU064	0	0	2	0	0	2	0
	Placebo	1	0	0	1	1	0	2
Evening dose	10 mg LOU064	0	0	0	1	0	0	0
	25 mg LOU064	0	0	0	0	1	0	0
	50 mg LOU064	0	0	0	0	0	2	0
	Placebo	2	2	2	1	1	0	2

Treatment duration

All subjects will receive their respective LOU064 or placebo capsules for 12 weeks (from Day 1 until Week 12).

[redacted]

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Throughout the study (from Day -14 until Day 113), subjects must take a second generation H1-antihistamine at a locally approved licensed dose and posology (background therapy). Background therapy must not be changed throughout the study. For detailed information on the background medication, refer to the corresponding SmPC.

Prior medication for treatment of CSU will be recorded in the eCRF. In addition, all concomitant medication at screening and prior medication that has been terminated within 4 weeks prior to screening will be recorded. The investigator should instruct the subject to notify the study site about any new medications (including medications that are not related to the treatment of CSU) he/she takes after the subject was enrolled into the study, ideally before initiating a new treatment. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the respective eCRF pages.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt the investigator should contact the Novartis medical advisor before randomizing a subject or allowing a new medication to be started. If the subject is already enrolled, Novartis should be contacted to determine if the subject should continue participation in the study.

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-3 are not allowed during the specified time period.

Table 6-3 Prohibited medication

Medication	Prohibition period
Biologics for treatment of CSU (including omalizumab and ligelizumab)	4 months prior to screening until end of study
Routine (daily or every other day during 5 or more consecutive days) doses of systemic corticosteroids	30 days prior to screening until end of study Note: from Day 1 (baseline) until Week 12 (end of treatment period) the use of systemic corticosteroids is not permitted at all.
Leukotriene antagonists (including montelukast and zafirlukast)	From screening until end of study
H2-antihistamines	From screening until end of study
First generation antihistamines	From screening until end of study
Second generation antihistamines other than the defined background medication and rescue medication	From screening until end of study
Other immunosuppressive medication with or without known effect on CSU including but not limited to hydroxychloroquine, methotrexate, cyclosporine A, cyclophosphamide, tacrolimus and mycophenolate mofetil	30 days or 5 half-lives (whichever is longer) prior to screening until end of study

[redacted]

Medication	Prohibition period
Intravenous (i.v.) immunoglobulins or plasmapheresis	30 days prior to screening until end of study
Regular (daily or every other day) doxepin (oral)	14 days prior to screening until end of study
Live attenuated vaccine	6 weeks prior to screening until end of study
Moderate and strong inhibitors of CYP3A4 (see Table 16-5 in Appendix 4), including grapefruit juice	From screening until end of study
Moderate and strong inducers of CYP3A4 (see Table 16-6 in Appendix 4)	From screening until end of study
Any drug known to prolong QTc interval (see https://crediblemeds.org for guidance)	5 half-lives or until pharmacodynamic effect has disappeared prior to baseline (whichever is longer) until end of study
Anti-platelet or anticoagulant medication (for example, warfarin, or clopidogrel or Novel Oral Anti-Coagulant - NOAC) other than acetylsalicylic acid (up to 100 mg/d)	From screening until end of study

6.2.3 Rescue medication

Second generation H1-antihistamines that are eliminated primarily via renal excretion (eg cetirizine, levocetirizine or bilastine) are allowed as rescue medication (at a locally approved licensed posology), used on an as needed basis for subjects with flare-ups of unbearable symptoms of their disease during screening, treatment and follow-up periods. The selection of the H1-antihistamines rescue medication should be made only once for an individual subject and documented in the source document. For each individual subject, the H1-antihistamine rescue medication used must differ from the H1-antihistamine used for background medication. For detailed information on the rescue medication, refer to the corresponding SmPC. A change of the rescue medication for an individual subject is not permitted. The usage of rescue therapy will be recorded in the eDiary (UPDD question 5). Name and dose of rescue medication will be reported in the eCRF. Rescue medication will be sourced locally and provided to the patient during the study.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

Each subject is identified in the study by a Subject Number (Subject No.), that is assigned when the subject is first enrolled for screening and is retained as the primary identifier for the subject throughout his/her entire participation in the trial. The Subject No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential subject number suffixed to it, so that each subject is numbered uniquely across the entire database. Upon signing the ICF, the subject is assigned to the next sequential Subject No. available.

