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Novartis Research and Development

LOU064

Protocol CLOU064A2201E1 / NCT04109313

An open-label, multicenter, extension study to evaluate the long-term safety and tolerability of LOU064 in eligible subjects with CSU who have participated in CLOU064A2201

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List of abbreviations

[redacted]	[redacted]
AE	Adverse Event
Alb	Albumin
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
AV block	Atrioventricular block
BCR	B Cell Receptor
BCRP	Breast cancer resistance protein
b.i.d.	bis in die / twice a day
BP	Blood Pressure
BTK	Bruton's Tyrosine Kinase
BTKi	Bruton's Tyrosine Kinase Inhibitor
BUN	Blood Urea Nitrogen
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CO	Country Organization
COA	Clinical Outcomes Assessment
COVID-19	Coronavirus Disease of 2019
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
CYP	Cytochrome P
DBP	Diastolic Blood Pressure
DDE	Direct Data Entry
DDI	Drug-Drug Interaction
DIN	Drug-Induced Nephrotoxicity
[redacted]	[redacted]
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	Estimated Glomerular Filtration Rate
EMA	European Medicines Agency
eSource	Electronic Source

[redacted]

EU	European Union
FAS	Full Analysis Set
FcεR	Fc epsilon receptor
FcγR	Fc gamma receptor
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	hour
HCP	Health Care Professional
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
ISS7	Weekly Itch Severity Score
IUD	Intrauterine device
IUS	Intrauterine system
i.v.	intravenous
LDH	lactate dehydrogenase
LDL	Low-Density Lipoprotein
LFT	Liver function test
LLOQ	lower limit of quantification
MAD	Multiple Ascending Dose
[redacted]	[redacted]
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)

[redacted]

MRI	Magnetic Resonance Imaging
ng	Nanogram(s)
NOAC	Novel Oral Anti-Coagulant
NOAEL	No-Observed Adverse Event Level
NSAID	Nonsteroidal Anti-Inflammatory Drug
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PCR	Protein-creatinine ratio
PD	Pharmacodynamic(s)
P-gp	Permeability glycoprotein, P-glycoprotein
[redacted]	[redacted]
[redacted]	[redacted]
PT	prothrombin 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
SOP	Standard Operating Procedure
SPT	Skin Prick Test
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total Bilirubin
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
WBC	White Blood Cell(s)
WHO	World Health Organization
WoCBP	Women of Child-Bearing Potential
XLA	X-linked Agammaglobulinemia

[redacted]

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 (e.g. 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 (e.g. 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 (e.g. 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.

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 Amendment 3 (08-Sep-2021)

Amendment rationale

The purpose of this 3rd protocol amendment is to implement a change [redacted]

The introduced changes do not significantly impact patient safety, study population, trial conduct, or scientific value of the trial, and, therefore, are considered non-substantial.

Additionally, this change will not affect the Informed Consent.

Changes to the protocol

- [redacted]
- List of abbreviations has been updated.

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~red strike through font for deletions~~ and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities, as applicable, according to local regulations.

The changes described in this amended protocol are considered non-substantial and do not require IRB/IEC and Health Authority approval prior to implementation.

The changes herein do not affect the Informed Consent.

[redacted]

Protocol Amendment 2 (05-Apr-2021)

Amendment rationale

This protocol amendment version 02 implements two changes [redacted] the removal of the male contraception requirement.

In addition:
- The local Protocol Amendment 1 (CLOU064A2201E1 01-CA.01) has been incorporated into the present Global Amended Protocol Version v02. Changes introduced in the local Protocol Amendment 1 CA.01 were issued on 30-Oct-2019 and are specific to Canada (for more details, refer to Local Protocol Amendment 1 (for Canada only, 30-Oct-2019)). These changes have been reviewed and approved by Health Canada.
- Specific guidance concerning public health emergency situations as declared by local or regional authorities (i.e., pandemic, epidemic or natural disaster) has been included (Section 4.6), as well as mitigation procedures to ensure participant safety and trial integrity in the relevant sections. A study-specific medical and safety risk assessment was performed, and it was concluded that based on the current data, the benefit/risk due to the COVID-19 pandemic remains unchanged. Infections are already described as a potential risk in Section 4.5 and no further updates are considered necessary for this amendment.

At the time of this amendment release, CLOU064A2201E1 has started and approximately 227 participants have rolled over from CLOU064A2201 study.

The major modifications to the protocol are:

- [redacted]
- The requirement for male contraception in this study has been removed following the reproductive toxicity assessment, which concluded a wide safety margin (>150 fold) for the exposure of a female partner of male subject receiving LOU064, as described in the LOU064 Investigator Brochure Edition 6, dated 17-Sep-2020. Consequently, exclusion criterion #11 has been deleted (Section 5.2).

As the study population is affected, the changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation. Additionally, the male contraception requirement affects the Informed Consent.

Changes to the protocol

- [redacted]

[redacted]

- **Section 4.6** added for Public Health Emergency mitigation procedures. Section 6.7, Section 7, Section 8, Section 8.3, Section 8.4, Section 8.4.1, Section 8.4.3 and Section 8.5.2 have been updated accordingly. **Section 5.2** - Deletion of exclusion criterion #11 pertaining to male contraception. All other relevant sections of the protocol have been updated to reflect this change (Section 4.5, Section 7, Section 8.4.3 and Section 10.1.4).

Changes to specific sections of the protocol are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

IRBs/IECs

A copy of this amended protocol will be sent to the Institutional Review Board (IRBs)/Independent Ethics Committee (IECs) and Health Authorities.

The changes described in this amended protocol require IRB/IEC and Health Authority approval according to local regulations prior to implementation.

The changes herein affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

[redacted]

Local Protocol Amendment 1 (for Canada only, 30-Oct-2019)

The purpose of this amendment is to:

1) Add a threshold for the estimated glomerular filtration rate (eGFR) to exclusion criterion #22

2) Update actions after detection of a renal adverse event.

Changes to protocol and rationale

- **Section 5.2 Exclusion criteria**: Following the recommendation of Health Canada for the preceding core study (CLOU064A2201), an eGFR <45 ml/min threshold was added to exclusion criterion #22.

- **Section 8.4.1 Laboratory evaluation:** eGFR added to Table 8-10 Laboratory assessments.

- **Section 10.2.2 Renal safety monitoring**: Following the recommendation of Health Canada for the preceding core study (CLOU064A2201), the timelines after detection of a renal adverse event have been changed.

- **Section 16.3 Appendix 3: Specific renal alert criteria and actions and event follow-up:** Following the request of Health Canada for the preceding core study (CLOU064A2201), necessary actions after the detection of a renal adverse event have been clarified and a rise of serum creatinine ≥50% compared to baseline now leads to a mandatory interruption of the investigational treatment.

[redacted]

Protocol Amendment 1 (02-Oct-2019)

The main purpose of this amendment is to address requests from health authorities and to align eligibility criteria of this study with amended eligibility criteria of the preceding core study CLOU064A2201:

- Deletion of inclusion criterion #4 (this change triggers several changes throughout the document, including changing the study title, modification of inclusion criterion #3 [redacted]).
- Lowering the minimum required resting heart rate to 50 bpm (from 60 bpm) to align with amended exclusion criterion #6b in CLOU064A2201. This also aligns the eligibility criterion for resting heart rate with normal resting heart rates of CSU patients and does not impact patient safety as LOU064 does not have a negative chronotropic effect.
- Clarification that investigators need to assess the benefit-risk ratio for each subject throughout the study. Both, lack of or inadequate treatment response and/or emergence of adverse events that outweigh the benefits, can lead to study treatment discontinuation.
- Adding urine pregnancy testing every 4 weeks with at home assessments between study visits for women of childbearing potential starting after the Week 20 visit of the treatment period.

Additionally, editorial errors were addressed and clarity was improved.

As the study population is affected, the changes described in this amended protocol require IRB/IEC approval prior to implementation. Additionally, some changes affect the Informed Consent. Sites are required to update and submit for approval a revised Informed Consent that takes into account the changes described in this protocol amendment.

Changes to protocol and rationale

Changes are shown in the track changes version of the protocol using ~~strike through red font for deletions~~ and red underlined for insertions.

- **Section 5.1:** Following a request from health authorities, inclusion criterion #4 (i.e. rollover of patients from not-yet specified studies with LOU064) was deleted. Additionally, inclusion criterion #3 needed to be updated to inclusion criterion #3a in order to clarify, that all subjects must have completed the Week 12 or Week 16 visit of CLOU064A2201 prior to enrollment into this extension study. As no patients from other studies can rollover from other not-yet specified preceding studies anymore, the reference to other preceding studies needed to be deleted in several sections of the protocol:
  - Protocol title
  - Section 1.2 (Purpose)
  - Section 2 (Objectives and Endpoints, including Table 2-1)
  - Section 3 (Study Design, including Figure 3-1)
  - Section 5 (Population)
  - Section 12.8.1 (Primary Endpoints, in Section 12.8, Sample size calculation)
- **Section 5.2, exclusion criterion #6 has been updated to exclusion criterion #6a:** This exclusion criterion aims to exclude patients with a pre-existing cardiac risk from

[redacted]

enrollment into this study. CSU patients are comparable to the general population with respect to cardiac health and resting heart rate in particular. In a general population, >5-10 % of subjects will have a resting heart rate <60 bpm (Avram et al. 2019). Accordingly, resting heart rates from 50 to 90 are regarded as normal (Nanchen, 2018). Neither in pre-clinical studies nor in phase 1 clinical studies LOU064 was reported to have a negative chronotropic effect (LOU064 Investigator's brochure, section 4 and 5). Therefore, defining a heart rate of 60 bpm as lower limit for the resting heart rate does not increase the safety of subjects in this study. However, it may prevent the enrollment of a significant number of otherwise eligible CSU patients who may benefit from participation in this study. In line with the definition of the physiological range for resting heart rate (Nanchen, 2018), bullet point 3 of the amended exclusion criterion #6a of the preceding core study defines 50 bpm as the lower limit for resting heart rate. To ensure that all subjects fulfilling the rollover criteria may enroll into this extension study, the corresponding exclusion criterion is amended (new bullet point 3: Resting heart rate (as measured by 12 lead ECG) <50 bpm at day 1 of treatment).

