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LOU064

Clinical Trial Protocol CLOU064D12201 / NCT03944707

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

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Site Operations Manual (SOM)

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study procedures. Note: The SOM will not be a part of the Clinical Study Report.

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List of abbreviations

ACQ-5	Asthma Control Questionnaire -5
AE	adverse event
ALP	alkaline phosphatase
AUC	Area under the concentration –time profile
b.i.d.	twice a day
BMI	Body Mass Index
BTK	Bruton's Tyrosine Kinase
BUN	blood urea nitrogen
CFR	U.S. Code of Federal Regulations
CK	creatinine kinase
Cmax	Maximum concentration observed in concentration/time profile
CMO&PS	Chief Medical Office & Patient Safety
CO_2	carbon dioxide
COA	Clinical Outcome Assessments
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CTT	Clinical trial team
CV	coefficient of variation
DPI	Dry Powder Inhaler
ECG	Electrocardiogram
EDC	Electronic Data Capture
ELISA	Enzyme-linked immunosorbent assay
eSource	Electronic Source
FEF	Forced Expiratory Flow
FEV1	Forced Expiratory Volume in 1 second
FSH	Follicle Stimulating Hormone
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	hour
HbsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human Chorionic gonadotropin
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICS	Inhaled Corticosteroids
IEC	Independent Ethics Committee

INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarinic antagonist
LDH	lactate dehydrogenase
LFT	Liver function test
LLOQ	lower limit of quantification
LTRA	Leukotriene receptor antagonist
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MRT	Mean residence time
FeNO	Fractionated exhaled Nitric Oxide
q.d.	once daily
PD	pharmacodynamic(s)
PEF	peak expiratory flow rate
PK	pharmacokinetic(s)
PT	prothrombin time
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell(s)
SABA	short-acting beta2-agonist
SAE	serious adverse event
sCR	serum creatinine
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SoC	standard of care
SOM	Site Operations Manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
T1/2	Half-life
TBL	total bilirubin
TEC	tec protein tyrosine kinase (TEC is a gene family of protein tyrosine kinases)
Tmax	Time of maximum concentration observed in concentration/time profile
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization

Glossary of terms

Assessment	A procedure used to generate data required by the study
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	Any drug(s) (an active drug or an inactive drug, such as a placebo) which is used as a comparator to the investigational drug being tested in the trial
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.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Epoch	Interval of time in the planned conduct of a study. An epoch is associated with a purpose (e.g. screening, randomization, treatment follow-up) which applies across all arms of a study.
eSource	eSource Direct Data Entry (DDE) refers to the capture of clinical study data electronically, at the point of care. eSource combines source documents and case report forms (eCRFs) into one 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	The study drug whose properties are being tested in the study; this definition is consistent with US CFR 21 Section 312.3 and Directive 2001/20/EC and is synonymous with “investigational new drug,” "Investigational Medicinal Product," or “test substance”
Medication pack number	A unique identifier on the label of each drug package in studies that dispense study treatment using an IRT system
Part	A single component of a study which contains different objectives or populations within that single study. Common parts within a study are: a single dose part and a multiple dose part, or a part in patients with established disease and in those with newly-diagnosed disease.
Patient	An individual with the condition of interest
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.
Randomization number	A unique identifier assigned to each randomized subject, corresponding to a specific treatment arm assignment
Run in Failure	A subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject’s medications or other intervention)
Screen Failure	A subject who is screened but is not treated or randomized
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

Study treatment	Any drug or combination of drugs administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the subject permanently stops taking study treatment prior to the defined study treatment completion date
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 number	A unique identifier assigned in non-randomized studies to each dosed subject, corresponding to a specific treatment arm
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Withdrawal of consent (WoC)	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

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Protocol summary

Protocol number	LOU064D12201
Full Title	A randomized, subject- and investigator-blinded, placebo-controlled study to assess the efficacy and safety of LOU064 in patients with inadequately controlled asthma
Brief title	Study of efficacy and safety of LOU064 in inadequately controlled asthma patients
Sponsor and Clinical Phase	Novartis/phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Asthma is characterized by chronic airway inflammation with symptoms of wheeze, shortness of breath, chest tightness and cough that vary over time and intensity. In addition, patients show variable airflow limitation. About 300 million people worldwide suffer from asthma and there are approximately 250,000 deaths caused by asthma every year. Up to 50 % of patients are still not well controlled despite existing therapies, and there is high unmet need in patients with severe asthma despite guideline-directed use of inhaled therapies. BTK inhibition is a promising therapeutic concept for the treatment of asthma. LOU064 is a low molecular weight compound for oral administration that covalently binds and inhibits BTK with high selectivity. Pre-clinical data have shown a reduction of lung eosinophils in mouse models of asthma. Clinically, LOU064 has been shown to effectively inhibit basophil activation in healthy volunteers as measured by the inhibition of CD63 upregulation. Based on these positive pre-clinical and clinical data, LOU064 may offer a novel therapeutic option for treating asthma. This Proof of Concept (Phase 2a) study is investigating the efficacy and safety of LOU064 in patients with inadequately controlled asthma. All subjects will be randomized to receive LOU064 100mg q.d. or LOU064 matching placebo (3:2) treatment for 12 weeks with standard background therapy of budesonide 80µg/formoterol 4.5µg, two inhalations b.i.d.. In order to optimize the rigor and integrity of the study and minimize bias, a randomized, subject- and investigator-blinded parallel group study design is used. This design is well-established in respiratory clinical trials and enables the study treatment to be given for an appropriate and practical length of time to assess the efficacy and safety of the treatment. A placebo control group is essential to provide an accurate estimation of the true treatment effect as placebo effects are known in asthma patients. In addition, to minimize any placebo effects from baseline, placebo will be administered during the run-in period prior to baseline. A treatment period of 12 weeks duration is needed to assess the anti-inflammatory mode of action. Shorter treatment periods may not fully cover the potential effect of a drug and may not show if the effect is stable. A 12-week treatment duration will also provide a solid safety database for planning of long-term studies.

Primary Objective(s)	The primary objective for this study is to determine the efficacy of LOU064 compared to placebo with respect to change from baseline in pre-dose FEV1 at Week 12
Secondary Objectives	Objective 1: To determine the efficacy of LOU064 compared to placebo on changes in morning and evening peak expiratory flow rate (PEF) over the 12-week treatment period Objective 2: To evaluate the safety and tolerability of LOU064 in subjects with inadequately controlled asthma by evaluating the safety endpoints (including vital signs, ECG intervals, safety laboratory parameters, adverse events, and serious adverse events) through the End of Study/Early Termination Visit Objective 3: To determine the efficacy of LOU064 compared to placebo on daytime and nighttime asthma symptom scores over the 12-week treatment period Objective 4: To determine the efficacy of LOU064 compared to placebo on change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score over the 12-week treatment period Objective 5: To determine the efficacy of LOU064 compared to placebo on total daily short-acting β-agonist (SABA) used over the 12-week treatment period Objective 6: To characterize the pharmacokinetic profile of LOU064 in subjects by measurement of concentrations of LOU064 in blood at steady state and calculation of respective PK parameters including but not limited to Cmax, Tmax, AUC
Study design	This is a non-confirmatory, multi-center, randomized, placebo-controlled, subject- and investigator-blinded, parallel-group study to evaluate the efficacy of LOU064 in patients with inadequately controlled asthma. All subjects will be randomized with 3:2 ratio to receive LOU064 100mg q.d. or LOU064 matching placebo treatment for 12 weeks with standard background therapy of budesonide 80µg/formoterol 4.5µg two inhalations b.i.d.. This study will enroll approximately 75 subjects for the primary analysis (subjects having week 12 FEV1 assessment). The total duration for each subject in the study is approximately 20 weeks.
Population	The study population will include male and female subjects with age range 18 to 70 with inadequately controlled asthma. Approximately 75 subjects will be randomized for the primary analysis. However, in case of a higher dropout rate than assumed (10% over 12 weeks), Commercially Confidential Information up to 154 subjects may be randomized. Subjects who prematurely discontinue after randomization will not be replaced.

Key Inclusion criteria	• Male and female adult patients aged ≥ 18 to ≤ 70 years at screening.
	• Patients must weigh at least 40 kg to participate in the study, and must have a body mass index (BMI) <35 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2 at screening
	• Patients with a physician-diagnosed history of asthma (according to GINA 2018) for a period of at least 6 months prior to screening.
	• Patients who have been treated with:
	  • Medium or high dose ICS, or
	  • ICS plus long-acting beta agonist (LABA), or
	  • ICS plus leukotriene receptor antagonist (LTRA), or
	  • ICS plus long-acting beta agonist (LABA) and long lasting muscarinic antagonist (LAMA)
	for at least 1 month prior to screening and on the same doses of the above mentioned medications over at least 2 weeks prior to start of the run-in period.
	• Post-bronchodilator reversibility of FEV1 ≥ 12% and ≥ 200 mL at screening. If reversibility is not demonstrated at screening, then two additional attempts are permitted, (one at the run-in visit and the last one during the run in period between run in visit and baseline visit).
	• Spirometry with pre-bronchodilator FEV1 ≥ 40% of predicted (at screening and baseline) and ≤ 85% of predicted at the baseline visit.
	• ACQ-5 score ≥ 1.5 at baseline visit
	• ≥ 80% compliance with peak expiratory flow measurement and recording of symptoms in the eDiary during the run-in period.