6.3.2 Treatment assignment, randomization

At Day 1, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a

[redacted]

randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from subjects and investigator staff. A subject randomization list will be produced by the IRT provider using a validated system that automates the random assignment of subject numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by geographical region and prior usage of anti-IgE biologics (including omalizumab and ligelizumab) for treatment of CSU. [redacted]

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Subjects, investigator staff, persons performing the assessments will remain blinded to the identity of the treatment from the time of randomization until final database lock.

Designated Novartis study team members will remain blinded until the primary endpoint analysis (Week 4 analysis).

Blinding will be maintained using the following methods:

(1) Randomization data are kept strictly confidential until the time of unblinding, and will not be accessible by anyone else involved in the study except in the case of subject emergencies (see Section 6.6.2) (2) the identity of the treatments will be concealed by the use of study treatment that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor.

The randomization codes associated with subjects from whom PK samples are taken will be disclosed to unblinded PK analysts who will keep PK results confidential until data base lock.

Unblinding will occur in the case of subject emergencies and at the conclusion of the study.

6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments and/or interruptions are not permitted.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator must promote compliance by instructing the subject to take the study treatment exactly as prescribed and by stating that compliance is necessary for the subject's safety and

[redacted]

the validity of the study. It should be emphasized to the patient that the study medication bottles are not identical. The patient must take one capsule from each morning bottle (identified with a sun symbol) in the morning and one capsule from each evening bottle (identified with a moon symbol) in the evening. The subject must also be instructed to contact the investigator if he/she is unable for any reason to take the study treatment as prescribed. Compliance with study treatment will be recorded by the subject in the eDiary. In addition, compliance will be assessed by the investigator and/or study personnel at each visit using capsules counts and information provided by the subject and captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the subject safely. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study subject who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a subject, he/she must provide the requested subject identifying information and confirm the necessity to break the treatment code for the subject. The investigator will then receive details of the investigational drug treatment for the specified subject and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- subject number

In addition, oral and written information to the subject must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

After emergency unblinding the subject will not receive further study treatment and will not be able to be enrolled into possible extension studies.

6.7 Preparation and dispensation

Each study site will be supplied with study treatment in packaging as described under investigational and control drugs section (6.1.1).

A unique medication number is printed on the study medication label.

Investigator staff will identify the study medication kits to dispense to the subject by contacting the IRT and obtaining the medication number(s). The study medication has a 2-part label (base plus tear-off label), immediately before dispensing the medication kit to the subject, site personnel will detach the outer part of the label from the packaging and affix it to the source document.

[redacted]

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 Handling of study treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the subject except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial. Subjects will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

6.7.1.2 Handling of additional treatment

The investigator should assess the compliance of each subject in regard to correct use of the background H1-antihistamine at every study visit. As with the study treatment, the importance of compliance with the background medication needs to be discussed with the subject. The use of the rescue H1-antihistamine will be recorded with the eDiary on a daily basis.

6.7.2 Instruction for prescribing and taking study treatment

Every subject should take 2 capsules of the assigned LOU064 dose or placebo in the morning and 2 capsules in the evening with a 12 hour interval at approximately the same time every day. Since the study medication bottles are not identical, the patient must take one capsule from each morning bottle (identified with a sun symbol) in the morning and one capsule from each evening bottle (identified with a moon symbol) in the evening. The study medication may be taken with or without a meal but subjects should adhere to their choice throughout the study. If taken without food, the study medication should be taken with a glass of water (250 ml) at least 2 hour after the last meal and 1 hour before the next meal. On days of PK assessment, all subjects need to take their study medication on site without food (as described above). Subjects should be instructed to swallow whole capsules and not to chew or open them.

If vomiting occurs during the course of treatment, subjects should not take the study treatment (LOU064) again before the next scheduled dose.

Subjects should be instructed not to make up missed doses. A missed dose is defined as a case when the full dose is not taken within 4 hours after the approximate time of the usually

morning/evening dosing. That dose should be omitted and the subject should continue treatment with the next scheduled dose.

Study medication intake will be recorded in the patient's eDiary. Subjects will be instructed to complete eDiary entries after they took their study medication throughout the treatment period.

H1-antihistamines taken as background medication and rescue medication, respectively, should be taken according to the local treatment instructions.

All kits of study treatment assigned by the IRT will be recorded in the IRT system.

7 Informed consent procedures

Eligible subjects may only be included in the study after providing (witnessed, where required by law or regulation), Institutional Review Board/Independent Ethics Committee (IRB/IEC)-approved informed consent.