- **Section 4.4** and **Section 12.7:** With the amended inclusion criteria, no patients from other studies can rollover from other not-yet specified preceding studies. [redacted] he sections have been updated accordingly.
- **Table 8-1** in **Section 8** and **Section 8.4.3**: Following a request from health authorities, the sections of the protocol were amended to ensure that all women of childbearing potential perform a urine pregnancy test every four weeks while receiving study medication. Test may be performed at home if there is no scheduled study visit.
- **Section 8.1:** Text has been updated for clarity.
- **Section 8.3:** Following a request from health authorities to clarify benefit-risk assessment, efficacy assessments and the responsibility of the investigator, to review efficacy assessments have been clarified.
- [redacted]
- [redacted]
- **Section 9.1.1:** Following a request from health authorities to ensure that subjects who do not benefit from study participation need to discontinue study treatment, the statement *"The investigator must discontinue study treatment for a given subject if, he/she believes that continuation would negatively impact the subject's well-being."* has been further clarified.
- **Appendix 1:** Amendment of clinically notable heart rates to <50 bpm and >100 bpm, respectively, in line with amended exclusion criterion #6a (see above).
- [redacted]

[redacted]

Protocol summary

Protocol number	CLOU064A2201E1
Full Title	An open-label, multicenter, extension study to evaluate the long-term safety and tolerability of LOU064 in eligible subjects with CSU who have participated in CLOU064A2201
Brief title	An open-label extension study to evaluate the long-term safety and tolerability of LOU064 in subjects with CSU
Sponsor and Clinical Phase	Novartis, phase 2
Investigation type	Drug
Study type	Interventional
Purpose and rationale	The purpose of this study is to evaluate long-term safety and tolerability as well as efficacy outcome of LOU064 in patients with CSU who rollover from CLOU064A2201. [redacted]
Primary Objective(s)	To assess the long-term safety and tolerability of LOU064 in patients with CSU who have participated in CLOU064A2201 study.
Secondary Objectives	To evaluate the long-term efficacy of LOU064 in patients with CSU who have participated in CLOU064A2201 study with respect to maintaining or achieving controlled disease (defined by a UAS7≤6) over time. To evaluate the long-term efficacy of LOU064 in patients with CSU who have participated in CLOU064A2201 study with respect to change from baseline in UAS7 over time. To evaluate the efficacy of LOU064 when given without H1-antihistamines in patients with CSU who have participated in CLOU064A2201 study with respect to change from baseline in UAS7, achieving controlled disease (defined by a UAS7≤6), and achieving complete response (defined by a UAS7=0) at Week 4 of treatment.
Study design	This is an open-label, single arm extension study consisting of • a treatment period with 100 mg LOU064 bid for 52 weeks followed by • a treatment free follow up period (4-16 weeks). Subjects rolling over from the core study CLOU064A2201 may be allocated to an observational period before they can enter the treatment period depending on their UAS7 response when rolling over.
Population	The study population will consist of male and female adult CSU patients who received various doses of LOU064 or placebo in the core study (CLOU064A2201). Approximately 250 are estimated to rollover into this extension study.
Key Inclusion criteria	Written informed consent must be obtained before any assessment is performed. Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules. Subjects must have completed the Week 12 visit (end of treatment period) or the Week 16 visit (end of the follow-up period) of CLOU064A2201 and will be allocated

[redacted]

	to the treatment period or the observational period of CLOU064A2201E1 based on the UAS7 score (of the 7 days prior to the respective visit) as follows: • Subjects rolling over at Week 12 of CLOU064A2201 with a UAS7≥16 will be allocated to the Treatment period *(note: **subjects with UAS7<16 at Week 12 are not eligible to roll-over** into CLOU064A2201E1 but need to enter the follow-up period of CLOU064A2201).* • Subjects rolling over at Week 16 of CLOU064A2201 with a UAS7≥16 will be allocated to the Treatment period. • Subjects rolling over at Week 16 of CLOU064A2201 with a UAS7<16 will be allocated to the Observational period.
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, e.g. 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, e.g. 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 (as measured by 12 lead ECG) < 50 bpm • Resting QTcF ≥450 msec (male) or ≥460 msec (female) at day 1 of the treatment period 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 (e.g. tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis), HIV, Hepatitis B/C
Study treatment	LOU064 capsules 50 mg
Efficacy assessments	• Urticaria Patient Daily Diary (UPDD), including Urticaria Activity Score (UAS) [redacted]

[redacted]

Key safety assessments	Adverse event (AE) monitoring Physical examinations Vital signs [redacted] ECG monitoring
Other assessments	[redacted]
Data analysis	Since this extension study is primarily to evaluate the long term safety and tolerability of LOU064, summary statistics will be provided for adverse events, laboratory measurements, other safety measurements and efficacy assessments over time; No statistical hypothesis testing will be performed. [redacted]
[redacted]	[redacted]
Key words	Chronic spontaneous urticaria BTK inhibitor Long-term safety Urticaria activity score [redacted]

[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, beyond the approved label dose, has not been studied in larger clinical studies. 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.

1.2 Purpose

The purpose of this study is to evaluate long-term safety and tolerability as well as efficacy outcome of LOU064 in patients who roll-over from CLOU064A2201. [redacted]

[redacted]

[redacted]

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 assess the long-term safety and tolerability of LOU064 in patients with CSU who have participated in CLOU064A2201.	• Safety endpoints will include but not be limited to: occurrence of treatment emergent (serious and non-serious) adverse events during the extension study
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of LOU064 when given without H1-antihistamines in patients with CSU who have participated in CLOU064A2201 with respect to change from baseline in UAS7, achieving controlled disease (defined by a UAS7≤6), and achieving complete response (defined by a UAS7=0) at Week 4 of treatment	• Change from baseline in UAS7 at Week 4 • UAS7≤6 response at Week 4 • UAS7=0 response at Week 4
• To evaluate the long-term efficacy of LOU064 in patients with CSU who have participated in CLOU064A2201 with respect to maintaining or achieving controlled disease (defined by a UAS7≤6) over time	• UAS7≤ 6 response over time
• To evaluate the long-term efficacy of LOU064 in patients with CSU who have participated in CLOU064A2201 with respect to change from baseline in UAS7 over time	• Change from baseline in UAS7 over time

[redacted]

[redacted]

[redacted]

3 Study design

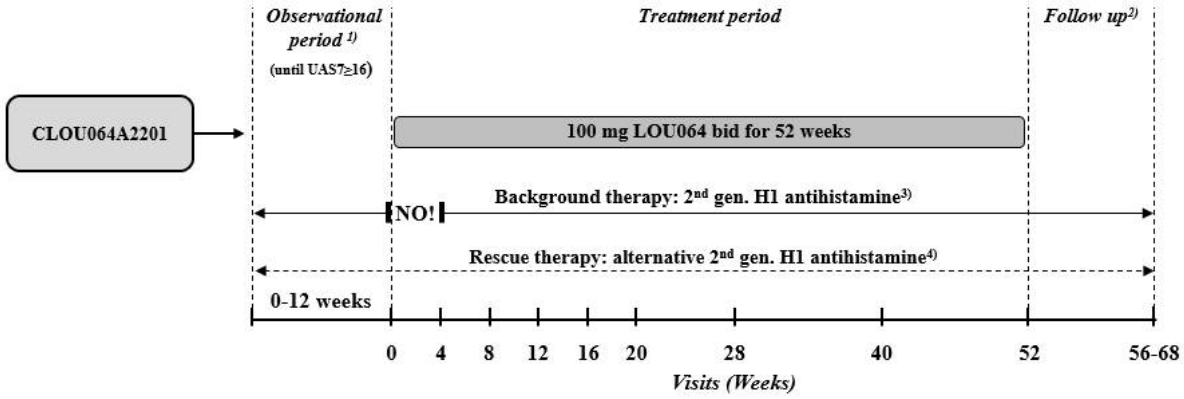
This study is an open-label, single arm, multicenter, long-term safety and tolerability extension study for CSU patients rolling-over from CLOU064A2201. It consists of three periods (Figure 3-1):

- ***Observational period:*** Subjects rolling over from CLOU064A2201 with UAS7<16 after the follow-up period at Week 16 will be further followed up without receiving LOU064 for up to 12 weeks. After relapse (UAS7≥16 at least once), the observational period can be terminated immediately at any time during these 12 weeks and subjects may enter the treatment period. Continuation of background therapy with an H1-antihistamine is at the discretion of the investigator; however, background therapy should only be interrupted in subjects with controlled CSU (e.g. UAS7≤6). Subjects who have never relapsed within 12 weeks will discontinue the study after the observational period.
- ***Treatment period:*** Subjects will be treated with 100 mg LOU064 bid for 52 weeks. Until Week 4 of treatment, no background medication with H1-antihistamines is permitted. After Week 4, subjects may start a background therapy with H1-antihistamines if deemed necessary by the investigator.
- ***Follow-up period:*** Treatment-free follow-up period following the treatment period. The minimum duration of treatment-free follow-up is 4 weeks for all subjects who stop treatment with LOU064 (either after completing the treatment period or after an early discontinuation of study treatment). Subjects who have a UAS7≤6 at Week 52 of the treatment period will extend their follow-up period until relapse (UAS7≥16) for up to a total of 16 weeks.