Key Exclusion criteria	• Patients who have had an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit within 6 weeks prior to screening or during the screening period.
	• Patients who have smoked or inhaled any substance other than asthma medications within the 6 month period prior to screening, or who have a smoking history of greater than 10 pack years (e.g. 10 pack years = 1 pack/day x 10 years or ½ pack/day x 20 years, etc.).
	• History of life-threatening asthma event such as significant hypercarbia (pCO_2 > 45 mmHg), endotracheal intubation, non-invasive positive pressure ventilation (NIPPV), respiratory arrest, or seizure as a result of asthma.
	• Patients with chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, clinically significant bronchiectasis, sarcoidosis, interstitial lung disease, cystic fibrosis, Churg-Strauss syndrome, allergic broncho-pulmonary aspergillosis, or clinically significant chronic lung diseases related to a history of tuberculosis or asbestosis.
	• 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 (physical exam or 12 lead ECG) < 50 bpm at screening

	• Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at screening or inability to determine the QTcF interval • Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of study • At screening and/or run-in period, any severe, progressive or uncontrolled, acute or chronic, medical or psychiatric condition, or other factors such as abnormal vital signs, ECG or physical findings, or clinically relevant abnormal laboratory values, that in the judgment of the investigator may increase the risk associated with study participation/treatment or may interfere with interpretation of study results, and thus would make the patient inappropriate for entry into or continuing the study. • Major surgery within 8 weeks prior to screening or surgery planned prior to end of study. • History of live attenuated vaccine within 6 weeks prior to randomization or requirement to receive vaccinations at any time during the study. • Hematology parameters at screening: • Hemoglobin: < 10 g/dl • Platelets: < 100 000/mm^3 • White blood cells: < 3 000/mm^3 • Neutrophils: < 1 500/mm^3 • Significant bleeding risk or coagulation disorders. • History of gastrointestinal bleeding, e.g. in association with use of Nonsteroidal Anti-Inflammatory Drug (NSAID). • Requirement for anti-platelet or anticoagulant medication (e.g., warfarin, or clopidogrel or Novel Oral Anti-Coagulant - NOAC) other than acetylsalicylic acid (up to 100 mg/d). • History or presence of thrombotic or thromboembolic event, or increased risk for thrombotic or thromborembolic event.
Study treatment	Investigational and control drugs • LOU064 capsules (dose strength: 50mg) • Placebo capsules Standard background therapy • budesonide 80µg/formoterol 4.5µg delivered by DPI (Turbohaler or equivalent if Turbohaler is not available in the country)
Efficacy assessments	• Spirometry: FEV1 • Daytime and nighttime asthma symptom score (captured in eDairy) • ACQ-5 score • number of puffs of SABA taken per day (captured in eDairy) • Peak expiratory flow rate
Pharmacokinetic assessments	PK profile of LOU064 in human blood, characterized by Cmax, Tmax, AUClast and AUC0-24h. Additional parameters such as mean residence time, terminal half-life or CL/F as needed

Key safety assessments	• Physical examinations • Vital signs • ECG • Monitoring of laboratory markers in blood and urine • Adverse events, serious adverse events monitoring
Other assessments	Commercially Confidential Information
Data analysis	The primary objective of this study is to determine the efficacy of LOU064 compared to placebo with respect to change from baseline in pre-dose FEV1 at Week 12. Repeated measurements of pre-dose FEV1 at week 2, week 4, week 8 and week 12 are considered in the primary analysis. The baseline pre-dose FEV1 is defined as the average of the FEV1 measurements performed 45 min and 15 min prior to dosing on Day 1. If one of the assessment is missing, then the non-missing pre-dose FEV1 will be considered as baseline. The primary endpoint will be analyzed using a Bayesian repeated measures model with change from baseline in pre-dose FEV1 as response, adjusting for effects of treatment*visit interaction, baseline pre-dose FEV1, and any additional covariate as deemed appropriate. Conditional on the aforementioned covariates, the responses are assumed to follow a multivariate normal distribution with a common unknown and unstructured covariance matrix explaining the association between repeated measures for a subject (similar to a covariance pattern model). For adjusted mean change from baseline in pre-dose FEV1 at week 12 under placebo, a weakly informative prior will be specified, while non-informative priors will be specified for all other unknown quantities, as appropriate. The quantity of primary interest is the 'true' LOU064 effect on primary endpoint over placebo at week 12 and inferences will be performed in terms of the posterior probabilities derived from the above model.
Key words	Asthma BTK inhibitor LOU064 FEV1 ACQ-5 score

1 Introduction

1.1 Background

Asthma is characterized by chronic airway inflammation with symptoms of wheeze, shortness of breath, chest tightness and cough that vary over time and intensity. In addition, patients show variable airflow limitation. About 300 million people worldwide suffer from asthma and there are approximately 250,000 deaths caused by asthma every year (D'Amato et al 2016).

Up to 50 % of patients are still not well controlled despite existing therapies, and there is high unmet need in patients with severe asthma despite guideline-directed use of inhaled therapies (GINA 2018). Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase. It 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 (Regan et al 2017). Thus, BTK inhibition is a promising therapeutic concept for the treatment of asthma.

LOU064 is a low molecular weight compound for oral administration that covalently binds and inhibits BTK with high selectivity.

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The pre-clinical and clinical safety profile of LOU064 is favorable. For detailed information please refer to the Investigator`s Brochure (IB).

1.2 Purpose

This Proof of Concept (Phase 2a) study is investigating the efficacy and safety of LOU064 in patients with inadequately controlled asthma who are on a standardized background therapy of inhaled corticosteroid plus long acting beta-2 agonist (ICS/LABA).

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 determine the efficacy of LOU064 compared to placebo with respect to change from baseline in pre-dose FEV1 at Week 12	• Change from baseline in pre-dose FEV1 at Week 12
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To characterize the pharmacokinetic profile of LOU064 in blood of asthma patients	• Concentrations of LOU064 in blood at steady state and calculation of respective PK parameters including but not limited to Cmax, Tmax, AUC0-24h
• To determine the efficacy of LOU064 compared to placebo on changes in morning and evening peak expiratory flow rate (PEF) over the 12-week treatment period	• Change from baseline in PEF (AM and PM), as assessed by mean morning and mean evening PEF over 12 weeks of treatment (captured in eDiary)
• To evaluate the safety and tolerability of LOU064 in patients with inadequately controlled asthma	• All safety endpoints (including vital signs, ECG intervals, safety laboratory parameters, adverse events, and serious adverse events) through the End of Study/Early Termination Visit
• To determine the efficacy of LOU064 compared to placebo on daytime and nighttime asthma symptom scores over the 12-week treatment period	• Change from baseline in daytime and nighttime asthma symptom score over 12 weeks of treatment (captured in eDiary)
• To determine the efficacy of LOU064 compared to placebo on change from baseline in Asthma Control Questionnaire-5 (ACQ-5) score over the 12-week treatment period	• Change from baseline in ACQ-5 score over 12 weeks of treatment (ACQ-assessment for the week preceding each planned visit up to End of Study)
• To determine the efficacy of LOU064 compared to placebo on total daily short-acting β-agonist (SABA) used over the 12-week treatment period	• Number of puffs of SABA taken per day over 12 weeks of treatment (captured in eDiary)

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3 Study design

This is a non-confirmatory, multi-center, randomized, placebo-controlled, subject- and investigator-blinded, parallel-group study to evaluate the efficacy of LOU064 in patients with inadequately controlled asthma. All subjects will receive a standardized background therapy of budesonide 80µg/formoterol 4.5 µg two inhalations b.i.d.. This study will enroll approximately 75 subjects (subjects having week 12 FEV1 assessment). However, in case of a higher dropout rate than assumed (10% over 12 weeks), Commercially Confidential Information up to 154 subjects may be randomized.

Note: the trade name for budesonide/formoterol may vary between countries.

The study consists of:

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

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

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Screening: After signing informed consent, subjects will complete safety assessments, pulmonary function tests, and the ACQ-5 to assess eligibility. All subjects must demonstrate FEV1 reversibility for study eligibility. If reversibility is not demonstrated at the screening visit, then two additional attempts are permitted (one at the run-in visit and the last one during the run in period between run in visit and baseline visit if needed).

Subjects will be provided with an electronic peak expiratory flow (ePEF)/eDiary device in which they will record their PEF, daytime and nighttime asthma symptoms, and the use of rescue medication. Subjects will be instructed on eDiary completion and how to use the device for the assessment of peak flow. Subjects will perform PEF measurements twice daily (morning and evening) beginning the evening of the screening visit through the EOS visit.

A short acting β2-agonists (SABA; salbutamol, known also as albuterol) will be provided to all subjects as rescue medication. The investigator will check that the vaccination status of the subject is complete and there are no vaccinations planned during the study period. A complete vaccination status for an asthma patient to be considered for this study includes vaccination against influenza, diphtheria, pertussis and pneumococci.

Run-in: Subjects will return to the study site for the run-in visit on or by Day -35 for safety assessments and pulmonary function tests to assess eligibility.

During this visit, subjects will discontinue their current asthma therapy and be placed on budesonide 80µg /formoterol 4.5µg delivered by DPI (turbohaler or equivalent device if turbohaler not available) two inhalations b.i.d.. By the time of randomization, all subjects must have received a minimum of 3 weeks budesonide 80 µg/formoterol 4.5µg two inhalations b.i.d. as background therapy. The budesonide dose level must remain constant throughout the study. If required, to adjust for the subject's needs (e.g., holiday, family or work), the run-in period has a minimum duration of three weeks (21 days) and may be extended by up to two weeks for a maximum of 5 weeks (35 days).