If applicable, in cases where the subject's representative(s) gives consent (if allowed according to local requirements), the subject must be informed about the study to the extent possible given his/her understanding. If the subject is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (eg all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the subject source documents.

Novartis will provide to investigators in a separate document a proposed ICF that complies with the ICH Good Clinical Practice (GCP) guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the subject.

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male subjects must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

[redacted]

8 Visit schedule and assessments

Assessment schedule lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the subject's source documentation.

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

[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]

[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]

Subjects who are randomized and fail to start treatment, eg subjects randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

8.2 Subject demographics/other baseline characteristics

Baseline CSU activity will be assessed using the eDiary from Day -7 to Day -1. Subject demographic and baseline characteristic data to be collected on all subjects include age, sex, race and ethnicity. Relevant medical history (including evaluation of inclusion/exclusion criteria, CSU history and cardiovascular history) andcurrent medical condition present before signing the informed consent will be captured. Where possible, diagnoses, and not symptoms, will be recorded. Data on subjects' family history of malignancies will be collected on the respective eCRF page, only when a subject has a malignancy event reported during the study, to assess possible risk factors related to any malignancies.

Country specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

8.3 Efficacy

All subjects will be provided with an electronic device (eDiary) that contains the following assessments: Urticaria Patient Daily Diary (UPDD), Angioedema Activity Score (AAS), and Dermatology Life Quality Index (DLQI).

Site and subjects will receive appropriate training and guidance on the use of the eDiary and will receive clear instructions on the completion of the assessments.

Assessments will be completed twice daily (UPDD), once daily (AAS, if triggered by opening question within the UPDD) or as detailed in the assessment schedule.

In general, subject complete eDiary questionnaires at home and independent of study visits. Subjects will be instructed to complete eDiary entries after they took their study medication throughout the treatment period. DLQI questionnaire will be administered during respective visits on site and should be completed prior to any other study specific procedure. Site personnel must allow subjects to complete the questionnaire on their own without any assistance from the site staff.

8.3.1 eDiary assessments

8.3.1.1 Urticaria Patient Daily Diary (UPDD)

UPDD includes Urticaria Activity Score (UAS) which assesses twice daily severity of itch and number of hives, use of rescue medication, sleep and activity interference, angioedema occurrence, its management and records the calls to an healthcare professional (HCP) (see Appendix 5). The components are presented in the Table 8-2 and the relevant weekly scores are described below.

Table 8-2 UPDD

Diary component	When assessed
Urticaria Activity Score (UAS)	Morning & evening
• Itch severity	

[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]

[redacted]

[redacted]

[redacted]

8.3.2 Other Patient Reported Outcomes (PRO) assessments

8.3.2.1 Dermatology Life Quality Index (DLQI)

The Dermatology Life Quality Index (DLQI) is a 10-item (grouped in 6 domains) dermatology-specific quality of life (QoL) measure (Finlay et al 1994). The DLQI was validated for patients aged 16 and above. Subjects rate their dermatology symptoms as well as the impact of their skin condition on various aspects of their lives thinking about the previous 7 days.

An overall score is calculated and ranges from 0 to 30 (higher score meaning worse disease-related QoL). Domain scores are calculated for: Symptoms and Feelings (0-6), Daily Activities (0-6), Leisure (0-6), Work and School (0-3), Personal Relationships (0-6), Treatment (0-3).

The overall DLQI score range was split into score bands (Hongbo et al 2005) and validated in terms of their meaning/relevance to patients as follows:

Table 8-7 DLQI score bands and impact on patient's life

DLQI band	Significance of score
0-1	No effect on patient's life
2-5	Small effect on patient's life
6-10	Moderate effect on patient's life
11-20	Very large effect on patient's life
21-30	Extremely large effect on patient's life

A DLQI score of > 10 is relevant for a very large impact on patients' life and justification for a biologic prescription for example in psoriasis (Kaplan et al 2005). The DLQI questionnaires are completed at randomization (Day 1), Weeks 4 (Day 29) and Week 12 (Day 85) in the eDiary. The DLQI should be completed prior to any other assessment and prior to administration of investigational medication.

8.3.3 Other assessments: evidence of urticaria

The investigator must confirm the presence of urticaria (i.e. the presence of hives) in each subject before randomization by direct physical examination. In the absence of active disease at the screening and/or randomization visit, the following will be acceptable: (a) a clearly identifiable photograph of the subject that is no older than 3 months showing the presence of urticaria, (b) the investigator must have seen the subject with active CSU in the past 3 months,

[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]

- 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]

Novartis will continue to keep and use collected study information (including any data resulting from the analysis of a subject's samples until their time of withdrawal) according to applicable law.