Rescue therapy to treat unbearable symptoms of urticaria on a day-to-day basis with an H1-antihistamine will be allowed throughout the study. A post-trial access program (which may be another extension study or a managed access program) for subjects who complete this study is under consideration.

[redacted]

Figure 3-1 Study design



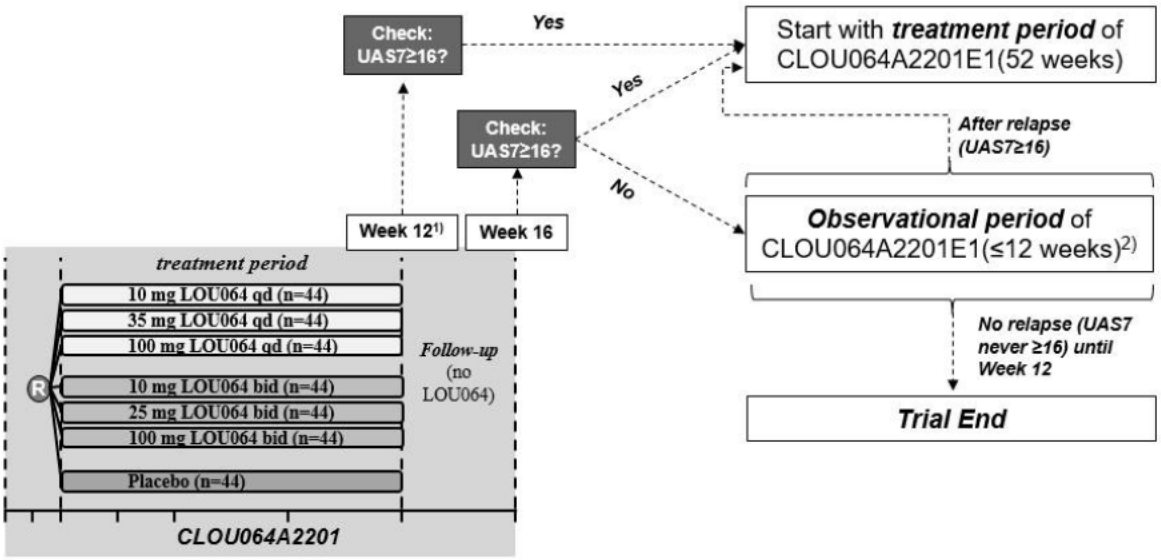
1) Only when UAS7<16 at Week 16 of CLOU064A2201: Treatment-free observational period for up to 12 weeks. After relapse (UAS7≥16 at least once), subjects may immediately initiate treatment period. Subjects who have never relapsed within 12 weeks will discontinue the study after the observational period.
2) The minimum duration of the follow-up period will be 4 weeks for all subjects who stop treatment with LOU064. Subjects who achieve a UAS7≤6 at Week 52 of the treatment period will extend their follow-up period until they relapse (UAS7≥16). Follow-up will stop at Week 68 for all subjects.
3) Background therapy is a second generation H1-antihistamine at a locally approved licensed posology given with a stable treatment regimen. Administration/discontinuation of the background H1-antihistamine is at the discretion of the investigator. Background therapy must not be taken from Day 1 until Week 4 of the Treatment period. It may be re-initiated at Week 4 if deemed necessary.
4) Rescue therapy is a second generation H1-antihistamine at a locally approved licensed posology that is eliminated primarily via renal excretion (e.g. 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.

Subjects rolling over from CLOU064A2201 will be assigned to one of the periods as follows (Figure 3-2):

- Subjects with a UAS7≥16 at Week 12 or Week 16 will directly enter the treatment period.
- Subjects with a UAS7 < 16 at Week 12 will not rollover into the extension study but enter the follow-up period of the core study CLOU064A2201.
- Subjects with a UAS7<16 at Week 16 (i.e., who have not relapsed during the follow-up period of CLOU064A2201) will be assigned to the observational period.

[redacted]

Figure 3-2 Patient flow from CLOU064A2201



[1)] Only subjects with a UAS7≥16 at Week 12 of CLOU064A2201 are eligible to directly rollover into the extension study CLOU064A2201E1 (and directly start with the treatment period). Subjects with a UAS7<16 enter the follow-up period of CLOU064A2201.
[2)] After relapse (UAS7≥16 at least once), the observational period can be terminated immediately and subjects may enter the treatment period. Subjects who have never relapsed within 12 weeks will discontinue the study after the observational period.

4 Rationale

4.1 Rationale for study design

The major aims of this extension study are to obtain information on the long-term safety and efficacy of a dosing regimen of LOU064 with a high level of BTK occupancy and therefore pharmacological activity, LOU064 100 mg bid for 52 weeks. An open-label study design was chosen to minimize complexity and placebo exposure for CSU patients who have participated in the dose-range finding study CLOU064A2201. A follow-up period of (up to) 16 weeks after the treatment period will further assess safety [redacted]

4.1.1 Rationale for choice of background therapy

Following therapeutic principles for CSU as suggested by current treatment guidelines (Zuberbier et al 2018), the core study assessed efficacy and safety of different doses of LOU064 when given together with H1-antihistamines. The mechanism of action suggests, that the addition of H1-antihistamines is not mandatory to achieve the full therapeutic potential of LOU064. Therefore, the concomitant administration of a background H1-antihistamine is at the [redacted]

discretion of the investigator in this extension study. [redacted]

4.2 Rationale for dose/regimen and duration of treatment

As LOU064 covalently binds its target BTK, it is expected that the therapeutic effects of LOU064 directly correlate with BTK occupancy throughout the dosing interval. As the minimum level of BTK occupancy for full therapeutic efficacy is unknown, optimal dose and dosing interval remain to be determined. LOU064 100 mg bid was chosen for this long-term extension study as

[redacted]

- it is the maximum dose tested in CLOU064A2201,
- the safety margins established in preclinical toxicology studies support this dose, including chronic toxicology studies in 2 species, and
- LOU064 100 mg bid and higher doses were well tolerated in the MAD cohorts of CLOU064X2101 (please refer to the Investigator's brochure, Section 5.2, for further details).

Due to the chronic nature of CSU, early establishment of long-term safety and efficacy of a treatment with LOU064 is desirable. The selected duration of 52 weeks is based on the treatment objective to achieve long-term sustained remission in CSU patients and will provide the required safety exposure database to satisfy registration needs.

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

Not applicable.

[redacted]

4.5 Risks and benefits

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 2015) and LOU064 as well as other BTK inhibitors have been shown to effectively inhibit mast cell and basophil activation:

[redacted]

- LOU064 and ibrutinib, an approved BTK inhibitor used to treat B cell malignancies, have been shown to 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).

[redacted]

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.

To date, 213 healthy volunteers have received LOU064 up to 600 mg q.d. for up to 18 days in four studies. In the study CLOU064X2101, 30 healthy volunteers received total daily doses ≥100 mg for a period of 12 days. 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 Investigator's Brochure (Sections 4.3 and 5.2).

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 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 (e.g.: 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 kinase 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. Since BTK is not expressed in mature plasma cells, it is not expected that BTK inhibition in adults would lead to rapid or marked decrease in total immunoglobulin levels within the study time-frame. (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

[redacted]

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] 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 was implemented in the preceding core study and ECG will be further monitored throughout this extension study. 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] oncomitant 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 [redacted]

acalabrutinib, embryofetal toxicity in animals is reported (see SmPCs). Highly effective methods of contraception must be practiced for women of child-bearing potential while taking study treatment and for 7 days after stopping study medication.

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

4.6 Rationale for Public Health Emergency mitigation procedures

During a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, mitigation procedures to ensure participant safety and trial integrity are listed in relevant sections. Notification of the Public health emergency should be discussed with Novartis prior to implementation of mitigation procedures and permitted/approved by Local or Regional Health Authorities and Ethics Committees as appropriate.

5 Population

The study population will consist of male and female adult CSU patients who received various doses of LOU064 or placebo in the core study (CLOU064A2201). Subjects with a UAS7 $\geq$ 16 at Week 12 or Week 16 of the core study will directly enter the treatment period whereas subjects with a UAS7 < 16 at Week 16 of the core study will be allocated to the observational period (see Section 3). In theory, all expected 308 patients from the core trial CLOU064A2201 could enter the extension protocol. However, we estimate that approximately 250 patients will enroll into this extension study.

5.1 Inclusion criteria

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

1. Written informed consent must be obtained before any assessment is performed.
2. Willing and able to complete a daily symptom eDiary for the duration of the study and adhere to the study visit schedules.