If the time difference between the Screening and Run-in visits is less than two weeks, hematology, clinical chemistry, urinalysis and coagulation panel do not need to be tested again at the Run-in visit.

All subjects will receive LOU064 matching placebo once daily in the morning for the duration of the run-in period. Subjects will be blinded to the identity of the treatment.

Baseline: The run-in period will end with the Baseline visit. The Baseline visit assessments can occur between Day -3 and Day 1 to allow for flexibility and to ensure all data required are available for randomization. All baseline assessments must be completed and eligibility confirmed prior to randomization on Day 1.

Treatment: On Day 1 of the treatment period, after completion of all pre-dose assessments, eligible subjects will be randomized in a 3:2 ratio to receive either LOU064 100 mg q.d. or placebo q.d.. Subjects will take their first dose in the clinic on Day 1. For the remainder of the 12 week treatment period, subjects will take their daily dose in the morning at approximately the same time. Commercially Confidential Information

Each visit must be scheduled in the morning at approximately the same time, so that pre-dose FEV1 assessments can be performed between 6 AM and 10 AM +/- 1 hour. On visit days, subjects will take their dose in the clinic after completion of efficacy and safety assessments. Subjects will also take their standardized background therapy morning dose after the efficacy and safety measurements. Subjects will complete dosing on Day 85.

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

Post Study safety contact: A safety follow-up will be made at approximately 30 days following the last dose of study drug. Please refer to the Assessment Schedule for a list of procedures to be performed at each visit.

4 Rationale

4.1 Rationale for study design

This is a non-confirmatory, multi-center, randomized, placebo-controlled, subject- and investigator-blinded, parallel-group study with an minimum 3-week run-in period and a 12 week treatment period. All subjects will receive a standardized background therapy of budesonide 80µg/formoterol 4.5µg two inhalations b.i.d.. Key efficacy endpoints will be evaluated at Week 12.

Table 4-1 Rationale for study design

Study Design Aspect	Rationale
Overall study design	In order to optimize the rigor and integrity of the study and minimize bias, a randomized, subject- and investigator-blinded parallel group study design is used. This design is well-established in respiratory clinical trials and enables the study treatment to be given for an appropriate and practical length of time to assess the efficacy and safety of the treatment. The treatment duration of 12 weeks makes other study designs (e.g., cross-over) inefficient. Only patients who have symptoms (as defined by ACQ-5) and have room for improvement in FEV1 (<85% of personal predicted value) at baseline will be enrolled.
Placebo control	A placebo control group is essential to provide an accurate estimation of the true treatment effect as placebo effects are known in asthma patients. The study design includes a placebo control and not an active control because the study treatment will be added on top of standardized background therapy for each patient. In addition, to minimize any placebo effects from baseline, placebo will be administered during the run-in period prior to baseline.
Randomization (strata, allocation ratio)	A randomization ratio of 3:2 is used. As per sample size considerations (Section 12.8) by using prior information on placebo effects in other studies, the expected number of randomized placebo patients will be 15 fewer than LOU064.
Blinding	This is a subject- and investigator-blinded study. During the run-in period, patient will receive standardized background therapy along with LOU064 matching placebo, patients are blinded to the identity of the placebo treatment. During the treatment period, patients, investigators and other study personnel such as study nurses or monitors are blinded (except those who by the nature of their role must be unblinded, e.g., bioanalyst measuring drug concentrations) to avoid any bias instituted by knowledge of the treatment allocation to patients. Commercially Confidential Information
Duration of study periods	Screening period up to 2 weeks: to provide sufficient time for completion of all screening measures prior to entering the run-in period. Run-in period of minimum 3 weeks: to standardize subjects so that all have the same treatment and are in steady state condition for the baseline assessments. This period can be expanded up to 5 weeks to accommodate logistics or the schedule of the patient if needed. Treatment period of 12 weeks: to assess the anti-inflammatory mode of action. It is known from asthma patients that inflammation down-regulates over time. Shorter treatment periods may not fully cover the potential effect of a drug and may not show if the effect is stable. Follow-up period of 3 weeks: to assess the duration of effect post treatment. Sustained duration of action may be possible after BTK-inhibition gets less than targeted inhibition.

4.1.1 Rationale for choice of background therapy

All subjects will receive a standardized background therapy of budesonide 80µg/formoterol 4.5µg two inhalations b.i.d.. Budesonide 80µg/formoterol 4.5µg was selected because it ensures that subjects receive an ICS/LABA as recommended in the applicable guidelines for treating patients with asthma. The ICS-component is administered at a lower dose level to make the study sensitive for the anti-inflammatory effects resulting from BTK-inhibition.

The standardization of the background therapy minimizes the variation that would be observed if patients enrolled in the study on variable doses or variable asthma control therapy. All subjects will receive a minimum of 3 weeks background therapy of budesonide 80µg/formoterol 4.5µg two inhalations, twice daily prior to randomization so that all have the same treatment and are in steady state condition for the baseline assessments.

In addition, subjects can manage their symptoms with short acting β2-agonists as rescue medication when required (Section 6.2.3).

Despite receiving a standardized background therapy of ICS/LABA, subjects may still experience a worsening of their asthma symptoms. Refer to Section 4.5.2 and Section 9.1.1 for details on the monitoring and management of worsening asthma symptoms.

4.2 Rationale for dose/regimen and duration of treatment

In this study, LOU064 will be administered as 100 mg q.d. The treatment duration of 12 weeks is covered by pre-clinical data and is considered sufficient to allow assessment of anti-inflammatory effects resulting in lung function improvement and symptom control in patients with asthma.

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In CLOU064X2101 study, 132 healthy volunteers have been dosed with LOU064 in single ascending dose cohorts (SAD; up to 600 mg LOU064) and in multiple ascending dose cohorts (MAD; up to 600 mg LOU064 q.d. and up to 200 mg LOU064 b.i.d. for 12 days). LOU064 was well-tolerated and there was no serious or severe adverse event related to LOU064 intake in any of the cohorts completed. Observed adverse events (AEs) did not appear to be dose dependent, the majority were single events, and were generally mild in nature. Thus, preclinical and clinical safety information support the doses selected for this proof-of-concept study.

The dose-level and dosing regimen of LOU064 100 mg q.d. in this study were based on the following analyses from study CLOU064X2101:

- Daily doses of 15 mg and above established a peak target occupancy approaching 100% in blood in nearly all subjects, which remained above 80% at 24 h. Full BTK inhibition in tissue will likely require higher doses. Tissue occupancy of 85% at the end of the 24h dosing interval should be achieved with daily doses of 100 mg.
- Inhibition of basophil activation (monitored by CD63 and CD203c up-regulation) was on the plateau of the dose-response curve at the 100 mg dose level.

- Effects on wheal size in skin prick tests (SPT) were on the plateau of the dose response curve (approximately 50% mean reduction of wheal size in SPT corresponding to the maximum effect size observed in CLOU064X2101) at the dose suggested in this study.

Since LOU064 is covalently bound to its target, it provides sustained coverage based on the target engagement over 24h despite its relatively short elimination half-life. Thus a once daily dosing regimen is considered appropriate. Recurrence of BTK related disease activity requires resynthesis of BTK in sufficient amounts to reactivate the pathway. Sufficient resynthesis of BTK is not expected to occur within one day.

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

Placebo was chosen as the comparator for this study in order to demonstrate that LOU064 adds a significant improvement in efficacy to background ICS/LABA therapy in moderate to severe asthmatic patients. The primary endpoint in the study, FEV1, is an effort dependent measurement. The secondary endpoints (ACQ-5, patient diary) are patient reported outcomes. Thus the placebo control arm is essential to account for effects not mediated by BTK inhibition (placebo effects). The placebo arm is also expected to control for potential bias in safety assessments in this study.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

A transient benefit may be observed if LOU064 provides efficacy. A positive outcome from this study may lead to further development of LOU064 for eligible patients with asthma.

The risk to subjects in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring, avoidance of prohibited concomitant medications, regular safety reviews, adequate safety follow up, and study stopping rules. Appropriate eligibility criteria and stopping rules are included in this protocol.

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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 this 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 marketed BTK inhibitors (eg: ibrutinib and acalabrutinib) and LOU064, the relevance and importance of the study patient populations must be taken into consideration.

- Infections: BTK is an important signaling node downstream of cell surface receptors and expressed in several immune cells of the adaptive and innate system, including B cells, macrophages and mast cells/basophils. Therefore, LOU064 has the potential to increase the risk of infections. Patients with X-linked agammaglobulinemia (XLA) – a genetic defect associated with a lack of BTK – suffer from recurrent bacterial and enteroviral infections which may be associated with neutropenia (Kumar et al 2006). However, in XLA BTK deficiency leads to impaired B cell and plasma cell development and in turn to a close to complete absence of immunoglobulins. In adult patients, BTK inhibition primarily interferes with B cell activation but not plasma cell function and is therefore not associated with a marked decrease of immunoglobulins (Hendriks et al 2014; Sun et al 2015; Nutt et al 2015). Administration of ibrutinib (Imbruvica®) and acalabrutinib (Calquence®) is associated with a risk of infection in patients suffering from B cell malignancies (see Imbruvica® PI 2018 and Calquence® PI 2017). 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 history of infections will be excluded from the study (refer to Section 5.2 for details). Vaccination records of patients will be checked via patient report to ensure there are no outstanding vaccinations recommended for this patient population.
- 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 affecting approximately 50% of patients with hematologic malignancies. Warnings on hemorrhagic events including deaths have also been described (see Imbruvica® PI 2018 and Calquence® PI 2017). Compared to other drugs in the same class, LOU064 demonstrated a higher selectivity for BTK vs. other TEC kinases. Thus bleeding may be less a safety concern when compared to ibrutinib and acalabrutinib. Patients receiving LOU064 must be closely monitored for any signs and symptoms of bleeding while in the study. Subjects with a known history of bleeding disorder, subjects taking medication that is known to increase the bleeding risk (other

than acetylsalicylic acid), and subjects with an increased thromboembolic/thrombosis risk must be excluded from the study (refer to Section 5.2 for details).