For US and Japan: All biological samples not yet analyzed at the time of withdrawal may still be used for further testing/analysis in accordance with the terms of this protocol and of the ICF.

For EU and rest of the world: All biological samples not yet analyzed at the time of withdrawal will no longer be used, unless permitted by applicable law. They will be stored according to applicable legal requirements.

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, eg dates of telephone calls, registered letters, etc. A subject should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, practical reasons (including slow enrollment), or for regulatory or medical reasons. In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the investigator, or in the event of an early study termination decision, the date of that decision.

Eligible subjects may roll-over into an extension study (which is in development) after completing investigational treatment (at Week 12) or the follow-up period (at Week 16), following roll-over criteria defined in the extension study protocol, in case the study will be locally implemented.

[redacted]

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events (AEs)

An AE is any untoward medical occurrence (eg, any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual subject and identifying AEs.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of AEs must be sought by non-directive questioning of the subject at each visit during the study. AEs also may be detected when they are volunteered by the subject during or between visits or through physical examination findings, laboratory test findings, or other assessments.

AEs must be recorded under the signs, symptoms or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. the severity grade:
    - mild: usually transient in nature and generally not interfering with normal activities
    - moderate: sufficiently discomforting to interfere with normal activities
    - severe: prevents normal activities
2. its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected'. The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease and can only be evaluated meaningfully by an analysis of cohorts, not on a single subject.
3. its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported.
4. whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. action taken regarding with study treatment.

   All AEs must be treated appropriately. Treatment may include one or more of the following:
    - dose not changed
    - dose reduced/increased
    - drug interrupted/withdrawn
6. its outcome i.e., its recovery status or whether it was fatal

[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]

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]

For more information on AE and SAE definition and reporting requirements, please see the respective sections (10.1.1 and 10.1.2).

10.2 Additional safety monitoring

10.2.1 Liver safety monitoring

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities/AEs have to be considered during the course of the study (irrespective of whether classified/reported as AE/SAE):

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and contributing factors are recorded on the appropriate eCRFs

Please refer to Table 16-1 in Appendix 2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 in Appendix 2.

- Repeat liver chemistry tests (i.e. ALT, AST, Total Bilirubin (TBL), PT/INR, ALP and GGT) to confirm elevation. These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated including consideration of treatment interruption if deemed appropriate
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event. These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy
- Obtaining a more detailed history of symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Exclusion of underlying liver disease
- Obtaining a history of exposure to environmental chemical agents

[redacted]

- Considering gastroenterology or hepatology consultations

All follow-up information, and the procedures performed must be recorded as appropriate in the eCRF(s).

10.2.2 Renal safety monitoring

The following two categories of abnormal renal laboratory values have to be considered during the course of the study:

- Serum creatinine increase ≥ 25% compared to baseline during normal hydration status
- Urine protein-creatinine ratio ≥1g/g or ≥100 mg/mmol, OR new onset dipstick proteinuria ≥ 3+ OR new onset dipstick hematuria ≥ 3+ (after excluding menstruation, Urinary Tract Infection (UTI), extreme exercise, or trauma)

Renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

Every renal laboratory trigger or renal event as defined in Table 16-3 in Appendix 3 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-4 in Appendix 3.

10.2.3 Data monitoring committee

There will be no external data monitoring committee for this study. An internal independent safety monitoring board will be convened in case of the detection of two or more similar severe or serious potentially treatment-related AEs or laboratory abnormalities as described in Section 9.1.1 in two or more different subjects. Additional triggers for convening the internal independent safety monitoring board may be defined in the respective charter. The internal independent safety monitoring board will consist of Novartis designated associates from medical, statistical and patient safety departments who are not part of the CLOU064A2201 study team.

The internal independent safety monitoring board will review unblinded safety data information for the affected subjects and will then decide on appropriate subsequent measures to ensure patient safety or to gain more information, if deemed necessary. The review process will follow the internal independent safety monitoring board charter. Appropriate subsequent measures may include:

- unblinded safety review of all enrolled subjects by the internal independent safety review board
- amendment(s) to the study protocol, which may include discontinuation of treatment arms or even stopping the study.

10.2.4 Steering committee

A steering committee (SC) may be established with experts in the field of CSU including investigators participating in the trial and Novartis representatives.

