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LOU064

Clinical Trial Protocol CLOU064E12201

ClinicalTrials.gov Identifier: NCT04035668

An adaptive Phase 2 randomized double-blind, placebo-controlled multi-center study to evaluate the safety and efficacy of multiple LOU064 doses in patients with moderate to severe Sjögren's Syndrome (LOUiSSe)

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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

ACR	American College of Rheumatology
AD	Atopic Dermatitis
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
anti-HBc	Hepatitis B core antibody
Anti-TNF-α mAb	Anti-Tumor Necrosis Factor-alpha monoclonal antibody
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Classification
AUC	area under the curve
AV-Block	atrioventricular block
BCR	B cell receptor
BCRP	Breast Cancer Resistance Protein
bid	twice a day (for Latin: “bis in die”)
BMI	Body Mass Index
BTK	Bruton’s tyrosine kinase
BUN	blood urea nitrogen
CBC	complete blood count
CK	creatinine kinase
cm	Centimeter
CMO&PS	Chief Medical Office & Patient Safety
CNS	central nervous system
COA	Clinical outcome assessments
CRF/eCRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CRP	C-reactive protein
CSR	Clinical study report
CSU	Chronic Spontaneous Urticaria
COVID-19	Coronavirus disease 2019
CV	coefficient of variation
CYP	Cytochrome P450
DDE	Direct Data Entry
DDI	Drug-drug interactions
DIN	Drug Inducted Nephrotoxicity
DMARDs	disease-modifying antirheumatic drugs
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ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay

EMG	Electromyography
EOS	End of Study
EQ-5D	EuroQual 5 dimensions (Standard instrument to measure the health-related quality of life)
(e)SAE	(Electronic) Serious Adverse Event
eSource	Electronic Source
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index
EULAR	European League against Rheumatism
FACIT-F	Functional Assessment of Chronic Illness Therapy-Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration (US Agency for drug and food control)
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GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
h	Hour
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	human immunodeficiency virus
HRCT	high resolution computer tomography
i.v.	Intravenous
IA	Interim analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
Ig	Immunoglobulin
IMP	investigational medicinal product
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
IUD	intrauterine device
IUS	intrauterine system
kg	Kilogram
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LDH	lactate dehydrogenase
LFT	Liver function test

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mAb	monoclonal antibody
MATE1	Multidrug and toxin extrusion protein 1
MCP-Mod	Multiple Comparison Procedure – Modelling
MedDRA	Medical dictionary for regulatory activities
mg	milligram(s)
mL	milliliter(s)
MMRM	Mixed effect Model Repeat Measurement
MRT	mean residence time
ng	Nanogram
NOAC	Novel Oral Anti-Coagulant
NSAID	Nonsteroidal Anti-Inflammatory Drug
NTI	Narrow Therapeutic Index
PD	Pharmacodynamic(s)
P-gp	P-glycoprotein
PhGA	Physician global assessment scale
PK	Pharmacokinetic(s)
PNS	peripheral nervous system
PT	prothrombin time
PTT	partial thromboplastin time
PXR	Pregnane-X-Receptor
qd	once a day (for Latin “quaque die”)
OAT3	Organic anion transporter 3
OATP1B1	Organic anion transporting polypeptide 1B1
OCT1	Organic cation transporter 1 (liver)
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia’s formula
RBC	red blood cell(s)
RF	rheumatoid factor
ROTEM	Rotational thromboelastometry
RoW	Rest of World
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SjS	Sjögren's Syndrome
SmPC	Summary of Product Characteristics
SMQ	Standardized MedDRA Query
SOM	Site Operations Manual
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SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reactions
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TBL	total bilirubin
TEC	tyrosine-protein kinase
Tfh	follicular T helper cell
ULN	upper limit of normal
UTI	Urinary Tract Infection
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent
XLA	X-linked agammaglobulinemia
µL	Microliter

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study subject
Cohort	A specific group of subjects fulfilling certain criteria
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Cycles	Number and timing or recommended repetitions of therapy are usually expressed as number of days (e.g., q28 days)
Dosage	Dose of the study treatment given to the subject in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care.
End of the clinical trial	The end of the clinical trial is defined as the date of last visit of the last subject or at a later point in time as defined by the protocol.
Enrollment	Point/time of subject entry into the study at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
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/treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized subjects	Mis-randomized subjects are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Part	A sub-division of a study used to evaluate specific objectives or contain different populations. For example, one study could contain a single dose part and a multiple dose part, or a part in subjects with established disease and in those with newly-diagnosed disease
Patient	An individual with the condition of interest for the study
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis

Perpetrator Drug	A drug which affects the pharmacokinetics of the other drug
Personal Data	Subject information collected by the Investigator that is transferred to Novartis for the purpose of the clinical trial. This data includes subject identifier information, study information and biological samples
Premature subject withdrawal	Point/time when the subject exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized subject
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 intervention or other treatment)
Screen Failure	A subject who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first subject
Study treatment	Any single drug or combination of drugs or intervention administered to the subject as part of the required study procedures
Study treatment discontinuation	When the subject permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Subject	A trial participant (can be a healthy volunteer or a patient)
Subject number	A unique number assigned to each subject upon signing the informed consent. This number is the definitive, unique identifier for the subject and should be used to identify the subject throughout the study for all data collected, sample labels, etc.
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts
Variable	A measured value or assessed response that is determined in specific assessments and used in data analysis to evaluate the drug being tested in the study
Victim drug	The drug that is affected by the drug-drug interaction
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	CLOU064E12201
Full Title	An adaptive Phase 2 randomized, double-blind, placebo-controlled multicenter study to evaluate the safety and efficacy of multiple LOU064 doses in patients with moderate to severe Sjögren's Syndrome (LOUiSSe)
Brief title	A Phase 2 study to evaluate the safety and efficacy of LOU064 in patients with Sjögren's Syndrome (SjS)
Sponsor and Clinical Phase	Novartis. Phase II
Investigation type	Drug
Study type	Interventional
Purpose and rationale	This study with LOU064 is an adaptive phase 2 study designed to establish safety and efficacy CCI of LOU064 in patients with moderate to severe SjS to allow further development of the compound for treatment of this disease.
Primary Objective(s)	Commercially Confidential Information
Secondary Objectives	Commercially Confidential Information Objective 2: To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline on patient and physician-reported outcomes (ESSPRI, FACIT-F, EQ-5D, PhGA) over time. Objective 3: To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in ESSDAI over time. Objective 4: To evaluate the safety and tolerability of LOU064 by reporting the occurrence of treatment emergent AEs (both serious and non-serious), abnormal vital signs, laboratory and ECG values during the study. Objective 5: To assess PK parameters of LOU064 (Cmax, AUC, Tmax and MRT and others as needed) at steady state.
Study design	This is an adaptive phase 2 randomized, double-blind, placebo-controlled, multi-center, CCI study to evaluate the safety and efficacy of multiple LOU064 doses in patients with moderate to severe Sjögren's Syndrome (SjS) over 24 weeks of treatment. Total study duration for each patient will be up to 35 weeks.
Study Population	Female and male patients aged 18 to 75 years with moderate to severe SjS; a total of approximately 252 patients will be enrolled.