- 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 Imbruvica® PI 2018 and Calquence® PI 2017). Therefore, patients will 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 Screening must be excluded from the study (refer to Section 5.2 for details).
- Risk of cardiovascular origin: LOU064 is an in vitro inhibitor of the hERG channel protein, without affecting other ion channels.

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For ibrutinib, atrial fibrillation was described for 3% to 6% of subjects across multiple trials which might be associated with Na-channel inhibition (see Imbruvica® PI 2018). For acalabrutinib, both atrial fibrillation and atrial flutter of any grade were reported in 3% of patients (see Calquence® PI 2017). Therefore, ECGs will be collected post-dose at each visit in this 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 (refer to Section 5.2 for details).

- Drug-drug interactions: LOU064 is a high clearance drug and metabolic clearance by CYP3A4/5 is expected to be the predominant clearance pathway.

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Precautions and guidelines regarding the use of those medications is provided in Section 6.2.2 and Section 16.4 of the protocol.

- Reproductive toxicity: The risk of teratogenicity is currently unknown but reproductive toxicology studies of LOU064 are ongoing.

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

In summary, asthma patients participating in this clinical trial may temporarily benefit from treatment with LOU064. This study will help to improve the scientific understanding of LOU064 in the management of asthma and offer the potential of developing an innovative drug that could potentially improve the quality of life for asthma patients. Potential risks of treatment with LOU064 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.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of approximately 20 weeks from each subject as part of the study. Additional samples may be required for safety monitoring.

Timings of blood sample collection are outlined in the Assessment schedule.

A summary blood log is provided in the Site Operations Manual (SOM). Instructions for all sample collection, processing, storage and shipment information is also available in the SOM and/or central laboratory manual.

See the section on the potential use of residual samples.

4.5.2 Risk of asthma worsening

Despite receiving a standardized background therapy of inhaled corticosteroid and long acting beta-2 agonist, subjects may still experience a worsening of their asthma symptoms. Subjects will receive an ePEF/eDiary in which symptoms, morning and evening PEF, and the use of rescue medication are documented. Subjects will be instructed to alert the investigator if they experience a worsening of symptoms for review of their asthma control. Subjects with a history of a life-threatening asthma event are excluded from the study (see Section 5.2). Subjects who require a treatment with systemic (e.g., oral) steroid for treating an asthma exacerbation will be withdrawn from the study.

5 Population

The study population will include male and female subjects with inadequately controlled asthma. All subjects will receive budesonide 80µg/formoterol 4.5µg two inhalations b.i.d. for a minimum of 3 weeks prior to randomization. Approximately 75 subjects will be randomized for the primary analysis. However, in case of a higher dropout rate than assumed (10% over 12 weeks) Commercially Confidential Information
up to 154 subjects may be randomized. Subjects who prematurely discontinue after randomization will not be replaced.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all applicable eligibility criteria at screening and baseline. A relevant record (e.g., checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from any entry criteria excluded a subject from eligibility for the 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 including any adjustment to asthma medication.
2. Male and female adult patients aged ≥ 18 to ≤ 70 years at screening
3. Patients must weigh at least 40 kg to participate in the study, and must have a body mass index (BMI) <35 kg/m^2. BMI = Body weight (kg) / [Height (m)]^2 at screening
4. Patients with a physician-diagnosed history of asthma (according to GINA (2018)) for a period of at least 6 months prior to screening.
5. Patients who have been treated with:
   - Medium or high dose ICS, or
   - ICS plus long-acting beta agonist (LABA), or
   - ICS plus leukotriene receptor antagonist (LTRA), or
   - ICS plus long-acting beta agonist (LABA) and long lasting muscarinic antagonist (LAMA)

   for at least 1 month prior to screening and on the same doses of the above mentioned medications over at least 2 weeks prior to start of the run-in period.
6. Post-bronchodilator reversibility of FEV1 ≥ 12% and ≥ 200 mL at screening.
   If reversibility is not demonstrated at screening, then two additional attempts are permitted (one at the run-in visit and the last one during the run in period between run in visit and baseline visit if needed) .
7. Acceptable and reproducible spirometry with pre-bronchodilator FEV1 ≥ 40% of predicted (at screening and baseline) and ≤ 85% of predicted at the baseline visit.
8. ACQ-5 score ≥ 1.5 at baseline visit

9. ≥ 80% compliance with peak expiratory flow measurement and recording of symptoms in the eDiary during the run-in period.
10. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

5.2 Exclusion criteria

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

1. Patients who have had an asthma exacerbation requiring systemic corticosteroids, hospitalization, or emergency room visit within 6 weeks prior to screening or during the screening and/or run in period.
2. Use of other investigational drugs at the time of screening, or within 5 half-lives of screening, or within 30 days, whichever is longer; or longer if required by local regulations.
3. History of hypersensitivity to any of the study treatments or excipients or to drugs of similar chemical classes.
4. 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 5 years of screening, regardless of whether there is evidence of local recurrence or metastases.
5. Donation or loss of 400 mL or more of blood within 8 weeks prior to baseline, or longer if required by local regulation.
6. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test at any time-point prior to enrollment.
7. 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 5 days after stopping of investigational drug. *Highly effective contraception methods include:*
    - Total abstinence from heterosexual intercourse (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 8 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 be stable on the same pill for a minimum of 3 months before taking investigational drug.

If local regulations deviate from the contraception methods listed above and require more extensive measures to prevent pregnancy, local regulations apply and will be described in the ICF.

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 prior to screening. 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. Refer to Section 8.4.3 (Pregnancy and Assessments of Fertility).

8. Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for 7 days after stopping investigational drug. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of the investigational drug via seminal fluid to their partner. In addition, male participants should not donate sperm for the time period specified above. If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the Informed Consent Form.
9. Patients who have smoked or inhaled any substance other than asthma medications within the 6 month period prior to screening, or who have a smoking history of greater than 10 pack years (e.g. 10 pack years = 1 pack/day x 10 years or ½ pack/day x 20 years, etc.).
10. History of life-threatening asthma event such as significant hypercarbia ($pCO_2 > 45$ mmHg), endotracheal intubation, non-invasive positive pressure ventilation (NIPPV), respiratory arrest, or seizure as a result of asthma.
11. Patients with chronic lung diseases other than asthma, including (but not limited to) chronic obstructive pulmonary disease, clinically significant bronchiectasis, sarcoidosis, interstitial lung disease, cystic fibrosis, Churg-Strauss syndrome, allergic broncho-pulmonary aspergillosis, or clinically significant chronic lung diseases related to a history of tuberculosis or asbestosis, immune deficiency, splenectomy or impaired immune function.
12. Taking medications prohibited by the protocol (see Section 6.2.2 (Prohibited medication) and Table 6-3 and Table 6-4).
13. 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 (physical exam or 12 lead ECG) < 50 bpm at screening

- Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at screening or inability to determine the QTcF interval
- Use of agents known to prolong the QT interval unless they can be permanently discontinued for the duration of study

14. Any severe, progressive or uncontrolled, acute or chronic, medical or psychiatric condition, immune deficiency, spleen dysfunction or other factors such as abnormal vital signs, ECG or physical findings, or clinically relevant abnormal laboratory values, that in the judgment of the investigator may increase the risk associated with study participation/treatment or may interfere with interpretation of study results, and thus would make the patient inappropriate for entry into or continuing the study.
15. Major surgery within 8 weeks prior to screening or surgery planned prior to end of study.
16. History of live attenuated vaccine within 6 weeks prior to randomization or requirement to receive vaccinations at any time during the study. Recommended vaccination schemes for asthma patients must be complete, including influenza, pertussis, diphtheria, pneumococci vaccination.
17. Hematology parameters at screening:
    - Hemoglobin: < 10 g/dl
    - Platelets: < 100 000/mm^3
    - White blood cells: < 3 000/mm^3
    - Neutrophils: < 1 500/mm^3
18. Significant bleeding risk or coagulation disorders.
19. History of gastrointestinal bleeding, eg in association with use of Nonsteroidal Anti-Inflammatory Drug (NSAID).
20. Requirement for anti-platelet or anticoagulant medication (eg, warfarin, or clopidogrel or Novel Oral Anti-Coagulant - NOAC) other than acetylsalicylic acid (up to 100 mg/d).
21. History or presence of thrombotic or thromboembolic event, or increased risk for thrombotic or thromboembolic event.
22. History or current treatment for hepatic disease including but not limited to acute or chronic hepatitis, cirrhosis or hepatic failure or Aspartate Aminotransferase (AST)/Alanine Aminotransferase (ALT) levels or International Normalized Ratio (INR) of more than 1.5x upper limit of normal (ULN) at screening.
23. History of renal disease or creatinine level above 1.5x ULN at screening.
24. Known or suspected history of ongoing, chronic or recurrent infectious disease including but not limited to opportunistic infections (eg tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis), HIV, Hepatitis B/C.
25. Any disease or illness, other than asthma, that may require the use of systemic corticosteroids during the study period.