3a Subjects must have completed the Week 12 visit (end of treatment period) or the Week 16 visit (end of the follow-up period) of CLOU064A2201 and will be allocated to the

[redacted]

treatment period or the observational period of CLOU064A2201E1 based on the UAS7 score (of the 7 days prior to the respective visit) as follows:

- Subjects rolling over at Week 12 of CLOU064A2201 with a UAS7≥16 will be allocated to the Treatment period *(note: **subjects with UAS7<16 at Week 12 are not eligible to rollover** into CLOU064A2201E1 but need to enter the follow-up period of CLOU064A2201).*
- Subjects rolling over at Week 16 of CLOU064A2201 with a UAS7≥16 will be allocated to the Treatment period.
- Subjects rolling over at Week 16 of CLOU064A2201 with a UAS7<16 will be allocated to the Observational period.

5.2 Exclusion criteria

1. Use of other investigational drugs within 5 half-lives of enrollment, or within 30 days (for small molecules) prior to enrollment 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 drugs 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, e.g. atopic dermatitis, bullous pemphigoid, dermatitis herpetiformis, senile pruritus or psoriasis

6a 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, e.g. 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 (as measured by 12 lead ECG) < 50 bpm at day 1 of treatment
- Resting QTcF ≥450 msec (male) or ≥460 msec (female) at day 1 of the treatment period 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. Patients/subjects taking medications prohibited by the protocol (see Section 6.2.2, Table 6-2)

[redacted]

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 during dosing 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 (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) total hysterectomy or tubal ligation at least six weeks before taking investigational drug. 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 investigational drug.

    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 (e.g. 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. Exclusion criterion had become irrelevant.
12. Major surgery within 8 weeks prior to enrollment or surgery planned prior to end of the treatment period.
13. History of live attenuated vaccine within 6 weeks prior to enrollment 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 last visit before Day 1 of the Treatment period (either last available value from CLOU064A2201 or most recent value taken during observational period):

[redacted]

- Hemoglobin: < 10 g/dl
- Platelets: < 100 000/mm3
- White blood cells: < 3 000/mm3
- Neutrophils: < 1 500/mm3

17. Significant bleeding risk or coagulation disorders
18. History of gastrointestinal bleeding, e.g. 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 of more than 1.5 x upper limit of normal (ULN) at last visit before Day 1 of the Treatment period (either last available value from CLOU064A2201 or most recent value taken during observational period)
22. History of renal disease or creatinine level above 1.5x ULN at last visit before Day 1 of the Treatment period (either last available value from CLOU064A2201 or most recent value taken during observational period)

    [**Canada only**: History of renal disease, creatinine level above 1.5x ULN or eGFR <45ml/min (using the Cockcroft-Gault equation) at last visit before Day 1 of the Treatment period (either last available value from CLOU064A2201 or most recent value taken during observational period)]
23. Known or suspected history of an ongoing, chronic or recurrent infectious disease including but not limited to opportunistic infections (e.g. 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

Novartis Global Clinical Supply (GCS) will provide the IMP for the study. Background and concomitant medication will not be supplied by Novartis GCS.

6.1.1 Investigational and control drugs

Table 6-1 Investigational drug

Investigational Drug	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor (global or local)
LOU064 50 mg	Hard gelatin capsule	Oral use	Open-label supplies, bottles	Novartis Pharma AG (Global)

[redacted]

6.1.2 Additional study treatments

No additional treatment beyond investigational treatment is included in this trial. After Week 4, subjects may restart to take background medication (second generation H1-antihistamines at (locally) approved licensed doses; see Section 6.2.1). For rescue medication, see Section 6.2.3.

6.1.3 Treatment arms/group

Subjects will be treated with 100 mg LOU064 bid open label (i.e. two capsules of LOU064 50 mg in the morning and two capsules of LOU064 50 mg in the evening) for 52 weeks. Subjects rolling over from CLOU064A2201 with a UAS7<16 at Week 16 will be assigned to the observational period (see Section 3).

6.1.4 Treatment duration

The planned duration of treatment is 52 weeks. Subjects may be discontinued from treatment earlier if treatment response and/or tolerability is unacceptable in the opinion of the investigator or the subject. A post-trial access program (which may be another extension study or a managed access program) for subjects who complete this study is under consideration.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

In contrast to the core study CLOU064A2201, LOU064 may be given with or without background medication, as deemed appropriate by the investigator. However, all subjects must start the treatment period (day 1 until Week 4) with LOU064 as a monotherapy without concomitant administration of H1-antihistamines. After Week 4, subjects may start a background therapy with H1-antihistamines at a locally approved licensed dose and posology if deemed necessary by the investigator.

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 medications (see Table 6-2). If in doubt the investigator should contact the Novartis medical advisor before enrolling a subject or allowing a new medication to be started. If the subject is already enrolled, Novartis should be contacted immediately to determine if the subject should continue participation in the study.

[redacted]

[redacted]

[redacted]

6.2.2 Prohibited medication

Use of the treatments displayed in the below table are not allowed during the specified time period.

Table 6-2 Prohibited medication

Medication	Prohibition period
Biologics for treatment of CSU (including omalizumab and ligelizumab)	4 months prior to enrollment until end of study
Routine (daily or every other day during 5 or more consecutive days) doses of systemic corticosteroids	30 days prior to enrollment until end of study
Leukotriene antagonists (including montelukast and zafirlukast)	From enrollment until end of study
H2-antihistamines	From enrollment until end of study
First generation antihistamines	From enrollment until end of study
Second generation antihistamines other than the defined background medication and rescue medication	From enrollment 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 enrollment until end of study
Intravenous (i.v.) immunoglobulins or plasmapheresis	30 days prior to enrollment until end of study
Regular (daily or every other day) doxepin (oral)	14 days prior to enrollment until end of study
Live attenuated vaccine	6 weeks prior to enrollment until end of study
Moderate and strong inhibitors of CYP3A4 (see Table 16-5), including grapefruit juice	From enrollment until end of study
Moderate and strong inducers of CYP3A4 (see Table 16-6)	From enrollment 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 enrollment (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 enrollment until end of study

[redacted]

6.2.3 Rescue medication

Second generation H1-antihistamines that are eliminated primarily via renal excretion (e.g. 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 throughout the study. 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 (if used). For detailed information on the rescue medication, refer to the corresponding SmPC. The rescue medication should be changed only if deemed necessary by the investigator. [redacted]

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 patient is first enrolled 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/sponsor 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 informed consent form, the patient is assigned to the next sequential Subject No. available. Each subject number in this extension study will be linked to the respective study number in the core study via Prior study participation form.

6.3.2 Treatment assignment, randomization

After enrollment, subjects will be assigned to the treatment period or the observational period based on their UAS7 score (see Section 5).

6.4 Treatment blinding

Treatment will be open to subjects, investigator staff, persons performing the assessments, and the CTT.

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 the validity of the study. The patient must take two capsules of LOU064 50 mg in the morning and two capsules of LOU064 50 mg in the evening with a dosing interval of approximately [redacted]

12 hours. 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

Not applicable.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs Section 6.1.1.

An IRT system would be used in the study for medication management purposes.

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.

At each dispensation visit, study personnel delegated for this activity would contact IRT and provide the patient with the assigned bottles to accommodate patient needs till the next dispensation visit. The number of bottles dispensed would vary depending on the duration between visits.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, delivery of IMP directly to a participant's home may be permitted (if allowed by Local or Regional Health Authorities and Ethics Committees as appropriate) in the event the Investigator has decided that an on-site visit by the participant is no longer appropriate or possible and that it is in the interest of the participant's health to administer the study treatment even without performing an on-site visit. The dispatch of IMP from the site to the participant's home remains under the accountability of the Investigator. Each shipment/provisioning will be for a maximum of one-month supply. In this case, regular phone calls or virtual contacts (every 4 weeks or more frequently if needed) will occur between the site and the participant for instructional purposes, safety monitoring, drug accountability, investigation of any adverse events, ensuring participants continue to benefit from treatment, and discussion of the participant's health status until the participants can resume visits at the study site.

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

[redacted]

instructions specified on the labels and in the Investigator's Brochure. Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CPO 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.

[redacted]

6.7.2 Instruction for prescribing and taking study treatment

Subjects should take 2 capsules of LOU064 50 mg twice daily with a 12 hour interval in the morning and in the evening at approximately the same time each day. Subjects should take LOU064 without regard to food. Each dose may be taken with a glass of water. [redacted] 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 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. This 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.

[redacted]

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), IRB/IEC-approved informed consent.

[redacted]

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 (e.g. 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 informed consent form that complies with the ICH 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 Investigator's Brochure (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.

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

The study includes the option for the participant to have certain study procedures performed off-site by an off-site healthcare professional instead of at the study site, for which a separate signature is required if the participant agrees. It is required as part of this protocol that the Investigator presents this option to the participant, as permitted by national and local governing regulations. The process for obtaining consent should be exactly the same as described above for the main informed consent.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities i.e. pandemic, epidemic or natural disaster, that may challenge the ability to obtain a standard written informed consent due to limits that prevent an on-site visit, Investigator may conduct the informed consent discussion remotely (e.g. telephone, videoconference) if allowable by a local Health Authority.

Guidance issued by local regulatory bodies on this aspect prevail and must be implemented and appropriately documented (e.g. the presence of an impartial witness, sign/dating separate ICFs by trial participant and person obtaining informed consent, etc.).

8 Visit schedule and assessments

The assessment schedule lists all of the assessments and indicates with an “X” or “S”, the visits when they are performed. All data obtained from these assessments must be supported in the subject’s source documentation.