Key Inclusion criteria	• Male or female patients aged 18 to 75 years at screening • Classification of Sjögren's Syndrome according to the 2016 ACR/EULAR criteria at screening • Screening ESSDAI (based on weighted score) ≥ 5 from 8 defined domains (biologic, hematologic, articular, cutaneous, glandular, lymphadenopathy, renal, constitutional). Patients with involvement of one or more of the remaining 4 domains are eligible but scores of these domains will not contribute to the assessment for eligibility, but will be part of the overall ESSDAI score for that subject • Screening ESSPRI ≥ 5 • Seropositive for anti-Ro/SSA antibodies at or within 3 months prior to screening • Unstimulated whole salivary flow rate of > 0 mL/min at screening

Key Exclusion criteria	• Sjögren's Syndrome overlap syndromes where another autoimmune disease constitutes the primary illness
	• Rituximab or other B cell depleting drug within 12 months of Screening. For subjects who received such drug, their B cell count should be within normal range.
	• Prior treatment with any of the following within 6 months of baseline
	  • CTLA4-Fc Ig (abatacept)
	  • Anti-TNF-α mAb
	  • Intravenous Ig
	  • Plasmapheresis
	  • i.v. or oral cyclophosphamide
	  • i.v. or oral cyclosporine A
	• Required regular use of medications known to cause, as a major side effect, dry mouth / eyes, and which have not been on a stable dose for at least 30 days prior to Screening, or any anticipated change in the treatment regimen during the course of the study.
	• Significant bleeding risk or coagulation disorders, including but not limited to:
	  • Requirement for anti-platelet or anticoagulant medication (for example, warfarin, or clopidogrel or Novel Oral Anti-Coagulant - NOAC) other than acetylsalicylic acid (up to 100 mg/d)
	  • History of gastrointestinal or intracerebral or otherwise severe prior bleeding events, including in association with use of Nonsteroidal Anti-Inflammatory Drug (NSAID)
	• Screening CBC laboratory values as follows:
	  • Hemoglobin levels below 10 g/dL
	  • Total leukocyte count less than 3,000/μL
	  • Platelets less than 100,000/μL
	  • Neutrophil count ≤ 1,500/ μL

Study treatment	CCI LOU064 hard gelatin capsules Placebo hard gelatin capsules Commercially Confidential Information
Efficacy assessments	• ESSDAI, ESSPRI, FACIT-F, EQ-5D, PhGA
Pharmacodynamic assessments	• Commercially Confidential Information
Pharmacokinetic assessments	• PK parameters AUCtau, AUC0-4h, Cmax, Tmax and MRT and others as needed
Key safety assessments	• Adverse event monitoring • Physical examinations • Monitoring of laboratory markers in blood and urine • Central ECG assessment • Additional liver and renal safety monitoring
Other assessments	Commercially Confidential Information
Data analysis	Commercially Confidential Information The change from baseline in ESSDAI, ESSPRI, FACIT-F, EQ-5D and PhGA will be analyzed using a MMRM including treatment group, visit, treatment group by visit interaction, stratification factor baseline ESSDAI (<10 or ≥10) and geographic region as fixed factors as well as baseline value of variable analyzed as a covariate. The estimated means per dose and visit and the differences between LOU064 treatment groups and placebo will be derived together with 2-sided 95% confidence intervals.
Key words	Sjögren's Syndrome, ESSDAI, BTK inhibitor, LOU064, adaptive trial design

1 Introduction

1.1 Background

Sjögren's syndrome (SjS) is a systemic autoimmune disease of unknown etiology characterized by lymphoid infiltration and progressive destruction of exocrine glands (Brito-Zerón et al 2016). Although the disease primarily affects the lacrimal and salivary glands, the inflammatory process can target any organ with approximately 15 % of patients showing severe extraglandular manifestations (Baldini et al 2014). The clinical presentation is most often primarily characterized by exocrinopathy of salivary and lacrimal glands presenting with dryness of the mouth and eyes. However, symptoms can be very heterogeneous and range beyond dryness to also include musculoskeletal pain and fatigue affecting nearly all patients, to severe, extra-glandular and systemic involvement (characterized by peri-epithelial lymphocytic infiltration and immune complex deposition) in a more limited subset. The mechanism underlying the development of SjS is the destruction of the epithelium of the exocrine glands, as a consequence of autoreactive B cells and T cells (Brito-Zerón et al 2016). The high prevalence of autoantibodies, especially against Ro/SSA, even at a very early stage suggests that autoreactive B cells participate in the pathomechanism of SjS (Nocturne and Mariette 2018). The B-cell pathology also results in an increased risk for malignant transformation, with B-cell lymphomas occurring at a 10-fold elevated lifetime risk in 5% of SjS patients (Baldini et al 2014).

SjS has an estimated prevalence of 0.3 to 1 per 1,000 persons (Qin et al 2015) and is second only to rheumatoid arthritis as a systemic autoimmune disease. The disease affects mainly women with a female/male ratio of 9:1 and can occur at any age. A major effect of the symptoms in SjS is a severe impact on quality of life and productivity, often caused by disabling fatigue associated with the disease (Mariette and Criswell 2018). There are also a number of potentially severe systemic complications including arthritis, cutaneous vasculitis, peripheral neuropathy, glomerulonephritis, interstitial nephritis, biliary cholangitis, obstructive bronchiolitis and others, involving multiple organ systems and affecting 20-40% of patients (Seror et al 2014).