6 Treatment

6.1 Study treatment

Details on the requirements for storage and management of study treatment, and instructions to be followed for subject numbering, prescribing/dispensing and taking study treatment are outlined in the SOM.

6.1.1 Investigational and control drugs

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

Table 6-1 Investigational and control drugs

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

6.1.2 Additional study treatments

All subjects will receive a standardized background therapy of budesonide 80µg/formoterol 4.5µg two inhalations b.i.d. beginning at the Run-in visit through the EOS visit. Budesonide 80µg/formoterol 4.5µg delivered by DPI (turbohaler or equivalent device if turbohaler is not available in the site/country) will either be supplied to the study sites locally by Novartis or provided by the study site to the subject and reimbursed by Novartis. Note that dose designations may vary between countries. In some countries the metered dose (budesonide 100µg/formoterol 6µg) released into the inhaler chamber is found on the product labels. This dose is the same as budesonide 80µg/formoterol 4.5µg delivered (from the inhaler mouthpiece).

6.1.3 Treatment arms/group

At the Run-in visit, all subjects will be assigned to receive placebo q.d.. Subjects will take two placebo capsules in the morning at home for the duration of the run-in period.

On Day 1, subjects will be randomized to one of the following 2 treatment arms in a ratio of 3:2

- LOU064
- Placebo

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All subjects will take LOU064 or matching placebo in the morning at home (except for Days 15, 29, 57 and 85, which are to be taken on site during the clinic visit). All subjects will receive their respective LOU064 or placebo capsules for 12 weeks (from Day 1 through Day 85).

6.2 Other treatment(s)

6.2.1 Concomitant therapy

Medication for treatment of asthma taken within the 3 months prior to screening will be recorded in the Prior and Concomitant Asthma Medications CRF. The dose of asthma treatment should be stable for at least 2 weeks prior to start of the run-in period.

The investigator will instruct the subject to notify the study site about any new medications (including medications that are not related to the treatment of asthma) 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 in the concomitant medications / significant non-drug therapies or procedures pages.

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

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Table 6-2 Medication allowed under certain conditions if taken as follows

Class of Medication	Condition under which medication is permitted
intra nasal corticosteroids	stable dose for start of run-in period until end of study
H1-antagonists	stable dose for start of run-in period until end of study
topical corticosteroids	permitted
inactivated influenza, pneumococcal or any other inactivated vaccine	not administered within 14 days prior to the 1st dose in treatment period and anytime thereafter during the trial

6.2.2 Prohibited medication

Use of the treatments displayed in Table 6-3 and Table 6-4 need to be avoided according to the specifications provided. Subjects should be instructed to abstain from these medication unless absolutely necessary. Each concomitant drug must be individually assessed against all exclusion criteria and the tables below to see if it is allowed. If in doubt, the investigator must contact the Novartis medical monitor or designee before randomizing a patient or allowing a new medication to be started.

Restrictions for medications other than study drug apply according to below tables:

Table 6-3 Prohibited medications not related to asthma treatment

Medication	Prohibition period
Other investigational drugs	30 days or 5 half-lives, whichever is longer prior to Screening until end of study
Immunosuppressive medication with or without known effect on asthma 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 start of run-in period until end of study
Intravenous (i.v.) immunoglobulins or plasmapheresis	30 days prior to start of run-in period until end of study
Regular (daily or every other day) doxepin (oral)	14 days prior to start of run-in period until end of study
Live attenuated vaccine	6 weeks prior to randomization until end of study
Moderate and strong inhibitors of CYP3A4 (see Table 16-5 in Appendix 4)	From start of run-in period until end of study
Moderate and strong inducers of CYP3A4 (see Table 16-6 in Appendix 4)	From start of run-in period 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 start of run-in period (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 start of run-in period until end of study
parental or oral corticosteroids	30 days prior to start of run-in period until end of study
systemic anticholinergics	7 days prior to run-in until end of study
Non-selective systemic β-blocking agents	7 days prior to run-in until end of study

Table 6-4 Prohibited asthma medications

Medication	Prohibition period
Other investigational drugs	30 days or 5 half-lives, whichever is longer prior to Screening until end of study
Short-acting anticholinergics	8 hours prior to spirometry assessment at run-in visit until end of study
Long-acting anticholinergics	7 days prior to start of run-in period until end of study
Fixed combinations of short-acting β_2 agonists and short-acting anticholinergics	8 hours prior to spirometry assessments at run-in visit until end of study
Mast cell stabilizers (e.g., cromoglycate, nedocromil, ketotifen) and leukotriene antagonists (e.g., montelukast)	7 days prior to start of run-in period until end of study
Monoclonal antibodies, investigational or approved, for the treatment of asthma (e.g., omalizumab)	5 months prior to start of run-in period until end of study
long-acting β_2 agonists (for twice daily treatment) or fixed dose combination of ICS/LABA b.i.d other than study medication (standard background therapy)	24 hours prior to start of run-in period until end of study
ultra-long-acting β2 agonists (for once daily treatment) or fixed dose combination of ICS/LABA o.d other than study medication (standard background therapy)	48 hours prior to start of run-in period until end of study
Xanthines	7 days prior to start of run-in period until end of study

6.2.3 Rescue medication

At the Screening visit all subjects will be provided with a SABA (salbutamol [100 µg] corresponding to albuterol [90 µg]) which they will be instructed to use throughout the study as rescue medication on as needed basis. Subjects will be advised that between visits they can take their rescue medication for symptoms of asthma. Rescue medication will either be supplied to the study sites locally by Novartis or provided by the study site to the subject and reimbursed by Novartis.

Nebulized salbutamol/albuterol is not allowed as rescue medication and will not be supplied.

No other rescue treatment is allowed at any time throughout the study.

To standardize measurements, subjects will be instructed not to use their rescue medication (withhold the rescue medication for at least 6 hours prior to spirometry assessment) upon rising in the morning on days requiring spirometric assessments indicated in Table 8-1, unless absolutely necessary. If rescue medication is taken within 6 hours prior to spirometry at any of the scheduled visits (starting from the Run-in visit), the visit should be rescheduled to the next possible day. Additionally, if it's not possible to reschedule the visit, rescue medication is taken within 6 hours prior to spirometry, this information will be recorded by the study site staff using the equipment provided by the central spirometry vendor.

Daily use of rescue medication (the number of puffs taken in the previous 12 hours) will be recorded (once in the morning and once in the evening) by the subject using the eDiary.

Unless clinically indicated, the type of rescue medication a subject used, the device used to deliver the medication and the way it is administered must not be adjusted.

6.2.4 Restriction for study subjects

For the duration of the study, the subjects should be informed and reminded of the restrictions outlined in this section.

6.2.4.1 Dietary restrictions and smoking

Study participants must refrain from smoking or inhaling nicotine or tobacco products or other recreational inhaled foreign substances such as marijuana, e-cigarettes, etc. for the duration of the study.

Subjects should refrain from alcohol and caffeine intake 12 hours and 8 hours respectively prior to each study visit.

All subjects will be asked to fast (i.e., no food and liquid except water) for at least 8 hours prior to dose administration on Day 15 (Week 2) and Day 85 (Week 12) and will continue to fast for 1 hour thereafter. This is due to the fact that blood samples for pharmacokinetic measurements are taken on this day. There is no restriction of fasting at other visits.

6.3 Subject numbering, treatment assignment, randomization

6.3.1 Subject numbering

The subject number assigned to a subject at screening remains the unique identifier for the subject throughout the study. For information on subject numbering, please see ‘Subject numbering’ section in the Site Operations Manual.

6.3.2 Treatment assignment, randomization

On Day 1, all eligible subjects will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the subject fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the subject, which will be used to link the subject to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the subject.

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

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

Follow the details outlined in the Site Operations Manual regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

This is a subject and investigator-blinded study. Subjects and investigators will remain blinded to study treatment (i.e., LOU064 or placebo) throughout the study; except for during run-in period, when all subjects will receive LOU064 matching placebo along with background therapy, only subjects are blinded to the identity of this treatment.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Site staff

All site staff (including study investigator and study nurse) will be blinded to study treatment throughout the study with the exception of the run-in period. Only the subject will be blinded to study treatment (i.e., placebo) during the run-in period. Unblinding a single subject at site for safety reasons (necessary for subject management) will occur via an emergency system in place at the site.

Sponsor staff

The following unblinded sponsor roles are required for this study:

- Unblinded sample analyst(s) (PK,)
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The sample analysts will receive a copy of the randomization schedule (via request to the Randomization Office), to facilitate analysis of the samples. The sample analysts will provide the sample data to the study team under blinded conditions unless otherwise allowed.

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All unblinded personnel will otherwise keep randomization lists and data or information that could unblind other study team members confidential and secure except as described above.

Following final database lock all roles may be considered unblinded.

6.5 Dose escalation and dose modification

LOU064 and background therapy dose adjustments and/or interruptions are not permitted unless they are absolutely necessary for subject's safety. Any dose adjustments and/or interruptions will be recorded as protocol deviations. All changes must be recorded on the Dosage Administration Record eCRF.

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 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 will be assessed by the investigator and/or study personnel at each visit using capsule counts and information provided by the subject. This information should be captured in the source document at each visit. All study treatment dispensed and returned must be recorded in the Drug Accountability Log. Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LOU064, as detailed in Section 8.5.1.