If established, the SC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SC will review protocol amendments as appropriate. Together with the clinical trial team, the SC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in the steering committee charter.

[redacted]

10.2.5 Adjudication committee

Not applicable.

11 Data collection and database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the eCRFs. The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The investigator must certify that the data entered are complete and accurate

After final database lock, the investigator will receive copies of the subject data for archiving at the investigational site.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

11.2 Database management and quality control

Novartis personnel (or designated Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff is required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and AEs will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis.

ECG readings will be processed centrally and results will be sent electronically to Novartis.

Patients will fill in their eDiary data on a device at home. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis personnel.

Randomization codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

[redacted]

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis/delegated CRO representative will review the protocol and data capture requirements (i.e. electronic source (eSource) DDE or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will visit the site to check the completeness of subject records, the accuracy of data capture/data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. Continuous remote monitoring of each site's data may be performed by a centralized Novartis/delegated CRO/Clinical Research Associate (CRA) organization. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information on eCRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original ICF signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

12 Data analysis and statistical methods

The analysis will be conducted on all subjects' data at the time the trial ends.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Randomized Set will consist of all randomized subjects, regardless of whether or not they actually received study medication. Subjects will be analyzed according to the treatment

[redacted]

assigned to at randomization. Unless otherwise specified, mis-randomized subjects (mis-randomized in IRT) will be excluded from the randomized set. Mis-randomized subjects are defined as cases where IRT contacts were made by the site either prematurely or inappropriately prior to confirmation of the subject's final randomization eligibility and no study medication was administered to the subject.

The Full Analysis Set (FAS) will consist of all randomized subjects who received at least one dose of study medication. Following the intent-to-treat principle, subjects will be analyzed according to the treatment and strata assigned to at randomization. Mis-randomized subjects (mis-randomized in IRT) will be excluded.

The Safety Set will consist of all subjects who received at least one dose of study medication whether or not being randomized. Subjects will be analyzed according to treatment received.

12.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics will be summarized using the safety set and FAS including disease characteristics, prior and background medications to treat urticaria, and relevant medical histories. Summary statistics will be presented for continuous demographic and baseline characteristic variables for each treatment group. The number and percentage of subjects in each category will be presented for categorical variables for each treatment group.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25^{th} and 75^{th} percentiles will also be presented.

Any significant prior or active medical condition at the time of signing informed consent will be coded using the MedDRA dictionary. These medical conditions will be summarized by primary system organ class and preferred term.

12.3 Treatments

Analyses of treatment will be based on the Safety Set.

Study treatment

The duration of exposure to study treatment will be summarized by treatment group. In addition, the number of subjects with exposure of at least certain thresholds (eg, any exposure, ≥1 week, ≥2 weeks, ≥4 weeks, ≥8 weeks, etc.) will be displayed.

Prior and concomitant medication

Prior and concomitant medications will be summarized by treatment separated for urticaria related background medications and non-urticaria related medications. Urticaria related background medications will be summarized by pre-specified categories (including dose) and preferred term. Non-urticaria related concomitant medications will be summarized by preferred term. Use of rescue medication will be summarized as well.

12.4 Analysis of the primary endpoint(s)

All analyses for efficacy data will be based on the FAS.

[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]

[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]

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]

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]

[redacted]

[redacted]

12.8 Sample size calculation

Primary endpoint(s)

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 and 100 mg b.i.d) and placebo with respect to change from baseline in UAS7 at Week 4. The sample size was determined with the software R, version 3.0.3.

[redacted]

[redacted]

[redacted]

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the IRB/IEC for the trial protocol, written ICF, consent form updates, subject recruitment procedures (eg advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (eg defined as last subject last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (eg Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

[redacted]

13.4 Quality control and quality assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal Standard Operating Procedures (SOPs), and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and health authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for subject safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

[redacted]

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References are available upon request.

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[redacted]

16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

The following specific criteria have been identified for this study. Should these criteria be met, a re-test must be done within 5 days after the first assessment. Discontinuation of the study treatment should be considered if the abnormal hematology parameter is confirmed:

Hemoglobin: < 10 g/dl

Platelets: < 75 000/mm^3

White blood cells: < 3 000/mm^3

Neutrophils: < 1 500/mm^3

For all other laboratory assessments, the central laboratory will flag laboratory values falling outside of the normal ranges on the central laboratory report (which the investigator should review and sign-off) and the investigator will report any values considered clinically significant in the eCRF.

Notable values for vital signs and change from baseline will be summarized.