[redacted]

Subjects should be seen/contacted 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.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster that limits or prevents on-site study visits, alternative methods of providing continuing care may be implemented by the investigator as the situation dictates. If allowed by local Health Authority and depending on operational capabilities, phone calls, virtual contacts (e.g., tele consult) or visits by site staff/home nursing staff to the participant's home can replace on-site study visits for the duration of the disruption until it is safe for the participant to visit the site again.

[redacted]

Table 8-1 Assessment Schedule, Treatment period and Follow-up period

Period	Open Label Treatment									Treatment free follow-up				Unscheduled visit
Visit	Scree-ning								EoTV[10]				Study Completion Visit[13]	
Days	1	29	57	85	113	141	197	281	365 (or early termination)	393[11]	421[12] ☎	449[12] ☎	393-477	NA
Weeks	1	4	8	12	16	20	28	40	52	56	60	64	56-68	NA
Informed consent	X													
Prior study participation	X													
Inclusion / Exclusion criteria	X													
Demography	X													
Physical Examination[1]	S[8]	S	S	S	S	S	S	S	S	S			S	S
Vital Signs	X[8]	X	X	X	X	X	X	X	X	X			X	X
Body Weight	X[8]						X		X				X	X
Electrocardiogram (ECG)	X[8]	X	X	X		X	X	X	X				X	X
Concomitant medications	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X[8]	X	X	X	X	X	X	X	X	X	X	X	X	X
Drug dispensation	X	X	X	X	X	X	X	X						X
IRT transaction	X	X	X	X	X	X	X	X	X					X

[redacted]

[redacted]

Period	Open Label Treatment									Treatment free follow-up				Unscheduled visit
Visit	Screening								EoTV[10]				Study Completion Visit[13]	
Days	1	29	57	85	113	141	197	281	365 (or early termination)	393[11]	421[12] ☎	449[12] ☎	393-477	NA
Weeks	1	4	8	12	16	20	28	40	52	56	60	64	56-68	NA
Subjects' eDiary review[3] - UPDD (incl. UAS)	S[8]	S	S	S	S	S	S	S	S	S	S	S	S	S
[redacted]														
Study drug compliance Assessment		S	S	S	S	S	S	S	S					S
[redacted]														
Urinalysis	X[8]	X	X	X	X	X	X	X	X	X			X	X
Clinical Chemistry	X[8]	X	X	X	X	X	X	X	X	X			X	X
Hematology	X[8]	X	X	X	X	X	X	X	X	X			X	X
Coagulation Panel	X[8]						X		X				X	X
[redacted]														
Total IgE				X			X		X				X	X
[redacted]														
Pregnancy Test (serum)[6]	X													
Pregnancy test (urine)[7]		S	S	S	S	S	S	S	S	S			S	S

[redacted]

Period	Open Label Treatment									Treatment free follow-up				Unscheduled visit
Visit	Scree-ning								EoTV[10]				Study Completion Visit[13]	
Days	1	29	57	85	113	141	197	281	365 (or early termination)	393[11]	421[12] ☎	449[12] ☎	393-477	NA
Weeks	1	4	8	12	16	20	28	40	52	56	60	64	56-68	NA
Check eligibility for entering extended Follow-up (up to 16 weeks)									S					
Disposition (end of treatment and study disposition)	X													

X: recorded in the eCRF; S: recorded in the source documents only
[1] Detailed description of physical exam in Table 8-9. Complete physical exam: day 1 of the treatment period. Short physical exam: all other visits.
[redacted]
[3] UPDD: Urticaria Patient Daily Diary; UAS: Urticaria Activity Score; [redacted]
[redacted]
[6] Only performed in women of childbearing potential
[7] Only performed in women of childbearing potential. In addition to tests during study visits, urine pregnancy tests can be performed at home at Week 24, 32, 36, 44, and 48. Sites must contact subjects to obtain test results. Any positive or undetermined test result must be confirmed by a serum pregnancy test done by central lab.
[8] Only assess if day 1 is more than 1 week after roll-over date from core study (Week 12 or Week 16)
[9] Only assess if subjects rollover at Week 16 or if subjects rollover at Week 12 and day 1 of treatment period is more than 1 week after Week 12 of core study
[10] EoTV (End-of-Treatment Visit) is after completion of the treatment period (Week 52 Visit), or directly after early discontinuation of study treatment (see Section 9.1)
[11] Only for subjects eligible for extended follow-up
[12] Phone call visits: after Week 56, all eligible subjects in extended follow-up should be contacted every 4 weeks by phone until Study Completion visit which is a site visit
[13] SCV (Study Completion Visit) is 4-16 weeks after EoTV:

- all subjects should be followed-up for a minimum of 4 weeks after EoTV
- the extended follow-up of eligible subjects (completion of treatment period and a UAS7≤6 at Week 52) should be stopped after relapse of CSU, initiation of a prohibited therapy (see Section 6.2.2), decision of the subject or the investigator to stop the follow-up, rolling-over into a post-trial access program (if available), or reaching the maximum follow-up time (16 weeks, Week 68 Visit)

[redacted]

Table 8-2 Assessment Schedule, Observational period

Visit	Screening			EoOP[5]	Unscheduled visit
Days	**1**	**29[4]**	**57[4]**	**8-85**	**NA**
Weeks	**1**	**4**	**8**	**1-12**	**NA**
Informed consent	X				
Prior study participation	X				
Inclusion / Exclusion criteria	X				
Demography	X				
Short Physical Examination	S			S	S
Adverse Events	X[3]	X	X	X	X
Concomitant medications	X[3]	X	X	X	X
[redacted]					
Subjects' eDiary review[1] : - UPDD (incl. UAS)	S[3]	S	S	S	S
[redacted]					
Clinical Chemistry		X	X	X	X
Hematology		X	X	X	X
[redacted]					
Total IgE				X	X
[redacted]					
Study disposition	X				

[redacted]

X: recorded in the eCRF; S: recorded in the source documents only

[1] UPDD: Urticaria Patient Daily Diary; UAS: Urticaria Activity Score; [redacted]

[redacted]

[3] Only assess if day 1 of observational period is more than 1 week after Week 16 of core study

[4] If CSU relapse is detected at the visit: please directly perform an EoOP visit instead of the preplanned day 29 or day 57 visit

[5] EoOP: End of Observational Period can be directly after a CSU relapse (defined as UAS7≥16) was detected (either during a scheduled or an unscheduled visit); in case, EoOP and day 1 of the treatment period are at the same day, assessments only need to be done once.

[redacted]

[redacted]

8.1 Screening

At day 1 of the treatment period and at day 1 of the observational period (if applicable), all inclusion and exclusion criteria will be checked. For all laboratory assessments, the results from the last visit before Day 1 of the treatment period (either the last available value from CLOU064A2201 or most recent value taken during observational period) will be used.

Eligibility for this study will be assessed at Week 12 and Week 16 of the preceding core study CLOU064A2201. Subjects who are not eligible for enrollment into this extension study at Week 12 for any reason will not be assigned to a subject number for this extension study but will enter the follow-up period of CLOU064A2201. Re-screening of subjects who are not eligible at Week 16 is not permitted.

8.1.1 Information to be collected on screening failures

Patients who sign an informed consent but fail to be started on treatment for any reason other than never relapsing during the observational period will be considered a screen failure. The reason for not being started on treatment will be entered on the screening phase disposition page. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure patients. No other data will be entered into the clinical database for patients who are screen failures, unless the patient experienced a serious adverse event during the screening phase (see SAE Section for reporting details).

8.2 Subject demographics/other baseline characteristics

Baseline CSU activity will be assessed using the eDiary from Day -7 to Day -1 of the day 1 visit of the treatment period. Subject demographic and baseline characteristic data including sex, race and ethnicity that was collected as a part of the core study will be used for this extension study. Relevant medical history (including evaluation of inclusion/exclusion criteria, CSU history and cardiovascular history) and current 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), [redacted].

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. Investigators need to review the eDiary at every visit.

Assessments will be completed twice daily (UPDD), [redacted] or as detailed in the assessment schedule.

[redacted]

In general, subjects 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. [redacted]
Site personnel must allow subjects to complete the questionnaire on their own without any assistance from the site staff.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, Clinical Outcomes Assessment (COA) data may be collected remotely (e.g., via web portal) depending on local regulations, technical capabilities and following any applicable training in the required process.

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, [redacted] angioedema occurrence, its management and records the calls to an healthcare professional (HCP) (Section 16.5). The components are presented in Table 8-3 and the relevant weekly scores are described below.

Table 8-3 UPDD

Diary component	When assessed
Urticaria Activity Score (UAS) • Itch severity • Number of hives	Morning & evening
[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 8-4). 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.