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events. Treatment of adverse events should be symptomatic. In case of questions regarding treatment of AEs caused by investigational product the investigator may contact the sponsor. Study drug discontinuation criteria as provided in Section 9.1.1 must be followed.

In case of exacerbations of asthma, adequate treatment of exacerbation as per the national or international (GINA 2018) recommendations should be instituted. These include administration of short acting beta-2 agonist, systemic steroids, short acting anticholinergics, administration of controlled oxygen and supervision until the patient is considered stable. Note that exacerbations that requiring treatment with systemic (e.g., oral or i.v. administration) steroids will require discontinuation of the patient from the study (Section 9.1.1).

In case of infections, institute the adequate antibiotic treatment. Check the immunoglobulin levels of the subject. In case of concurrent hypo-immunoglobulinemia and serious infection consider administration of immunoglobulins.

In case of bleeding events (e.g., bleeding or hematoma without trauma), bleeding into organs, stop treatment. In case of serious event consider administration of platelet concentrate.

Medication used to treat AEs must be recorded on the Concomitant Medications/Significant non-drug therapies CRF.

6.6.3 Emergency breaking of assigned treatment code

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

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

- protocol number
- subject number

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

After emergency unblinding, the subject will not receive further study treatment.

6.7 Preparation and dispensation

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

LOU064 or placebo will be administered to the subject via the following route of administration: oral. Administration will occur at home with the exception of the following visits: Day 1, Day 15 (Week 2), Day 29 (Week 4), Day 57 (Week 8) and Day 85 (Week 12), when drug administration will occur at the study site.

Whenever there is a scheduled site visit during the run in, treatment and follow-up period, subjects should come to site in the morning, the study medication and the morning dose of standard background therapy ICS/LABA will only be taken after the spirometry assessment at the visit day.

On the day of site visits with spirometry assessments, investigators should try to plan site visits at approximately the same time (no more than two hours different than the Baseline visit)

See the Site Operations Manual for further details.

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.

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. The date of signing of informed consent (and withdrawal, if later withdrawn) must be documented in the CRF.

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.

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

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

Refer to the Site Operations Manual for a complete list of ICFs included in this study.

8 Visit schedule and assessments

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

Subjects should be seen for all visits/assessments as outlined in the assessment schedule or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Subjects who prematurely discontinue the study for any reason should be scheduled for a visit as soon as possible, at which time all of the assessments listed for the final visit (i.e., end of study) will be performed. At this final visit, all dispensed investigational product should be reconciled, and the adverse event and concomitant medications recorded on the CRF.

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8.1 Screening

It is permissible to re-screen a subject once if he/she fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis.

In the case where a safety laboratory assessment at screening is outside of the range specified in the exclusion criteria, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject must be excluded from the study.

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

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

Information on what data must be collected for screening failures and further information on re-screening is outlined in the Site Operations Manual.

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 will be considered a screen failure. Information on what data must collected for screening failures and further information on re-screening is outlined in the SOM.

8.2 Subject demographics/other baseline characteristics

Subject demographic and baseline characteristic data will be collected on all subjects. Relevant medical history/current medical conditions data will also be collected until signature of informed consent. Details are outlined in the SOM.

Smoking history will also be collected. Details are outlined in the SOM.

Investigators have the discretion to record abnormal test findings on the medical history CRF, if in their judgement, the test abnormality occurred prior to informed consent signature.

8.2.1 Spirometry Reversibility Test

Spirometry reversibility testing will be performed at screening to assess eligibility for the study. If reversibility is not demonstrated at the screening visit, then two additional attempts are permitted (one at the run-in visit and the last one during the run in period between run in visit and baseline visit if needed).

Reversibility testing will be performed according to the American Thoracic Society guidelines. Details regarding equipment, study site personnel training and certification, and quality control are provided in the SOM and/or vendor manual.

8.2.2 Hepatitis screen

All subjects will be screened for Hepatitis B and C. Further details are provided in the SOM.

8.2.3 HIV and tuberculosis screen

If indicated by patient history (e.g., patient belongs to a HIV risk group but was not yet tested; known previous exposure to tuberculosis patients and/or living in an environment with known high tuberculosis rate), a HIV (by serological testing) or tuberculosis screen (serological testing, check for clinical symptoms, chest X-ray if applicable) should be considered.

8.2.4 Allergy skin test

The allergy skin testing is conducted to identify subjects who are sensitive to any of the allergen(s) being tested and to identify the specific substance (s) that the subject is sensitive to. If study centers cannot perform the allergen skin prick test, a screening for specific IgE will be performed (see Section 8.5.3.2). The tests are used to identify allergens that are causing symptoms and to determine if the patient's asthma is atopic or non-atopic.

An allergy skin test will be completed as per the Assessment Schedule: such test will include applying an extract of an allergen to the skin, scratching or pricking the skin to allow exposure, and then evaluating the skin's reaction.

If an allergen provokes an allergic reaction, a raised itchy bump (wheal) will develop. The size of the wheal (the raised area and not the redness) will be measured in millimeters with a ruler and recorded. The wheal size for each antigen will be recorded on the Skin Prick Test CRF.

8.3 Efficacy

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Efficacy outcomes and Commercially Confidential Information samples will be collected at the timepoints defined in the Assessment schedule, Section 8. Follow instructions outlined in the Site Operations Manual / vendor manual regarding lung function testing, symptom questionnaires, sample collection, numbering, processing, and shipment.

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8.3.1 Spirometry

Spirometry testing will be performed with the MasterScope system (manufactured by eResearchTechnology GmbH) according to the American Thoracic Society guidelines. Criteria for acceptability and reproducibility need to be met. Details regarding equipment, study site personnel training and certification, spirometric values captured in the database, and quality control are provided in the SOM and/or vendor manual. Spirometry testing will be subject to central reading.

8.3.2 Clinical Outcome Assessments (COAs)

The validated questionnaire (Asthma Control Questionnaire or ACQ 1999) will be administered at various timepoints during the study as depicted in the Assessment Schedule. Further details will be described in the SOM.

8.3.3 eDiary for daily asthma symptoms, peak flow and rescue medication use

The study will use the asthma diary reported by Santanello et al 1997. This asthma diary was validated in studies of patients aged 18 to 65 years (Santanello et al 1997). The diary was subsequently included as a measure in placebo-controlled studies of montelukast in patients aged 15 years and older (Reiss et al 1998, Malmstrom et al 1999) and shown to be responsive to both montelukast and inhaled beclomethasone therapy in this age range.

All subjects will be provided with a patient electronic diary (eDiary or eDiary/ePEF: Asthma Monitor AM3 Option G+, manufactured by eResearchTechnology GmbH) to record daily asthma symptoms, PEF and SABA (salbutamol/albuterol) use. Subjects will be instructed to routinely complete the patient diary twice daily - at the same time each morning and each evening, approximately 12 hours apart. The eDiary/ePEF recordings are to be reviewed at each clinic visit as detailed in the Assessment schedule. Sites and subjects will receive training and guidance on the use of the eDiary/ePEF device. Further details are provided in the SOM and/or vendor manual.

The data captured in the patient eDiary will be used in conjunction with the patient's asthma characteristics to monitor the patient's asthma. Subjects will be instructed to call the study site if they experience symptoms of worsening asthma. Additionally, the eDiary will be programmed to generate some alerts of signs of possible worsening asthma based on data collected. These alerts will be sent to the subject and/or to investigator.

8.3.3.1 Daily symptom scores

The asthma diary contains daytime and nocturnal asthma symptom questions (Santanello et al 1997). The format of the electronically administered diary may vary.

8.3.3.2 Number of inhalations of rescue medication

The total number of inhalations of SABA (number of puffs taken in the previous 12 hours) will be recorded in the morning and evening by the subject in the eDiary/ePEF.

8.3.3.3 Peak expiratory flow (PEF)

PEF will be measured at consistent times for a subject in the morning and evening each day as outlined in the Assessment schedule. The measurements will be performed using an eDiary/ePEF provided to the subjects.

Subjects must be encouraged to perform morning and evening PEF measurements BEFORE the use of any rescue medication (i.e., SABA), and subjects will be asked to record if they have taken their SABA 6 hours prior to the peak flow assessment.

At each time point, the subject will be instructed to perform 3 consecutive maneuvers within approximately 10 minutes. These PEF values are captured in the eDiary/ePEF.

8.3.3.4 Worsening of asthma (and related eDiary alerts)

The data captured in the patient eDiary will be used in conjunction with the patient's asthma characteristics to monitor the patient's asthma. Asthma worsening criteria will be programmed into the eDiary/ePEF. Subjects will be instructed to call the study site if they experience symptoms of worsening asthma. Additionally, the eDiary will be programmed to generate some alerts of signs of possible worsening asthma based on data collected. These alerts will be sent to the subject and/or to the investigator.

These alerts include:

- An increase in SABA use on at least 2 of any 3 consecutive days exceeding the equivalent of 8 puffs/day (diary alert)
- Night time awakenings requiring SABA use on at least 2 out of any 3 consecutive nights (diary alert)
- <60% of PEF compared to baseline (diary alert)

The subject's personal best PEF in the clinic at the Run-in visit will be set as the subject's baseline for the run-in period, and the personal best PEF in the clinic on Day 1 prior to dosing will be set as the subject's baseline for the treatment period.

If subjects develop any of the above criteria, the subject should notify the investigator and be evaluated by the investigator and treated as clinically appropriate.

If any of these criteria are met while a patient is in the screening, placebo run-in, or treatment periods of the study, they may be withdrawn if, in the opinion of the investigator, it is appropriate to do so.