Clinical features of Sjögren's syndrome can be divided into medically evaluable and patient-symptomatic manifestations. At the present time, there is no single assessment tool that can capture disease activity of both these clinical manifestations of SjS. Therefore, the "European League Against Rheumatism (EULAR) Sjoegren Syndrome (SS) Patient Reported Index" (ESSPRI) and the EULAR SS Disease Activity Index (ESSDAI) are widely accepted as well validated, gold-standard measures of symptomatic and systemic manifestations of SjS, respectively, and will be used in this study to measure the effectiveness of LOU064 (Section 8.3.6).

In terms of current treatment landscape, there are no internationally approved systemic therapies available for SjS. As far as dryness of mouth and eyes is concerned, treatment for SjS patients is limited to symptomatic care. Steroids and typical DMARDs are mostly ineffective, and no pharmacologic intervention is effective against the severe, disabling fatigue. The lack of effective treatment options underscores the need to evaluate newer therapeutic approaches for this highly debilitating disease. Because the pattern of B cell autoreactivity is to some extent similar to systemic lupus and rheumatoid arthritis, recently, B cell depletion therapy using the anti-CD20 monoclonal antibody (mAb) rituximab has been evaluated for both glandular and extra-glandular manifestations of SjS as well as for lymphoma management with varying degree of success. However, this approach is currently not an approved treatment of SjS. The insufficient efficacy of rituximab could be related to incomplete B cell depletion in the affected tissues (Brito-Zerón et al 2016) which may be better addressed by using a BTK-inhibitor and which will be evaluated in this study.

Bruton's tyrosine kinase (BTK) is a cytoplasmic tyrosine kinase and a member of the TEC kinase family. BTK is expressed in cells of both the adaptive and innate immune system including B cells, macrophages, basophils, mast cells 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). BTK inhibition has been shown to be an effective concept to treat B cell malignancies. The covalent BTK inhibitors ibrutinib (Imbruvica®) and acalabrutinib (Calquence®) are approved for the treatment of certain B cell malignancies (Thompson and Burger 2018). BTK inhibition has shown promising efficacy on B cell autoimmunity in preclinical and clinical studies (Tan et al 2013; Whang and Chang 2014; Satterthwaite 2017; Rip et al 2018). In addition, BTK levels were shown to be increased in circulating B cells of a significant percentage of patients with SjS, in association with high serum rheumatoid factor (RF) levels (Corneth et al 2017). Thus BTK inhibition is a potentially promising therapeutic option for the treatment of SjS.

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1.2 Purpose

This study with LOU064 is an adaptive phase 2 study designed to establish safety and efficacy of LOU064 in subjects with moderate to severe SjS to allow further development of the compound for treatment of this disease.

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2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s)	**Endpoint(s) for primary objective(s)**
• Commercially Confidential Information	• Change from baseline in ESSDAI at Week 24
Secondary objective(s)	**Endpoint(s) for secondary objective(s)**
• To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline on patient- and physician-reported outcomes over time	• Change from baseline in ESSPRI, FACIT-F, EQ-5D and PhGA over time
• Commercially Confidential Information	• Change from baseline in ESSPRI at Week 24
• To evaluate the efficacy of LOU064 compared to placebo with respect to change from baseline in ESSDAI over time	• Change from baseline in ESSDAI over time

• To evaluate the safety and tolerability of LOU064	• Safety endpoints will include
	  • Occurrence of treatment emergent adverse events (both serious and non-serious) during the study
	  • Occurrence of treatment emergent abnormal vital signs, laboratory and ECG during the study

• To assess PK parameters of LOU064	• PK parameters AUC, Cmax, Tmax and MRT and others as needed
Exploratory objective(s)	**Endpoint(s) for exploratory objective(s)**

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Objective(s)	Endpoint(s)

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3 Study design

This is an adaptive phase 2 randomized, double-blind, placebo-controlled, multi-center, CCI study to evaluate the safety and efficacy of multiple LOU064 doses in patients with moderate to severe Sjögren's Syndrome (SjS). In this study, moderate to severe SjS is defined as Sjögren's Syndrome according to ACR/EULAR criteria and an ESSDAI of at least 5 (in 8 out of 12 domains - see Section 5.1 and Section 16.4 for details) and an ESSPRI of at least 5. In case study subjects receive certain concomitant therapy for their underlying disease and still meet entry criteria, they will remain on this therapy provided it remains stable until the end of the study (for details, see Section 6.2.1).

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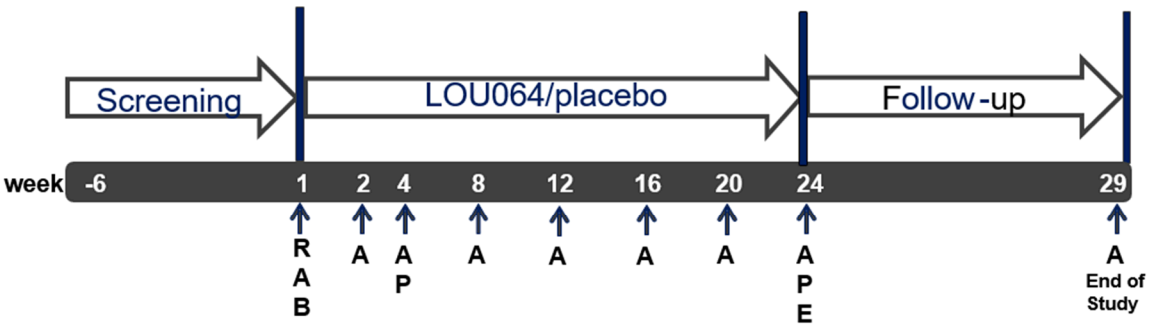
Study Conduct

Each individual study subject will first undergo a screening period of up to 6 weeks, a treatment duration of 24 weeks and a follow-up period of 30 days post last administration of study treatment, before the End of Study visit. The total duration for each subject in the study, including Screening, will be up to 35 weeks (see Figure 3-2).