Notable values are defined as follows: heart rate of < 60 and > 100 bpm; systolic blood pressure of < 90 and ≥ 140 mmHg; diastolic blood pressure of < 60 and ≥ 90 mmHg.

For ECGs a notable QTc value is defined as a QTc (Fridericia's) interval of greater than 450 msec for males or greater than 460 msec for females – all such ECGs will be flagged by the central CRO's cardiologist and require assessment for clinical relevance by the investigator.

[redacted]

16.2 Appendix 2: Liver event and laboratory trigger definitions and follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/threshold
LIVER LABORATORY TRIGGERS	3 x ULN < ALT/AST ≤ 5 x ULN 1.5 x ULN < TBL ≤ 2 x ULN
LIVER EVENTS	ALT or AST > 5 × ULN
	ALP > 2 × ULN (in the absence of known bone pathology)
	TBL > 2 × ULN (in the absence of known Gilbert syndrome)
	ALT or AST > 3 × ULN and INR > 1.5
	Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and TBL > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN)
	Any clinical event of jaundice (or equivalent term)
	ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia
	Any AE potentially indicative of a liver toxicity*

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms TBL: total bilirubin; ULN

Table 16-2 Follow-up requirements for liver events and laboratory triggers

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case[a]	-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)
ALT or AST		
> 8 × ULN	-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 × ULN and INR > 1.5	-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)
> 5 to ≤ 8 × ULN	-Repeat LFT within 48 hours -If elevation persists, continue follow-up monitoring -If elevation persists for more than 2 weeks, discontinue the study drug -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)

[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]

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]

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.

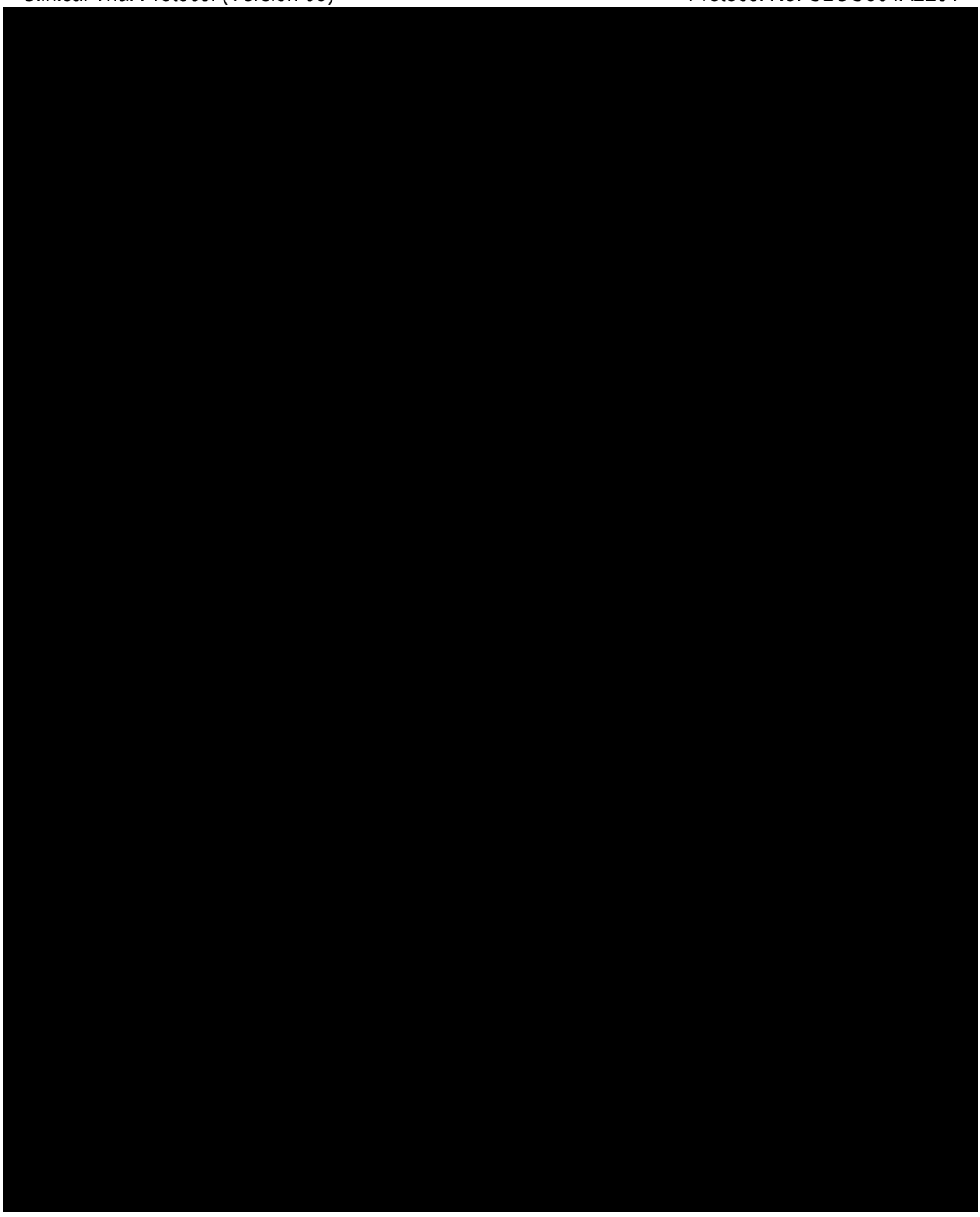
Table 16-5 Moderate and strong inhibitors of CYP3A4