[redacted]

Table 8-4 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)

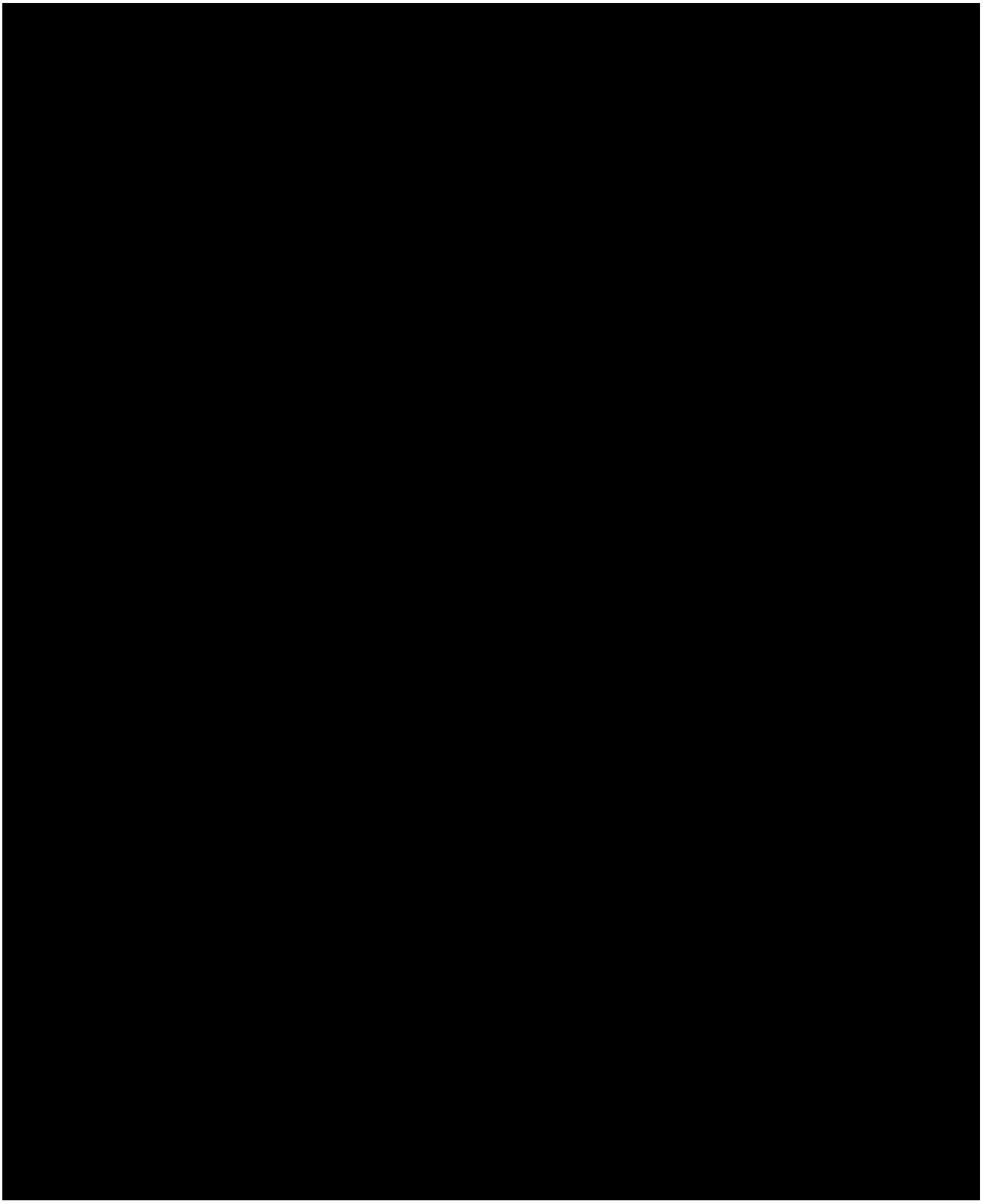
The severity of the itch will be recorded by the subject twice daily in their eDiary, on a scale of 0 (none) to 3 (severe) (Table 8-5). A weekly score (ISS7) is derived by adding up the average daily scores of the 7 days preceding the visit. The possible range of the weekly score is therefore 0 - 21.

Table 8-5 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]

8.3.3 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). [redacted]

[redacted]

8.4 Safety/Tolerability

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.

[redacted]

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 8-9 Physical Assessments

Assessment	Specification
Physical examination	A complete physical examination (performed at enrollment, see Table 8-1) 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 visits indicated in Table 8-1 and Table 8-2) 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). 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, e.g. 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 Section 16.1.
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.

As per Section 4.6, during a Public Health emergency as declared by Local or Regional authorities, i.e., pandemic, epidemic or natural disaster, that limits or prevents on-site study visits, regular phone or virtual calls can occur (every 4 weeks or more frequently if needed) for safety monitoring and discussion of the participant's health status until it is safe for the participant to visit the site again.

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all specimens detailed in this section (Table 8-10) 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.

[redacted]

If participants cannot visit the site for protocol specified safety lab assessments (per Section 4.6), an alternative lab (local) collection may be used.

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 8-10 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, Creatine Kinase (CK), Creatinine, total Bilirubin (in case of clinically significant elevation: direct Bilirubin and indirect Bilirubin will be assessed), [**Canada only**: eGFR] Only at baseline (day 1), Week 28 and 52: 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 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), Activated partial thromboplastin time (APTT)
Additional tests	IgE, [redacted] serum pregnancy test (for WoCBP)
Pregnancy Test	Urine pregnancy test for WoCBP

8.4.2 Electrocardiogram (ECG)

ECGs will be analyzed centrally and performed with ECG machines supplied by the central provider. Standard 12-lead ECGs (single readings) must be recorded after 10 minutes rest in the supine position according to the ECG investigator manual at the timepoints indicated in Table 8-1. 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.

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.

[redacted]

In the event that a clinically significant ECG abnormality is identified at the site (e.g. 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

All pre-menopausal women who are not surgically sterile will have pregnancy testing at day 1 of the treatment period (on serum), and every 4 weeks thereafter (compare Table 8-1) on urine (tests may be performed at home if there is no scheduled study visit). To obtain home-test results, sites must contact subjects. Any positive or undetermined urine test needs to be confirmed by a serum pregnancy test. If positive, the subject must be discontinued from study treatment.

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

If participants cannot visit the site to have pregnancy tests as scheduled at site, urine pregnancy test kits may be used. Relevant participants can perform the urine pregnancy test at home and report the result to the site. It is important that participants are instructed to perform the urine pregnancy test first, and only if the test result is negative are they to proceed with administration of the study treatment. A communication process should be established with the participant so that the site is informed and can verify the pregnancy test results (e.g., following country-specific measures).

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 continues ECG monitoring in this extension study. The laboratory evaluation plan will provide sufficient safety information for LOU064 in the target population.

[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. This may include but not be limited to

[redacted]

- lack of or inadequate response to study treatment in the opinion of the investigator and/or the subject,
- emergence of AEs that outweigh the benefits of study treatment in the opinion of the investigator and/or the subjects.

Study treatment must be discontinued under the following circumstances:

- Subject 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, e.g. required surgical interventions associated with a risk for clinically significant bleeding
- 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 (e.g. 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
  - 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 9.1.2). Subjects should perform the End-of-Treatment visit (EoTV) as quickly after their last dose as possible. Then, subjects should be asked to return to the study site 4 weeks later for Study Completion Visit (SCV). If they fail to return for these assessments for unknown reasons, every effort (e.g. 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
- adverse events/Serious Adverse Events

[redacted]

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

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 want any further visits or assessments
  and
- Does not want any further study related contacts
  and
- Does not allow analysis of already obtained biologic material

In this situation, the investigator should make a reasonable effort (e.g. 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.

Novartis will continue to retain and use all research results (data) that have already been collected for the study evaluation.

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, e.g. 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 (provide instruction for contacting the subject, when the subject should stop taking drug, when the subject should come for a final visit) and treated as a prematurely withdrawn subject. The investigator may be informed of

[redacted]

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.

In the event of an early study termination, all subjects should perform the Week 52 visit (End-of-Treatment visit) as quickly as possible after their last dose and the Week 56 Follow-up visit (4 weeks later).

A post-trial access program (which may be another extension study or a managed access program) for subjects who complete this study is under consideration.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g., 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 adverse events.

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

The occurrence of adverse events must be sought by non-directive questioning of the subject at each visit during the study. Adverse events 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.

Adverse events must be recorded in the Adverse Events CRF 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

[redacted]

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 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 adverse events 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
    - not recovered/not resolved
    - recovered/resolved
    - recovering/resolving
    - recovered/resolved with sequelae
    - fatal
    - unknown

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

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

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

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. 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 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 adverse events 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

[redacted]

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

A 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
  - 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, e.g. 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 serious adverse event irrespective if a clinical event has occurred (see details in Section 10.1.5).

[redacted]

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 (e.g. 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 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. An 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 Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a 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.

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 following the last administration of study treatment should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

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.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (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.

[redacted]

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 collected in the DAR (dose administration record) eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with a 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

For more information on AE and SAE definition and reporting requirements, please see Section 10.1.1, Section 10.1.2, and Section 10.1.3.

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 / adverse events 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 completion of the standard base liver CRF pages

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.

[redacted]

- Repeat liver chemistry tests (ALT, AST, TBL, PT/INR, ALP and G-GT) 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
- Imaging such as abdominal US, CT or MRI, as appropriate
- Obtaining a history of exposure to environmental chemical agents.
- Considering gastroenterology or hepatology consultations.

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

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.

[**Canada only**: Renal event findings must be confirmed within ≤ 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.

[redacted]

10.2.3 Data Monitoring Committee

In contrast to the core study CLOU064A2201, this extension study is not blinded. Therefore, an independent safety monitoring board as described in the protocol of the core study is not necessary.

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.

11 Data Collection and Database management

11.1 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, 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 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 are 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 WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

[redacted]

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.

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.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked 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.

[redacted]

12 Data analysis and statistical methods

12.1 Analysis sets

The **Safety Analysis Set (SAF)** includes all subjects who received at least one dose of study treatment during the treatment period of this extension study.