Worsening of asthma symptoms may require unscheduled evaluation between visits. Study site personnel must be available to monitor and document the subject's progress until the asthma worsening as resolved.

8.3.4 Appropriateness of efficacy assessments

The measures described above (spirometry, PEF-measurements, diaries, records of rescue medication and patient reported outcomes ACQ) are well-established and widely used outcome measures in asthma trials.

8.4 Safety

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

For details on AE collection and reporting, refer to AE section.

Table 8-2 Physical assessments

Assessment	Specification
Physical examination	A complete physical examination 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. The complete physical examination will be done at screening and End of Study visit. At the other visits it will be examination of general appearance, the lungs, skin, mucosa of eyes, throat, mouth cavity. 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 CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.
Vital signs	Vital signs include: • Body temperature • Blood pressure (BP) • Pulse
Height and weight	• Height (Screening only) • Body weight • Body mass index (BMI) will be calculated as (Body weight (kg) / [Height M)]^2) (Screening only)

The methods, assessment, specification, and recording for each assessment will be detailed in the SOM.

8.4.1 Laboratory evaluations

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

Clinically notable laboratory findings are defined in Section 16.1.

Clinically significant abnormalities must be recorded on the relevant section of the medical history/Current medical conditions/AE CRF /e(CRF) page as appropriate.

Table 8-3 Laboratory assessments

Test category	Test name
Hematology	Hematocrit, Hemoglobin , 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, ALT, AST, GGT, LDH, Calcium, Magnesium, Phosphorus, Chloride, Sodium, Potassium, Creatinine Kinase (CK), Creatinine, total Bilirubin (in case of clinically significant elevation: direct Bilirubin and indirect Bilirubin will be assessed), Amylase, Lipase, Blood Glucose; CRP; Blood Urea Nitrogen (BUN) or Urea, Uric Acid; in case of liver value deviations refer to Section 16.2 (liver events) Only at baseline (Day 1) and Week 12: total Cholesterol, Low density Lipoprotein (LDL), High density Lipoprotein (HDL), Total Protein, Triglycerides
Urinalysis	Done on site: Macroscopic Panel (e.g., Dipstick) (Color, Bilirubin, Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen); in case of abnormal findings pls. confirm and consider appropriate follow-up (e. g. urine protein analyses, urine microscopy, urine microbiolgy) for recommendations refer to Section 16.3 for definitions of alert criteria and recommendations for follow-up .
Coagulation	Prothrombin time (PT)/International normalized ratio (INR), Activated partial thromboplastin time (APTT)
Hepatitis markers	At Screening only: Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (HBsAb); Hepatitis B core antibody (anti-HBc) Hepatitis B-Deoxyribonucleic acid (HBV- DNA) if appropriate; Hepatitis C virus antibody (HCVAb); Hepatitis C-Ribonucleic acid (HCV-RNA) if appropriate
Additional tests	IgE, IgG, IgA, IgM; Follicle-stimulating hormone (FSH) (for female subjects with unclear fertility status; at screening); B-hCG for pregnancy (serum and urine)

8.4.2 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the Site Operations Manual.

PR interval, QRS duration, heart rate, RR interval, QT interval, QTc will be measured.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions.

Unless auto-calculated by the ECG machine, the investigator must calculate QTcF at the Screening visit to assess eligibility. See the SOM for additional details.

Clinically significant abnormalities must be reported as adverse events.

8.4.3 Pregnancy and assessments of fertility

A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner. In addition, male participants should not donate sperm after being randomized and exposed to LOU064.

All pre-menopausal women who are not surgically sterile will have a serum pregnancy test at Screening, Day 29 (Week 4), Day 57 (Week 8), Day 85 (Week 12) and End of Study. A urine pregnancy test will be performed at the placebo Run-in visit and randomization (Day 1; BEFORE administration of the study medication, Day 15 (Week 2)). A positive urine test needs to be confirmed with serum test. If positive, the subject must be discontinued from study treatment.

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

Assessments of fertility

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

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

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

8.4.4 Other safety evaluations

Not applicable

8.4.5 Appropriateness of safety measurements

The safety assessments selected will provide sufficient safety information for LOU064 in the target population.

8.5 Additional assessments

8.5.1 Pharmacokinetics

Pharmacokinetic (PK) samples will be collected at the visits defined in the Assessment schedule. Follow instructions outlined in the SOM regarding sample collection, numbering, processing and shipment. Residual PK samples may be used to explore additional PK aspects such as metabolite formation or plasma protein binding of LOU064.

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8.5.2 Biomarkers

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8.5.2.2 Use of residual biological samples

Residual blood and urine samples may be used for another protocol specified endpoint.

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8.5.3 Other Assessments

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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.

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

Study treatment must be discontinued under the following circumstances:

- Subject/guardian decision
- Pregnancy
- Current use of prohibited treatment as per recommendations in the prohibited treatment section (Section 6.2.2)
- Subject received a live virus vaccination since the last visit
- Any situation in which study participation might result in a safety risk to the subject
- Following emergency unblinding
- Emergence of the following adverse events:
  - AEs including hypersensitivity reactions for which continued exposure to the study drug would be detrimental
  - Abnormal liver laboratory results requiring discontinuation (see Section 16.2)
  - Abnormal renal laboratory results requiring discontinuation (see Section 16.3)
  - Spontaneous bleeding event
  - Platelets < 75 000/mm^3
  - Required interventions (surgery) with bleeding risk
  - Any laboratory abnormalities (for anemia or neutropenia criteria see Section 16.1) or safety findings that in the judgment of the investigator, taking into consideration the patient's overall status, prevents the patient from continuing participation in the study
  - An asthma exacerbation requiring treatment with systemic corticosteroids (e.g., oral/parenteral)
  - Need for prohibited asthma medication (as per Section 6.2.2) to achieve acceptable symptom control of asthma, e.g., patient requires higher amount of ICS; patient needs higher amount of rescue medication at a total daily dose level higher than labeled to achieve acceptable symptom control
  - Development of chronic or recurrent infections including but not limited to opportunistic infections

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 Section 9.1.2 withdraw of informed consent). **Where possible, they should return for the assessments indicated** in the assessment schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g., telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in Section 9.1.3. 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

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

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

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore

and

- Does not allow further collection of personal data

In this situation, the investigator should make a reasonable effort (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 keep and use collected study information (including any data resulting from the analysis of a subject's samples until the time of withdrawal) according to applicable law.

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

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

9.1.3 Lost to follow-up

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the subject, 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.

9.1.4 Study stopping rules

The study may be put on hold pending a full safety data review, if any of the following criteria are met:

- Two or more (in different subjects) similar study-treatment (LOU064) related SAEs are reported
- Two or more other clinically significant, severe events (in different subjects) that preclude to continue dosing (events that are considered study drug related: development of recrurrent/opportunistic infection, thromboembolism, spontaneous bleeding events, drug related renal or liver events, neutropenia, anemia, thrombocytopenia <75.000/microliter)
- The Sponsor considers that the number and/or severity of AEs, abnormal safety monitoring tests or abnormal laboratory findings justify putting the study on hold.

In these cases, ad hoc internal experts along with representative site investigators will carefully evaluate the safety data of the entire study. The experts and investigators will recommend whether the study can be continued, should be stopped or if other safety measures need to be taken. The findings and recommendations of the internal experts and investigators will be documented and will be made available to all investigators, their respective Institutional Review Board/Independent Ethics Committee (IRB/IEC) and health authorities, as appropriate.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination may include:

- Unexpected, significant, or unacceptable safety risk to subjects enrolled in the study
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data
- Discontinuation of study drug development.

In taking the decision to terminate, Novartis will always consider the subject welfare and safety. Should early termination be necessary, subjects must be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests. The investigator or sponsor depending on the local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last subject finishes their Study Completion visit (i.e., Last Subject Last 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 (e.g., each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

All randomized and/or treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3 and SOM. Documentation of attempts to contact the subject should be recorded in the source documentation.

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
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
   a. not recovered/not resolved;
   b. recovered/resolved;
   c. recovering/resolving,
   d. recovered/resolved with sequelae;
   e. fatal; or 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 Investigator Brochure (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

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 Section 16.1, Section 16.2, and Section 16.3 for alert ranges for laboratory and other test abnormalities.

Follow the instructions found in the Site Operations Manual for data capture methodology regarding AE collection for subjects that fail screening.

10.1.2 Serious adverse events

An SAE is defined as any adverse event [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).

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.

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.
2. Run-In Failures (e.g., a subject who is screened but not randomized/treated after the run-in period (where run-in period requires adjustment to subject's medications or other intervention)): SAEs collected between time subject signs ICF until time that subject is determined to be a run-in failure.
3. 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 Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

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. A minimum of 12 months of the newborn must be followed up.

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

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

10.1.5 Reporting of study treatment errors including misuse/abuse

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

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

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

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

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

Treatment error type	Document in Dose Administration (DAR) eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

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

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 are recorded in the source documentation

Please refer to Table 16-1 in Section 16.2 for complete definitions of liver laboratory triggers and liver events.

Every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 in Section 16.2.

- 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 reported on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated
- Discontinuation of the investigational drug (refer to the Section 9.1.1 Discontinuation of study treatment), if appropriate
- Hospitalization of the subject if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event. These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy
- Obtaining a more detailed history of symptoms and prior or concurrent diseases
- Obtaining a history of concomitant drug use (including nonprescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Exclusion of underlying liver disease
- Obtaining a history of exposure to environmental chemical agents
- Considering gastroenterology or hepatology consultations

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

Refer to the Site Operations Manual for additional details.