Figure 3-2 Study flow chart and visit schedule



Key: B: Baseline; **R**: Randomization; **A:** Assessments; **P:** PK sampling; **E**: end of treatment

For the entire duration of the treatment period (24 weeks), subjects will receive twice-daily doses of LOU064 or placebo, regardless of selected dosing regimen, so that the blind is maintained for subjects, investigators and site staff throughout CCI study. For further details, please refer to Section 6.1.3 and Section 6.4.

Safety assessments will include physical examinations, ECGs, vital signs, standard clinical laboratory evaluations (hematology, biochemistry and urinalysis) as well as adverse event and serious adverse event monitoring.

Screening

After signing informed consent, subjects will be assessed for ESSDAI and ESSPRI as well as completing safety and other assessments to evaluate eligibility. For logistical reasons, assessments may be performed on different days, during the 6 week screening period, if deemed appropriate by the Investigator. Subjects that fail screening, may be re-screened for one further occasion. Commercially Confidential Information

Baseline

Eligible subjects will return for the Baseline visit on Day 1. Subjects may reside overnight at the site for logistical reasons, although this would not be considered a hospital admission. Eligibility must be confirmed prior to randomization and required baseline assessments must be completed prior to dosing on Day 1. If preferred by the site for scheduling purposes, some Baseline assessments may be carried out on the evening prior to Day 1.

Treatment

Subjects will be randomized to the respective treatment arms per study part.

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Subjects will return to the site at approximately 4-weekly intervals, with an additional visit at the end of Week 2 (Day 15). At the study visits, subjects will undergo ESSDAI and ESSPRI assessments as well as other scales/questionnaires, safety and various PK, CCI
sample collections as indicated in the Assessment Schedule and described in Section 8. Subjects will be asked to take their morning dose of the study drug at the site on these days. Subjects will return their used drug supply packs for compliance and accountability assessment and will receive a new supply of study drug for the next 4 week treatment period.

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All study visits will be ambulatory, however, for logistical reasons, it may be necessary for subjects to come to the site the evening before their scheduled assessment visit. In these instances, the subjects may stay overnight at the site, but this would not be considered a hospital admission.

Subjects may be contacted by the Investigator/site staff during the study to ensure compliance/monitor safety by telephone or other means, if it is deemed appropriate or necessary by the Investigator.

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Follow up and End of Study visit (EoS)

After the last day of dosing, subjects will enter a 30-day follow-up period without study drug treatment. Subjects will then be asked to return to the site at Week 29 for the End-of-Study visit. At this visit, subjects will undergo final assessments as indicated in the Assessment schedule (Table 8-1) Commercially Confidential Information

Upon completion of this visit, subjects will be discharged from the study.

4 Rationale

4.1 Rationale for study design

The study is blinded for study subjects, investigators/site staff and sponsor staff until final database lock (except where indicated in Section 6.4) to reduce potential bias in the assessment of subjective readouts.

Treatment allocation is done by a stratified randomization procedure to achieve an equal distribution of disease severity among the different treatment groups.

The control group is placebo on top of standard care because there is no approved treatment to be used as active comparator for moderate to severe Sjögren's Syndrome. However, all subjects can continue with their current immunomodulatory therapy, if on a stable dose and as described in Section 6.2.1.

Two different dosing regimens (*qd* vs. *bid*) will be evaluated in CCI the study in line with the known pharmacological features (PK and PD) of LOU064 (as described in Section 4.2 and Investigator's Brochure). Commercially Confidential Information

The study treatment duration is 24 weeks, which is consistent with earlier studies conducted in this condition and is expected to allow a meaningful assessment of the safety and efficacy in SjS.

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4.2 Rationale for dose/regimen and duration of treatment

The highest dose planned for this study (100 mg *bid* or *qd*) has demonstrated a maximal effect for LOU064 based on predicted BTK occupancy in blood (B-cell blockade) and tissues, and inhibition of CD63 up-regulation in basophils (IB). This dose is therefore expected to provide maximum clinical effect in tissue, including lymphatic tissue for SjS. In Phase 1, doses up to 600 mg both as single and multiple doses and 200 mg as twice daily dose had been tested in human volunteers and proven to be safe (Section 5.2 in the IB).

Dose/regimen CCI

CCI the dose CCI (100 mg) is tested in a *qd* and in a *bid* regimen and compared to placebo. Due to the covalent nature of the binding of LOU064 to intracellular BTK, the duration of the treatment effect is dependent on the turn-over rate of the BTK molecule.

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The extent of BTK inhibition required for optimal clinical efficacy still needs to be established. However, it has been hypothesized that 70% inhibition for ~90% of each dosing period at steady state may be appropriate (Herman et al 2018) which would be exceeded clearly by both the *qd*- and *bid* regimen tested in CCI this study. Commercially Confidential Information

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4.3 Rationale for choice of control drug (placebo)

Comparator treatment will be placebo to provide objective evidence of potential AEs and other safety data, as well as clinical efficacy and PD data generated from subjects treated with LOU064 during the 24-week trial. Since there is no approved systemic treatment for SjS, the use of placebo is justified. Current standard-of-care for SjS patients is limited to symptomatic care for the mucosal signs and symptoms (dryness) and steroids and conventional DMARDs are often ineffective. No pharmacologic intervention is effective against the severe, disabling fatigue associated with SjS. Requirements for continuation of concomitant therapy throughout the study are described in Section 6.2.1.

4.4 Purpose and timing of interim analyses/design adaptations

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4.5 Risks and benefits

Study subjects suffering from Sjögren's Syndrome are not considered to be a specific risk population for COVID-19 infections unless caused by immunosuppressive medication. Treatment with LOU064 (remibrutinib) is expected to lead to an immunomodulatory effect with potential therapeutic consequences for the underlying immunological condition. Due to this immunomodulatory effect, a potential risk for the acquisition of infections in general cannot be excluded. This is however not considered to be specific for any viral infection including Coronavirus. It is still unclear whether the susceptibility for any viral infection during treatment with remibrutinib is increased. For established COVID-19 infections, initial reports on patients suffering from hematological malignancies and being chronically treated with a BTK-antagonist have reported relative mild disease courses (Thibaud et al 2020) and BTK-inhibitors are even considered to prevent lung injury in COVID-19 disease (Treon et al 2020). Several clinical studies have recently been initiated to test the effect of registered BTK-inhibitors on Coronavirus infections (NCT04375397, NCT04382586, NCT04380688). The most crucial measure to prevent study subjects from infection with Coronavirus is to decrease any potential exposure to the virus. Subjects with a known or suspected history of an ongoing, chronic or recurrent infectious disease (which includes Coronavirus infections) are excluded from this protocol according to Exclusion criterion #8. Based on these considerations, it is not considered that the COVID-19 pandemic changes the overall risk-benefit assessment for this study.