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]



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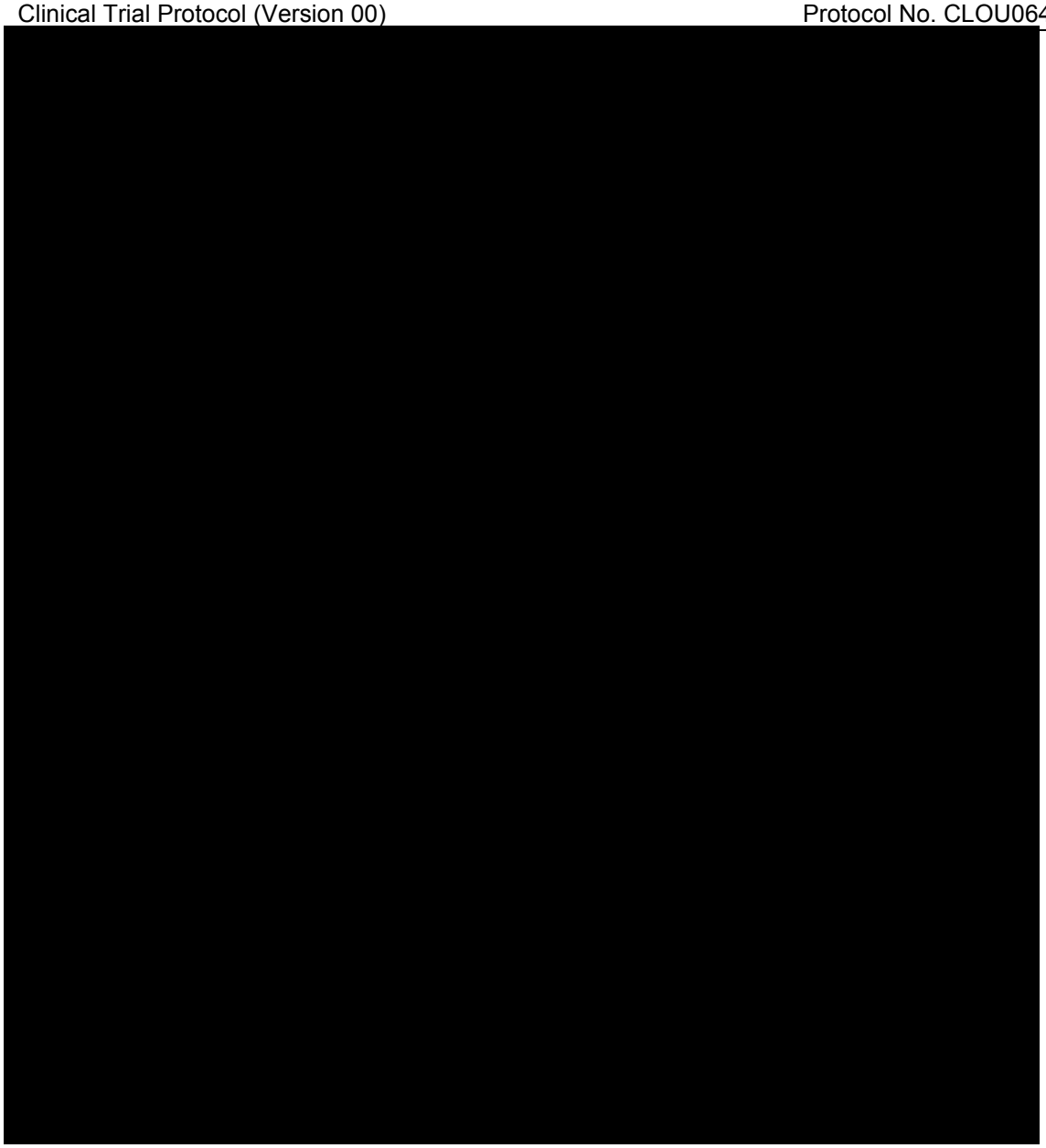