For the observational period, the observational Full Analysis Set **(oFAS)** includes all subjects who enrolled in the observational period.

All enrolled subjects includes all subjects who enrolled in this extension study.

12.2 Subject demographics and other baseline characteristics

Demographics and baseline characteristics

Demographic and baseline disease characteristics will be summarized for SAF and oFAS. Listing will be provided for all subjects enrolled.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, lower quartile, median, upper quartile, minimum, and maximum will be presented.

Medical history

Relevant medical histories and current medical conditions before first dose of study treatment in the treatment period will be summarized by system organ class and preferred term according to MedDRA dictionary for SAF. Urticaria related medical history will be summarized separately for SAF.

All relevant medical histories and current medical conditions will be listed for all subjects enrolled. Cardiovascular history and family malignancy history for subjects developed malignancy during the treatment period will be listed for SAF.

[redacted]

12.3 Treatments

Study Treatment

The duration of exposure (in weeks) will be summarized by means of descriptive statistics using the SAF. In addition, the number and percentage of subjects with exposure of at least certain thresholds (e.g. any exposure, >=1 week, >= 2 weeks, >= 3 weeks, >= 4 Weeks, ..., etc.) will be displayed.

Prior and Concomitant medication

Prior, non-urticaria related concomitant medications and urticaria related medication will be summarized separately by Anatomical Therapeutic Chemical (ATC) codes and main group for SAF.

Prior treatments are defined as treatment taken and stopped prior to first dose of study treatment in the treatment period. Any treatment given at least once between the day of first dose of study treatment during treatment period and the last day of study visit will be a concomitant treatment, including those which were started prior to enter the treatment period.

In addition, prior and concomitant medical procedures and significant non-drug therapies will be summarized by primary system organ class and MedDRA preferred term for SAF.

12.4 Analysis of the primary endpoint(s)

The primary analysis will focus on the safety variables. The primary safety analysis will be analyzed using SAF.

12.4.1 Definition of primary endpoint(s)

The primary objective of this study is to investigate the long-term safety and tolerability of LOU064 in subjects with CSU.

The primary variables are: AEs/SAEs, ECGs, laboratory assessment, and vital signs, etc. Baseline for safety analysis is defined as the last measurement before the first dose of study medication in the treatment period of this extension study.

Adverse events

All adverse events which newly start on the same day or after the first dose of study medication in the treatment period of this extension study OR get worsening on the same day or after the first dose of study medication and within end of study visit will be considered as treatment emergent adverse event for this extension study.

Number and percentage of subjects having any treatment emergent adverse events during the extension study, by system organ class and preferred term will be provided for:

- All adverse events
- Adverse events by maximum severity
- Drug related adverse events
- Serious Adverse events
- Adverse events leading to treatment discontinuation

[redacted]

Adverse events by standardized MedCRA Query (SMQ) and preferred term will be provided.

Separate summaries will be provided for deaths, SAEs, and other significant AEs leading to discontinuation. For the definition of AEs and SAEs please see Section 10.1.1 and Section 10.1.2.

Laboratory data

Baseline is defined as last assessment (including unscheduled assessments) before the first dose day of treatment period.

Descriptive summary statistics for laboratory data (hematology and serum chemistry) will be provided at baseline and post-baseline by test category, parameter, and visit during the treatment period.

Shift table on normal range between baseline and post baseline visits will be provided.

Number and percentage of patients with newly occurring clinical notable laboratory values (see Appendix 16.1, Appendix 16.2, and Appendix 16.3) will also be provided.

ECGs

Summary statistics will be provided for ECG parameters by visit during treatment period. Shift table on normal ranges and number and percentage of notable abnormalities will also be summarized.

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

12.4.2 Statistical model, hypothesis, and method of analysis

No hypothesis testing is planned for the primary objective.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum.

Summary statistics for discrete variables will be presented in contingency tables and will include absolute and relative frequencies.

12.4.3 Handling of missing values/censoring/discontinuations

Not applicable.

12.4.4 Sensitivity and Supportive analyses

Not applicable.

[redacted]

12.5 Analysis of secondary endpoints

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

UAS7 score change from baseline at Week 4

Summary statistics for absolute values, change from baseline and percentage change from baseline in UAS7 score at Week 4 will be presented for SAF.

UAS7 at baseline will be considered as the UAS7 derived over the last 7 days before day 1 of treatment period (which might be different from the UAS7 used for the eligibility of the subject during the observational period).

UAS7 <= 6 at Week 4

Number and percentage of patients achieved well controlled disease (UAS7<= 6) at Week 4 will be summarized for SAF.

UAS7 =0 at Week 4

Number and percentage of subjects with complete response (UAS7= 0) at Week 4 will be provided for SAF.

UAS7 <= 6 over time

Number and percentage of subjects with well control of disease (UAS7 <= 6) will be provided by each visit over time up to Week 52 for SAF. [redacted]

UAS7 score over time

Summary statistics of absolute score, change from baseline and percentage change from baseline in UAS7 will be presented by each visit over time up to Week 52 for SAF. Figure will be provided.

12.5.2 Safety endpoints

Adverse event and serious adverse event during observation period will be summarized by primary system organ class and preferred term for oFAS. For Safety reporting in the treatment period see Section 12.4.

All AEs will be listed for all subjects enrolled.

[redacted]

[redacted]

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

It is expected that approximately 250 subjects from CLOU064A2201 study will enroll in this extension study. [redacted]

[redacted]

12.8.2 Secondary endpoint(s)

Not applicable.

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 Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., 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 (defined as last patient 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

[redacted]

results website and all required Health Authority websites (e.g. 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

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 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

[redacted]

be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request.

Arm JP, Bottoli I, Skerjanec A, et al (2014) Pharmacokinetics, pharmacodynamics and safety of QGE031 (ligelizumab), a novel high-affinity anti-IgE antibody, in atopic subjects. Clin Exp Allergy; 44(11): 1371-85.

Avram, R, Tison, GH, Aschbacher, K, et al (2019) Real-world heart rate norms in the Health eHeart study. NPJ Digit Med; 2; 58.

[redacted]

Dispenza MC, Pongracic JA, Singh AM, et al (2018) Short-term ibrutinib therapy suppresses skin test responses and eliminates IgE-mediated basophil activation in adults with peanut or tree nut allergy. J Allergy Clin Immunol; 141(5):1914-1916.

Ferrer M (2015) Immunological events in chronic spontaneous urticarial. Clin Transl Allergy; 5: 30.

[redacted]

Finlay AY (2005) Current severe psoriasis and the rule of tens. Br J Dermatol; 152(5): 861-7.

Greaves MW (2003) Chronic idiopathic urticarial. Curr Opin Allergy Clin Immunol; 3(5): 363-8.

Guillen-Aguinaga S, Jauregui Presa I, Aguinaga-Ontoso E, et al (2016) Updosing nonsedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis. Br J Dermatol; 175(6): 1153-65.

Hendriks RW, Yuvaraj S, Kil LP (2014) Targeting Bruton's tyrosine kinase in B cell malignancies. Nat Rev Cancer; 14(4): 219-32.

Hongbo Y, Thomas CL, Harrison MA, et al (2005) Translating the science of quality of life into practice: What do dermatology life quality index scores mean?. J Invest Dermatol; 125(4): 659-64.

Kaplan A, Ferrer M, Bernstein JA, et al (2016) Timing and duration of omalizumab response in patients with chronic idiopathic/spontaneous urticarial. J Allergy Clin Immunol; 137(2): 474-81.

Kumar A, Teuber SS and Gershwin ME (2006) Current perspectives on primary immunodeficiency diseases. Clin Dev Immunol; 13(2-4): 223-59.

Maurer M, Staubach P, Raap U, et al (2017) H1-antihistamine-refractory chronic spontaneous urticaria: it's worse than we thought - first results of the multicenter real-life AWARE study. Clin Exp Allergy; 47(5): 684-92.

[redacted]

Nanchen, D (2018) Resting heart rate: what is normal? Heart; 104(13); 1048-9.

[redacted]

Nutt SL, Hodgkin PD, Tarlinton DM, et al (2015) The generation of antibody-secreting plasma cells. Nat Rev Immunol; 15(3): 160-71.

O'Donnell BF, Lawlor F, Simpson J, et al (1997) The impact of chronic urticaria on the quality of life. Br J Dermatol; 136(2): 197-201.

Regan JA, Cao Y, Dispenza MC, et al (2017) Ibrutinib, a Bruton's tyrosine kinase inhibitor used for treatment of lymphoproliferative disorders, eliminates both aeroallergen skin test and basophil activation test reactivity. J Allergy Clin Immunol; 140(3): 875-9.

Smiljkovic D, Blatt K, Stefanzl G, et al (2017) BTK inhibition is a potent approach to block IgE-mediated histamine release in human basophils. Allergy; 72(11):1666-76.

Sun C. Tian X, Lee YS, et al (2015) Partial reconstitution of humoral immunity and fewer infections in patients with chronic lymphocytic leukemia treated with ibrutinib. Blood; 126(19): 2213-9.

U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER) (2020) In vitro drug interaction studies - Cytochrome P450 enzyme- and transporter-mediated drug interactions, Guidance for Industry. Available at <https://www.fda.gov/media/134582/download>.

Zuberbier T, Aberer W, Asero R, et al (2018) The EAACI/GA(2)LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update. Allergy; 2018 Jan 15.