So far, no SjS patients have been treated with LOU064, and no reports about treatment of SjS patients with other BTK inhibitors have been published. Safety experience with LOU064 in humans is so far limited and primarily based on Phase 1 and 2 clinical studies and safety profiles from other BTK inhibitors. As of 04-Aug-2020, approximately 525 subjects (healthy volunteers and patients suffering from CSU, asthma, SjS or atopic dermatitis (AD), respectively) have been exposed to LOU064 at doses ranging from 0.5 mg to 600 mg or placebo. Administration of LOU064 did not raise any significant safety signal. A summary of AEs and pre-clinical safety data can be found in the IB.

Based on a thorough review of safety information currently available in the literature together with an assessment of safety data obtained from both clinical and preclinical experience with LOU064 as well as safety profiles from other BTK inhibitors, the following potential risks are considered for LOU064 and require close monitoring in the proposed study. When comparing the safety risks between the approved BTKi (e.g., ibrutinib and acalabrutinib) and LOU064, the relevance and importance of the study patient populations must be taken into consideration.

- ***Infections****:* BTK is an important signaling 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 nearly complete absence of immunoglobulins. In adult patients, BTK inhibition primarily interferes with B cell activation but not plasma cell function and is therefore not associated with a marked decrease of immunoglobulins (Hendriks et al 2014; Sun et al 2015; Nutt et al 2015). Administration of ibrutinib and acalabrutinib is associated with a risk of infection in patients suffering from B cell malignancies (Acalabrutinib SmPC 2017; Ibrutinib SmPC 2013). 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.
- ***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 (Acalabrutinib SmPC 2017; Ibrutinib SmPC 2013). Compared to other drugs in the same class, LOU064 demonstrated a higher selectivity for BTK vs. other TEC kinases. Therefore bleeding may be less a safety concern when compared to ibrutinib and acalabrutinb because these may be more caused by inhibiting other tyrosine kinases than BTK. 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 and subjects taking medication that is known to increase the bleeding risk (other than acetylsalicylic acid) must be excluded from the study (see details in Section 5.2).
- ***Myelomodulation***: The role of BTK inhibition in myelomodulation is not fully understood. Treatment emergent grade 3 or 4 cytopenias (neutropenia, thrombocytopenia and anaemia) were reported in patients with hematologic malignancies treated with ibrutinib and acalabrutinb (Acalabrutinib SmPC 2017; Ibrutinib SmPC 2013). Therefore, patients must be closely monitored for signs and symptoms of cytopenia while in the study, and those with a history of hematological disorders or with markedly altered hematologic parameters at baseline will be excluded from the study.

- ***Risk of cardiovascular origin***:

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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 (Ibrutinib SmPC 2013). For acalabrutinib, both atrial fibrillation and atrial flutter of any grade were reported in 3% of patients (Acalabrutinib SmPC 2017). Therefore, ECG monitoring will be implemented in this study. In addition, patients with a known history or current diagnosis of ECG abnormalities indicating a significant safety risk will be excluded from the study.

- ***Drug-drug interactions***:

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Please refer to the current IB (Section 5.1.5) for information on drug-drug interactions of LOU064.

- ***Reproductive toxicity***:

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  For ibrutinib and acalabrutinib, embryofetal toxicity in animals is reported (Acalabrutinib SmPC 2017; Ibrutinib SmPC 2013). Highly effective methods of contraception must be practiced for women of child-bearing potential while taking study treatment and for 7 days after stopping study medication.

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

In summary, SjS patients may benefit from treatment with LOU064 due to the effect on B-cells and autoantibodies. Additionally, this study will help improve the scientific understanding of LOU064 in the management of SjS and offer the potential of developing an innovative drug that could potentially improve the quality of life for SjS patients beyond the conventional treatment modalities currently available to them.

Potential risks are mitigated by compliance with inclusion/exclusion criteria, study procedures, close clinical monitoring and study drug discontinuation rules. As with investigational drugs in general, not all safety risks are known. Patients and investigators participating in this study will be informed should important new safety information become available.

4.5.1 Blood sample volume

A volume smaller than a typical blood donation is planned to be collected over a period of 24 weeks for the treatment period plus the 6 week screening and the 30 days follow-up period 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 (Table 8-1).

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 central laboratory manual.

4.6 Rationale for Public Health Emergency mitigation procedures

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

5 Study Population

The study population will consist of adult male and female Sjögren's Syndrome (SjS) patients with ESSDAI $\geq$ 5 derived from 8 of 12 domains.

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

5.1 Inclusion criteria

Subjects eligible for inclusion in this study have to fulfill all of the following criteria at the time of screening evaluations unless otherwise noted.

1. Signed informed consent must be obtained before any study assessment is performed.
2. Male or female patients aged 18 to 75 years
3. Classification of Sjögren's Syndrome according to the 2016 ACR/EULAR criteria (Shiboski et al 2017).
4. Screening ESSDAI (based on weighted score) ≥ 5 derived from 8 domains (biologic, hematologic, articular, cutaneous, glandular, lymphadenopathy, renal, constitutional). Subjects with involvement of one or more of the remaining 4 domains are eligible but scores of these domains will not contribute to the assessment for eligibility, but will be part of the overall ESSDAI for that subject.
5. Screening ESSPRI ≥ 5
6. Seropositive for anti-Ro/SSA antibodies at or within 3 months prior to screening
7. Unstimulated whole salivary flow rate of > 0 mL/min.
8. Able to communicate well with the Investigator to understand and comply with the requirements of the study.

5.2 Exclusion criteria

Subjects fulfilling any of the following criteria (at the time of screening evaluations unless otherwise noted) are not eligible for inclusion in this study.