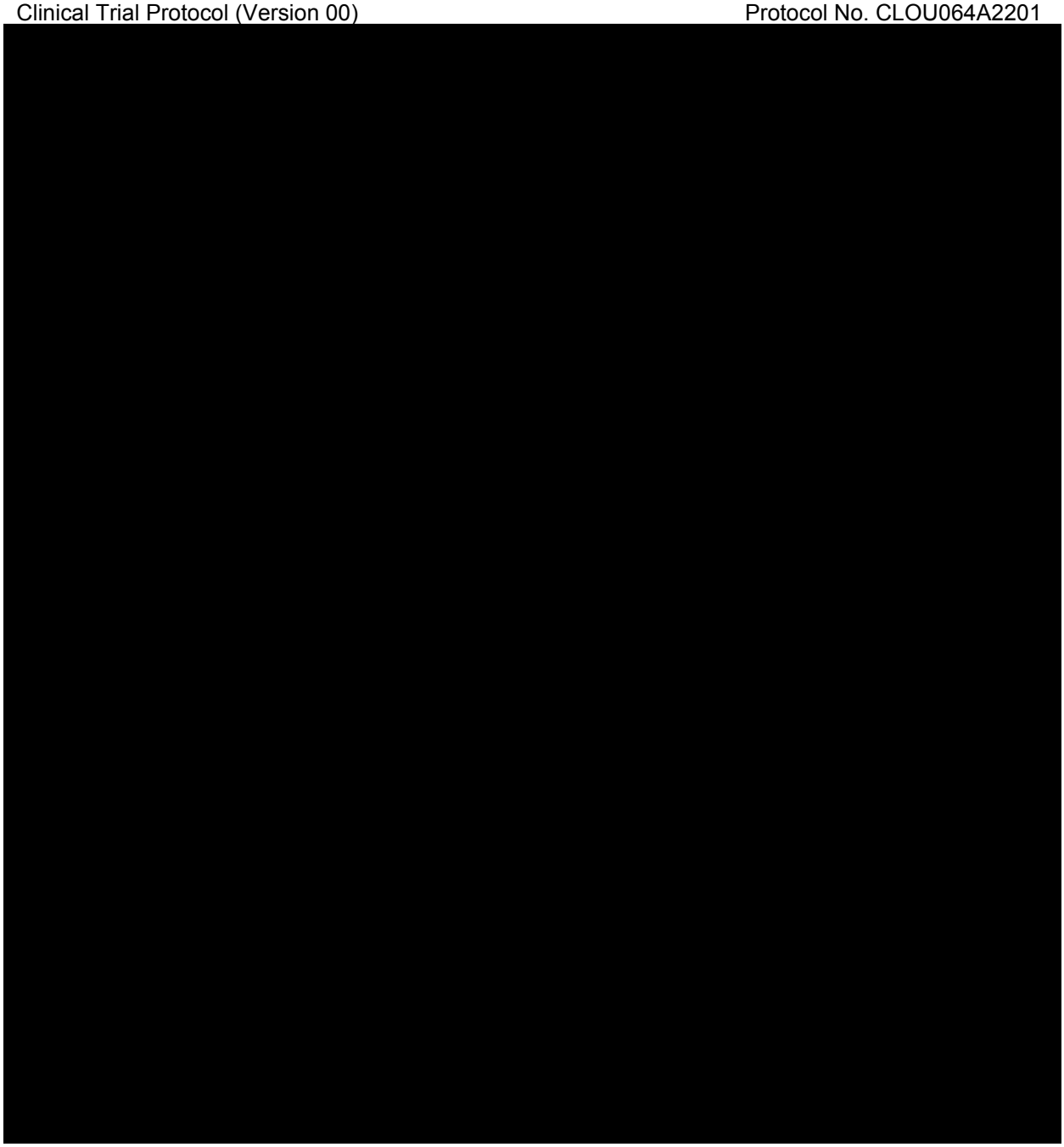

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