[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 < 50 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 adverse event 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: upper limit of normal

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 (e.g. 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 (e.g. 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 (e.g. 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)

Criteria	Actions required	Follow-up monitoring
> 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 (e.g. 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 accompanied by symptoms[b]	– Discontinue the study treatment immediately – Hospitalize, if clinically appropriate – Establish causality – Record the AE and contributing factors (e.g. 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 (patient 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 (e.g. concomitant medication, medical history, laboratory values) 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 (e.g. 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 (e.g., reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient 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 patient – Establish causality – Record the AE and contributing factors (e.g. 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	Investigator discretion

[redacted]

Criteria	Actions required	Follow-up monitoring
	− Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory values) in the appropriate eCRF	

[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 Alert	Actions
Confirmed serum creatinine increase 25 – 49% [**Canada only**]	• Consider causes and possible interventions • Follow up within 2-5 days; increase fluid intake before assessment if appropriate • Repeat follow-up (every 2-5 days) until creatinine is <125% of baseline value
Serum creatinine increase ≥ 50 % [1] [**Canada only**]	• Consider causes and possible interventions and initiate renal investigation • Repeat assessment within 24-48h if possible • Interruption of study drug, close follow-up (every 24-48 h), consider patient hospitalization and specialized treatment until creatinine is <125% of baseline value
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

[redacted]

to make slide specimen available for evaluation by the Renal Safety Group to potentially identify project-wide patterns of nephrotoxicity.)

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, e.g., 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

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.

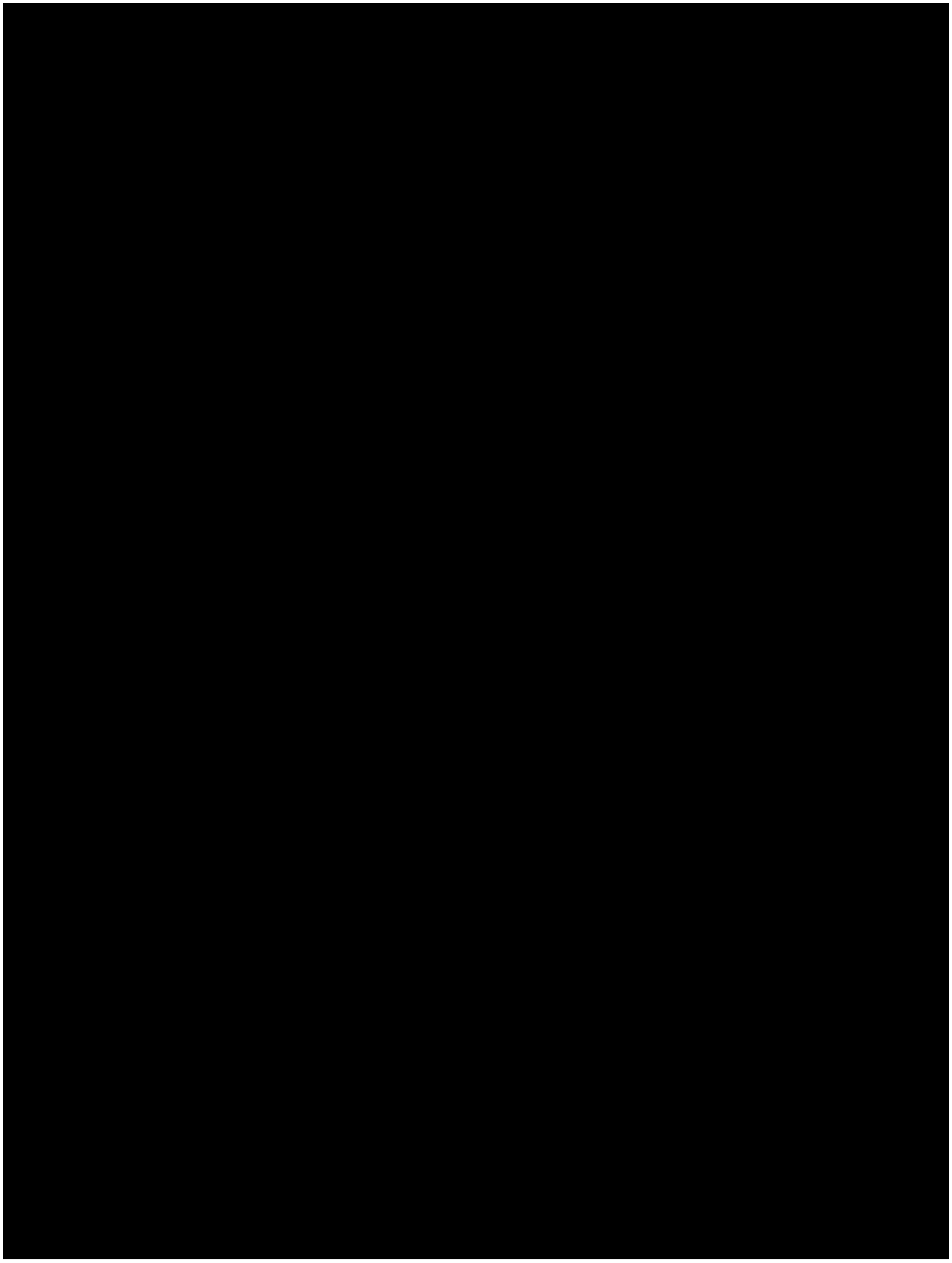
Table 16-5 Moderate and strong inhibitors of CYP3A4

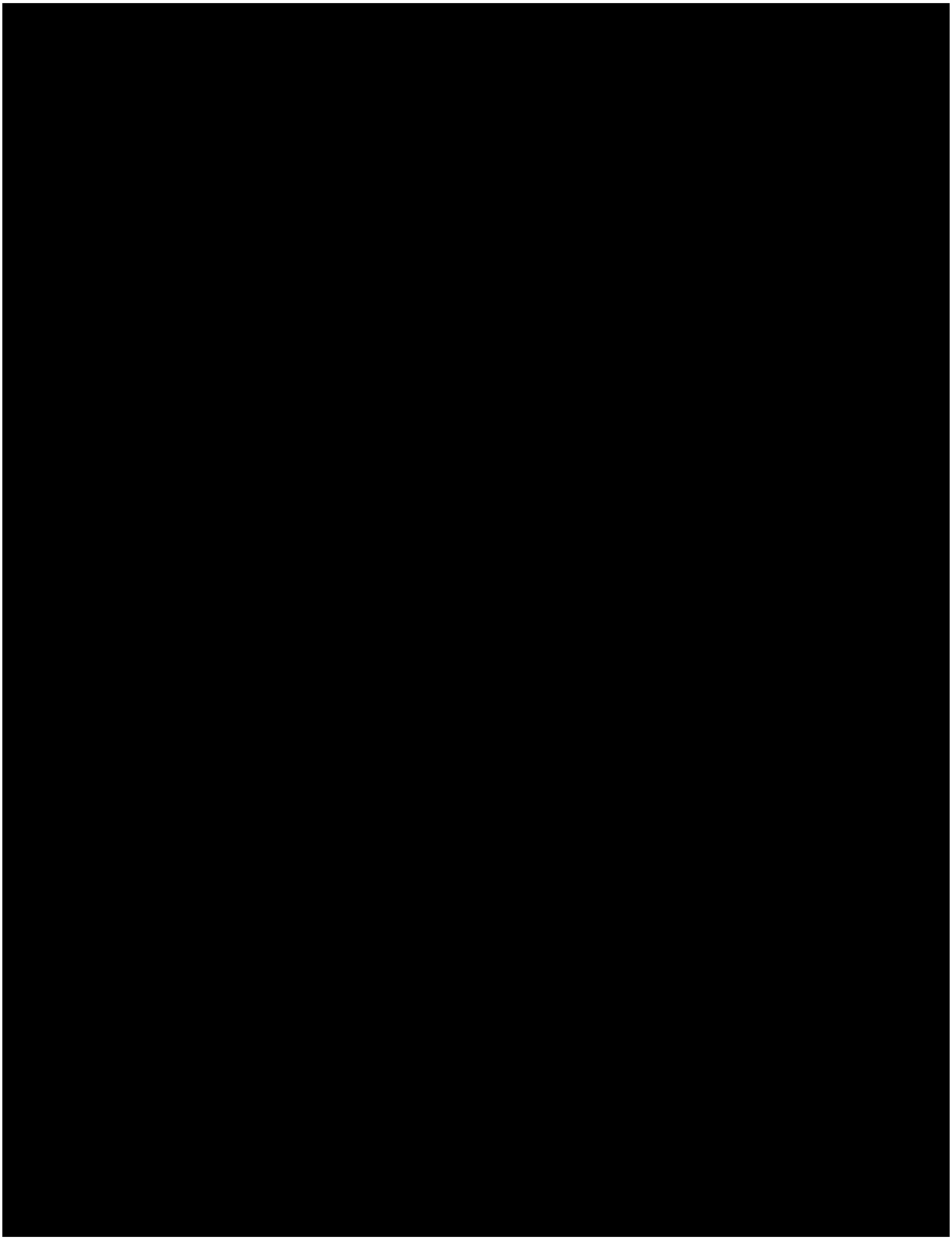
Strong inhibitors of CYP3A4	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir,darunavir/ritonavir, elvitegravir/ritonavir, grapefruit juice, idelalisib,indinavir, indinavir/ritonavir, itraconazole, ketoconazole, LCL161,lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole,ritonavir, 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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