1. Sjögren’s Syndrome overlap syndromes where another autoimmune disease constitutes the primary illness, specifically
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2. Commercially Confidential Information

3. Rituximab or other B cell depleting drug within 12 months of Screening. For subjects who received such drug, their B cell count should be within normal range.
4. Current use of prednisone or equivalent > 15mg/d or dose change within 2 weeks prior to baseline.
5. Prior treatment with any of the following within 6 months of baseline
   - CTLA4-Fc Ig (abatacept)
   - Anti-TNF-α mAb
   - Intravenous Ig
   - Plasmapheresis
   - i.v. or oral cyclophosphamide
   - i.v. or oral cyclosporine A
6. Disease-modifying antirheumatic drugs (DMARDs) or kinase inhibitors within 3 months prior to baseline are not allowed

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7. Required regular use of medications known to cause, as a major side effect, dry mouth / eyes, and which have not been on a stable dose for at least 30 days prior to Screening, or any anticipated change in the treatment regimen during the course of the study.
8. HIV, Hepatitis C, Hepatitis B (HBsAg positive). If HBsAg is negative and anti-HBc positive, patient can be included if HBV-DNA is negative and patient is monitored during the study for HBsAg and HBV-DNA.

   Known or suspected history of an ongoing, chronic or recurrent infectious disease including but not limited to opportunistic infections (e.g. tuberculosis, atypical mycobacterioses, listeriosis or aspergillosis).

9. History of live attenuated vaccine within 6 weeks prior to baseline or requirement to receive these vaccinations at any time during study drug treatment
10. Major surgery within 8 weeks prior to screening or surgery planned prior to end of study
11. 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 (12 lead ECG) < 50 bpm
    - Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at pretreatment (screening) or inability to determine the QTcF interval
12. Commercially Confidential Information

13. Significant bleeding risk or coagulation disorders, including but not limited to:

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    b. Requirement for anti-platelet or anticoagulant medication (for example, warfarin, or clopidogrel or Novel Oral Anti-Coagulant - NOAC) other than acetylsalicylic acid (up to 100 mg/d)
    c. History of gastrointestinal, intracerebral or otherwise considered severe bleeding, eg in association with use of Nonsteroidal Anti-Inflammatory Drug (NSAID)
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15. Commercially Confidential Information

16. Commercially Confidential Information
17. Commercially Confidential Information

18. Screening CBC laboratory values as follows:
    - Hemoglobin levels below10 g/dL
    - Total leukocyte count less than 3,000/µL
    - Platelets less than 100,000/µL
    - Neutrophil count ≤ 1,500/ µL
19. Commercially Confidential Information

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6 Treatment

6.1 Study treatment

The investigational drug will be provided by Novartis as appropriately blinded labeled bottles. CCI the bottles will contain capsules with either 50 mg active substance (LOU064) or matching Placebo.

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

6.1.1 Investigational and control drugs

Novartis Global Clinical Supply (GCS) will provide IMP supplies as detailed in the table below (Section 6.1). Commercially Confidential Information
Supplies will be provided in a double-dummy manner.

Table 6-1 Investigational and control drug

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Investigational/Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply type	Sponsor
LOU064 50 mg	Hard Gelatin Capsule	Oral	Double-blind supply	Novartis Pharma AG
LOU064 0 mg (Placebo)	Hard Gelatin Capsule	Oral	Double-blind supply	Novartis Pharma AG

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6.1.2 Additional study treatments

No other treatment beyond investigational drug and control drug are included in this trial.

6.1.3 Treatment arms/group

CCI subjects will be assigned on Day 1 to one of the following 3 treatment arms in a ratio of 1:1:1

- LOU064 100 mg bid
- LOU064 100 mg qd
- Placebo

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6.2 Other treatment(s)

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the subject was enrolled into the study must be recorded on the appropriate Case Report Forms.

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.

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Low-dose steroids (up to maximally 15 mg/day prednisone or equivalent) are allowed and study subjects must be on a stable dose for at least 2 weeks prior to randomization.

Concomitant treatment may include standard of care for dry eye and dry mouth symptoms, such as the use of artificial tears and artificial salvia/salivary stimulants (e.g. cevimeline, pilocarpine) at the discretion of the treating physician. Amount and frequency of use should be recorded. Please refer to Table 6-2 for guidance on suggested treatment time interval prior to assessment of clinical disease outcome measurements. Artificial tears and artificial saliva are to be provided by the study center or personal physician.

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Table 6-2 Treatments against dryness of eyes/mouth

Treatment Type	Time interval prior outcome assessment
Artificial tears or other topical ophthalmic medications	4 hrs
Artificial saliva	4 hrs
Pilocarpine	12 hrs
Cevimeline or other salivary stimulants	24 hrs or 5x half-life whichever is longer

6.2.2 Prohibited medication

Use of treatments displayed in the below table is not allowed in study periods as indicated.

Table 6-3 Prohibited Medication

Medication	Prohibition period	Action to be taken
Use of other investigational drugs	5 half-lives or within 30 days of baseline or until pharmacodynamic effect has disappeared prior to baseline (whichever is longer) until end of study	Discontinue study treatment
Routine use of systemic corticosteroids (>15mg/d prednisone or equivalent)	14 days prior to baseline until end of study	Subject's withdrawal from the study may be required on a case-by-case basis
Rituximab or other B cell depleting drug	Within 12 months prior to screening until end of study	Subject's withdrawal from the study may be required on a case-by-case basis

Medication	Prohibition period	Action to be taken
Other immunosuppressive medication with or without known effect on SjS including but not limited to cyclosporine A, cyclophosphamide, tacrolimus, leflunomide and mycophenolate mofetil or azathioprine, hydroxychloroquine / chloroquine and methotrexate in doses above those given in Section 6.2.1.	Within 6 months prior to baseline until end of study	Subject's withdrawal from the study may be required on a case-by-case basis
Intravenous (i.v.) immunoglobulins or plasmapheresis	Within 6 months prior to baseline until end of study	Subject's withdrawal from the study may be required on a case-by-case basis
Live attenuated vaccine	6 weeks prior to baseline until end of study	Subject's withdrawal from the study may be required on a case-by-case basis
Moderate and strong inhibitors of CYP3A4 (see Section 16.6)	From screening until end of study If LOU064 treatment is interrupted during the study to allow for transient treatment of CYP3A4 inhibitors (e.g. erythromycin) it may be resumed > 48hrs after the intermittent treatment has been stopped	Co-medication with moderate and strong CYP3A4 inhibitor is not allowed and subjects may interrupt LOU064 treatment if respective co-medication is required or cannot be replaced
Drugs which are substrates for efflux transporters P-gp and BCRP and are classified as sensitive substrates or have a narrow therapeutic index (NTI)	From screening until end of study	Co-administration may either be avoided and respective drugs (list to be provided) dosed in a staggered approach (3hrs after LOU064)
Moderate and strong inducers of CYP3A4 (see Section 16.6)	From screening until end of study	Subject's may be withdrawn from the study as the efficacy of LOU064 is compromised by concomitant use of CYP3A4 inhibitors
Any drug known to prolong QTc interval	5 half-lives or until pharmacodynamic effect has disappeared prior to baseline (whichever is longer) until end of study	Subject's withdrawal from the study may be required on a case-by-case basis
Anti-platelet or anticoagulant medication (for example, warfarin/VKAs, or clopidogrel or Novel Oral Anti-Coagulant - NOAC) other than acetylsalicylic acid (up to 100 mg/d)	From screening until end of study	Subject's withdrawal from the study may be required on a case-by-case basis