10.2.2 Renal safety monitoring

Every renal laboratory trigger or renal event as defined in Table 16-3 in Section 16.3 should be followed up by the investigator or designated personnel at the trial site as summarized in Table 16-4 in Section 16.3.

Refer to the Site Operations Manual for additional details.

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 Contract Research Organization (CRO)) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff 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.

Randomization codes and data about all study treatment(s) dispensed to the subject and all dosage changes will be tracked using 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.

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

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

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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., 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/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, electrocardiograms, 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 informed consent form signed by the subject (a signed copy is given to the subject).

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

12 Data analysis and statistical methods

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

12.1 Analysis sets

The Safety Set includes all subjects who received at least one dose of study treatment.

The PK analysis set will include all subjects with at least one available valid (i.e., not flagged for exclusion) PK concentration measurement, who received any study drug and with no protocol deviations that affect PK data.

The PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

Subjects will be analyzed according to the study treatment received, unless otherwise specified.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including key disease characteristics will be listed and summarized descriptively by treatment group based on PD analysis set.

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

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group, as applicable.

12.3 Treatments

The Safety set will be used for the analyses below.

The duration of study treatment exposure in months will be summarized using descriptive statistics. The number of subjects with permanent study drug discontinuation and the reasons will be summarized by treatment group. All dose administration records will be listed at a subject level.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)

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

12.4.1 Definition of primary endpoint(s)

The primary analysis variable is the change from baseline in pre-dose FEV1 after 12 weeks of treatment with LOU064 at 100mg q.d. or placebo.

The baseline pre-dose FEV1 is defined as the average of the FEV1 measurements performed 45 min and 15 min prior to dosing on Day 1. If one of the assessment is missing, then the non-missing pre-dose FEV1 will be considered as baseline.

Repeated measurements of pre-dose FEV1 at week 2, week 4, week 8 and week 12 are considered in the primary analysis.

12.4.2 Statistical model, hypothesis, and method of analysis

The primary endpoint will be analyzed using a Bayesian repeated measures model with change from baseline in pre-dose FEV1 as response, adjusting for effects of treatment*visit interaction, baseline pre-dose FEV1, and any additional covariate as deemed appropriate. Conditional on the aforementioned covariates, the responses are assumed to follow a multivariate normal distribution with a common unknown and unstructured covariance matrix explaining the association between repeated measures for a subject (similar to a covariance pattern model).

Prior distributions for the unknown quantities included in the model are specified as below.

A weakly informative prior will be used for adjusted mean change from baseline at week 12 under placebo (placebo response). The prior reflects the predicted placebo response as estimated from a Bayesian meta-analysis on similar historical trials, accounting for a substantial between-trial variability. A Bayesian meta analysis estimates that the placebo response to be normally distributed with a mean of 46ml and SD of 84ml at week 12. To ensure that this weakly informative Bayesian prior will be in alignment with the trial data, a robust mixture prior will be used in the analysis. The mixture prior allows for more uncertainty in the placebo response. The mixture has a second distribution that has 10% weight and assumes placebo is normally distributed with a mean of 46ml and larger SD of 260ml).

Integrating this prior with the observed FEV1 data implies an additional amount of information equivalent to 5 subjects on placebo.

For adjusted mean responses at all other time points under placebo treatment and for LOU064 treatment at all time points, non-informative prior will be used in the Bayesian repeated analysis model. An inverse wishart distribution will be used as a non-informative prior for the covariance matrix accounting for the association between responses at each time point.

The quantity of primary interest is the ‘true’ LOU064 effect on primary endpoint over placebo and inferences will be performed in terms of the posterior probabilities derived from the above model.

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12.4.3 Handling of missing values/censoring/discontinuations

The primary analysis methodology uses all available information on the primary endpoint without making any explicit imputation for missing FEV1 measurements. However, the modeling implicitly borrows information from the patient history and from similar patient profiles and provides consistent estimates of model parameters under 'Missing at random (MAR)' assumption. Alternative missing data handling may be used if there is substantial rationale for considering the missing values to be missing not at random (MNAR).

12.4.4 Sensitivity and Supportive analyses

Descriptive summaries will also be provided for change from baseline in pre-dose FEV1 by time and treatment group. Primary endpoint analysis may be repeated on the subgroups prospectively defined on demographic/ baseline characteristics. Details will be specified in the statistical analysis plan.

12.5 Analysis of secondary endpoints

All secondary efficacy/ Commercially Confidential Information endpoints will be analyzed based on PD analysis set, while the safety endpoints will be analyzed based on safety set, unless otherwise specified.

12.5.1 Efficacy Commercially Confidential Information endpoint(s)

All the secondary efficacy/ pharmacodynamic endpoints will be analyzed based on PD analysis set, unless specified otherwise. The secondary efficacy/ Commercially Confidential Information variables include -

1. Change from baseline in ACQ-5 score over 12 weeks of treatment (ACQ assessment for the week preceding each planned visit up to end of study)
2. Number of puffs of SABA taken per day over 12 weeks of treatment (captured in eDiary)
3. Change from baseline in PEF (AM and PM), as assessed by mean morning and mean evening PEF over 12 weeks of treatment (daily capture of PEF in eDiary)
4. Change from baseline in daytime and nighttime asthma symptom score over 12 weeks of treatment (captured in eDiary)

12.5.1.1 Analysis methods for secondary efficacy/ Commercially Confidential Information

All secondary endpoints except (2) (Number of puffs of SABA taken per day over 12 weeks of treatment) will be analyzed using a similar methodology as followed for primary endpoint, with the exception that –

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

For secondary endpoint (2), mean number of puffs of SABA taken in past 12 hours (morning/ evening) and overall will be calculated for each subject separately for run-in period (used as baseline value) and double blind treatment period of 12 weeks. Change from baseline in mean daily use of puffs of SABA over 12 weeks will be analyzed using a Bayesian regression model. The model will assess effects of treatment (LOU064/ placebo), baseline use of puffs of SABA per day, baseline pre-dose FEV1, baseline daytime asthma symptom score and any additional covariate as deemed appropriate.

In a similar manner as followed for primary endpoint (Section 12.4.2), for each of the secondary endpoints, the posterior probabilities of 'true' effect of LOU064 over placebo will be derived from the fitted model. The posterior probabilities will be compared to the pre-specified criteria mentioned in Section 12.4.2 at interim/ final stage as a guide for PoC evaluation of treatment effect on the endpoint.

For each endpoint except rescued medication usage, the adjusted posterior mean estimates over 12 weeks with 2-sided 80% credible limits will be plotted for each of the treatment for descriptive purposes. Frequency of use of rescue medications will be summarized by treatment group descriptively and will also be listed at a subject level.

12.5.2 Safety endpoints

All safety endpoints will be analyzed based on safety set and will be summarized by actually received treatment group.

Adverse events

Adverse event summaries will only include treatment emergent AEs, defined as any AE that develops after initiation of the study treatments or any event already present that worsens following exposure to the study treatment.

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

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

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

A subject with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

All AEs, deaths and serious adverse events will be listed by patient and treatment group.

Vital signs

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

12-lead ECG

All ECG data will be listed by treatment group, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.3 Pharmacokinetics

PK analysis set will be used for the analysis of all pharmacokinetic parameters.

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LOU064 blood concentration data and the derived PK parameters will also be listed by treatment, subject, and visit/sampling time point.

Graphical methods will be employed to show mean and individual time-concentration profiles.

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12.5.5 Patient reported outcomes

Refer to Section 12.5.1

12.6 Analysis of exploratory endpoints

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12.7 Interim analyses

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12.8 Sample size calculation

Approximately 75 subjects will be randomized to LOU064 100 mg q.d. or placebo in a 3:2 ratio in order to achieve at least 65 completers. The planned sample size is driven by the following considerations on primary endpoint. (The sample size used the freely available software (Fisch et al (2015).)

12.8.1 Primary endpoint(s)

The planned sample size is selected to ensure an optimal operating characteristic for evaluation of PoC regarding the treatment effect on the primary endpoint according to the criteria mentioned in Section 12.4.2.

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

15 References

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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 (specifically in case of worsening of value from baseline is observed) if the abnormal hematology parameter is confirmed:

- Hemoglobin: < 10 g/dl
- Platelets: < 75,000/mm^3
- White blood cells: < 3000/mm3
- Neutrophils: < 1500/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 require assessment for clinical relevance by the investigator.

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 γGT 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 γGT 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 γGT 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 γGT 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 γGT 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 patient	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

Criteria	Actions required	Follow-up monitoring
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 γGT 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 patient	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 γGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. concomitant medication, medical history, laboratory values) in the appropriate eCRF.	Investigator discretion

[a]Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN [b](General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia [c]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

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 concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

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

Table 16-3 Specific renal alert criteria and actions

Renal Event	Actions
Confirmed serum creatinine increase 25 – 49%	• Consider causes and possible interventions • Follow up within 2-5 days
Serum creatinine increase ≥ 50%[+]	• 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) ≥ 1 g/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	Assess & document • 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

[+] Corresponds to KDIGO criteria for Acute Kidney Injury Additional specialized assessments are available to assess renal function or renal pathology. *(Note: In exceptional cases, when a nephrologist considers a renal biopsy, it is recommended to make slide specimen available for evaluation by the RSG 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 eCRF • Urine dipstick and sediment microscopy evidence of 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 eCRF. 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, rifampin, 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