Medication	Prohibition period	Action to be taken
Newly installed DMARDs or other immune suppressive agents or changes in an existing DMARD regimen (hydroxychloroquine / chloroquine or methotrexate)	From 3 months prior to baseline until end of study	Subject's withdrawal from the study may be required on a case-by-case basis

6.2.3 Rescue medication

There is no established, approved immunosuppressive treatment for SjS. Patients may receive nonsteroidal anti-inflammatory drugs (NSAIDs), paracetamol, or symptomatic care at the discretion of the treating physician as outlined in Section 6.2.1. Each concomitant drug must be individually assessed against all exclusion criteria and prohibited medication (Table 6-3). When in doubt the investigator should contact the Novartis medical monitor before randomizing a patient or allowing a new medication to be started. If any of the medications listed in Table 6-3 is deemed a necessary rescue therapy, the investigator must follow the actions to be taken outlined in this table. Any potential rescue medication is to be provided by the study center or personal physician. Patients should be encouraged to come for the end-of-study visit even when discontinued permanently from study medication.

There is no specific rescue medication for LOU064. LOU064 is eliminated within a few hours from the body and no specific antidote is necessary. Pharmacodynamic activity of LOU064 may take longer as the elimination time because of the covalent binding to the BTK-molecule. However, any direct immunosuppressive activity is not expected to take more than a few days.

6.2.4 Restriction for study subjects

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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 SOM.

6.3.2 Treatment assignment, randomization

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. Randomisation will occur once eligibility is confirmed and prior to dosing; this will occur on Day 1 as per Assessment Schedule (Table 8-1), but may be performed on Day -1, if preferred by the site for logistical reasons.

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 Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

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Follow the details outlined in the SOM regarding the process and timing of treatment assignment and randomization of subjects.

6.4 Treatment blinding

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is subject and investigator-blinded. Subjects and investigators will remain blinded to the study treatment throughout the study, except where indicated below in Table 6-4.

The identity of the treatments will be concealed by the use of study drug that are all identical in packaging, labeling, schedule of administration, appearance, taste and odor. To keep the dosing schedule blinded, there will be a morning and an evening dose for all subjects.

The following unblinded sponsor roles are required for this study: Unblinded sample analyst(s) (PK). 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.

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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.

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

Following final database lock all roles may be considered unblinded. See the Table 6-4 for an overview of the blinding/unblinding plan.

Table 6-4 CCI **Blinding levels**

Role	Time or Event			
	Randomization list generated	**Treatment allocation & dosing**	**Safety event (single subject unblinded)**	
Subjects/Patients	B	B	UI	CCI
Site staff	B	B	UI	
Drug Supply and Randomization Office	UI	UI	UI	
Unblinded sponsor staff (see text for details)	B	B	UI	
Statistician/statistical programmer/data analysts	B	B	UI	
Independent committees used for assessing interim results	B	B	UI	
All other sponsor staff not identified above	B	B	UI	

B Remains blinded

UI Allowed to be unblinded on individual patient level

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6.5 Dose escalation and dose modification

Investigational or other study treatment dose adjustments are not permitted. Study subjects are treated according to their allocation in the randomization process.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

The investigator and site staff 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. Compliance will be assessed by the investigator and/or study personnel at each visit using information provided by the subject for hard gelatin capsule CCI counts at visits where new supply is provided to the subject. This information - including any missed doses - must be captured in the source document at each visit.

All study treatment dispensed and returned must be recorded in the Drug Accountability Log.

6.6.2 Recommended treatment of adverse events

At present there is insufficient information to provide specific recommendations regarding treatment of adverse events (AEs).

Medication used to treat adverse events (AEs) must be recorded on the appropriate CRF.

6.6.3 Emergency breaking of assigned treatment code

Breaking the randomization code will only be undertaken when it is required for subject's safety. Blinding codes may also be broken after a participant discontinues study treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. 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 monitor for the site and the study team that the code has been broken.

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

- protocol number
- subject number

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

After emergency unblinding the subject will not receive further study treatment and will be withdrawn from the study.

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 6.1.1.

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

7 Informed consent procedures

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

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

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

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

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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 SOM 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.

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

Table 8-1 Assessment Schedule

Period	Screening	Treatment																		
Visit Name	Screening	Baseline	Week 2	Week 4							Week 8	Week 12	Week 16	Week 20	Week 24					
Days	-42	1	15	29							57	85	113	141	169					
Time (post-dose)	-	-	-	pre-dose	0h	0.5h	1h	2h	3h	4h	-	-	-	-	pre-dose	0h	0.5h	1h	2h	3h
Informed consent	X																			
CCI	X																			
Inclusion / Exclusion criteria	X																			
Demography	X																			
Medical history/current medical conditions	X																			
Prior therapy for Sjögren's Syndrome	X																			
Contact IRT		S																		
Drug dispensation at site		S						S			S	S	S	S						
Dose administration		X			X						X	X	X	X		X				
HIV screen	X																			
Hepatitis screen / monitoring	X			X[1]							X[1]	X[1]	X[1]	X[1]	X[1]					
CCI	S																			
Physical Examination	S	S	S	S							S	S	S	S	S					
Vital Signs	X	X	X	X							X	X	X	X	X					

Period	Screening	Treatment																	
Visit Name	Screening	Baseline	Week 2	Week 4							Week 8	Week 12	Week 16	Week 20	Week 24				
Days	-42	1	15	29							57	85	113	141	169				
Time (post-dose)	-	-	-	pre-dose	0h	0.5h	1h	2h	3h	4h	-	-	-	-	pre-dose	0h	0.5h	1h	2h	3h
Body Temperature	X	X		X								X			X					
Body Height	X																			
Body Weight [13]	X																			
ESSDAI	X	X	X				X[12]				X	X	X	X				X[12]		
ESSPRI	X	X	X				X[12]				X	X	X	X				X[12]		
Anti-Ro/SSA	X	X					X[12]					X						X[12]		
PhGA - VAS		X	X				X[12]				X	X	X	X				X[12]		
FACIT-Fatigue		X	X				X[12]				X	X	X	X				X[12]		
EQ5D		X	X				X[12]				X	X	X	X				X[12]		
Hematology	X	X	X	X							X	X	X	X	X					
Clinical Chemistry	X	X	X	X							X	X	X	X	X					
Coagulation Panel	X	X	X	X							X	X	X	X	X					
Urinalysis	X	X	X	X							X	X	X	X	X					
PK blood collection				X		X	X	X	X	X					X		X	X	X	X
Electrocardiogram (ECG)	X	X[2]	X	X[2]			X[2]				X	X	X	X	X[2]			X[2]		
CCI	X[4]	X	X				X[12]				X	X	X	X				X[5, 12]		
CCI	X	X					X[12]					X						X[12]		
Salivary flow rate (unstimulated)	X																			
CCI		X										X						X[12]		
CCI		X																		

Period	Screening	Treatment																	
Visit Name	Screening	Baseline	Week 2	Week 4							Week 8	Week 12	Week 16	Week 20	Week 24				
Days	-42	1	15	29							57	85	113	141	169				
Time (post-dose)	-	-	-	pre-dose	0h	0.5h	1h	2h	3h	4h	-	-	-	-	pre-dose	0h	0.5h	1h	2h	3h
CCI		X		X								X[8]			X					
CCI		X										X[8]								
CCI		X		X								X[8]			X					
CCI		X		X								X[8]			X					
CCI		X		X								X[8]			X					
CCI		X																		
Pregnancy CCI	X	X	X	X							X	X	X	X	X					
Study completion information																				
Concomitant medications	X																			
Adverse Events	X																			

Period	Treatment	Follow Up
Visit Name	Week 24	Week 29/EOS[15]
Days	169	199
Time (post-dose)	4h	-
Informed consent		
Commercially Confidential Information		
Inclusion / Exclusion criteria		
Demography		
Medical history/current medical conditions		
Prior therapy for Sjögren's Syndrome		
Contact IRT		
Drug dispensation		
Dose administration at site		
HIV screen		
Hepatitis screen / monitoring		
Commercially Confidential Information		
Physical Examination		S
Vital Signs		X
Body Temperature		
Body Height		
Body Weight		
ESSDAI		X
ESSPRI		X
Anti-Ro/SSA		
PhGA - VAS		X
FACIT-Fatigue		X
EQ5D		X
Hematology		X
Clinical Chemistry		X

Period	Treatment	Follow Up
Visit Name	Week 24	Week 29/EOS[15]
Days	169	199
Time (post-dose)	4h	-
Coagulation Panel		X
Urinalysis		X
PK blood collection	X	
Electrocardiogram (ECG)		X
Commercially Confidential Information		
Commercially Confidential Information		X
Salivary flow rate (unstimulated)		
Commercially Confidential Information		
Commercially Confidential Information	X	
Commercially Confidential Information		
Commercially Confidential Information		
Commercially Confidential Information		
Commercially Confidential Information		
Commercially Confidential Information		
Commercially Confidential Information		
Pregnancy Commercially Confidential Information		X
Study completion information		X
Concomitant medications	X	
Adverse Events	X	

X Assessment to be recorded in the clinical database or received electronically from a vendor
S Assessment to be recorded in the source documentation only
1 Hepatitis B monitoring only for subjects who were HBsAg negative and anti-HBcAb positive with a negative HBV DNA test at Screening.
2
3
4 Commercially Confidential Information
5
6 SjS symptom section is to be completed weekly and dosing compliance section daily. SjS symptom section only until EOS visit.
7 at selected sites only
8 to be taken pre-dose
9 Commercially Confidential Information
10 Serum pregnancy test will be done at Screening and EOS. For remaining visits urine pregnancy test will be performed.
11 Commercially Confidential Information
12 Suggested time point but assessment can be done at any time during the visit
13 Note that monitoring of weight loss is part of the constitutional domain of ESSDAI. While body weight is only captured in the CRF for screening, measurements have to be done if required for the assessment of ESSDAI
14 Commercially Confidential Information
15 Mandatory to all participants, including those who have discontinued the study prematurely.

8.1 Screening

It is permissible to re-screen a subject if she/he fails the initial screening; however, each case must be discussed and agreed with the Sponsor on a case-by-case basis. Patients can be re-screened only once and no study-related re-screening procedure should be performed prior to written re-consent by the patient.

- Tests for HIV, Hepatitis B and HCV do not need to be repeated if they satisfied eligibility criteria in the initial screening, and have been conducted within 12 weeks prior to planned date of randomization.
- If tested positive in screening anti-Ro/SSA, results do not need to be repeated in re-screening.

In the case where a safety laboratory or ECG 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.

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

8.1.1 Eligibility screening

Subjects will be screened for HIV, Hepatitis C and for Hepatitis B surface antigen (HBsAg) and Hepatitis B core antibody (anti-HBcAb). HBsAg negative and anti-HBcAb positive subjects with a negative HBV DNA test are eligible for randomization but will be monitored every 4 weeks throughout the study treatment phase for HBsAg and HBV DNA. Any subject testing positive for HBsAg or HBV DNA during this monitoring process will need to be discontinued from the study.

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Positive anti-Ro/SSA results obtained as part of routine medical care and within 3 months prior to screening can be used to satisfy inclusion criterion, and do not need to be repeated at screening.

Additional information and guidance are provided in the SOM.

8.1.2 Information to be collected on screening failures

Subjects who sign an informed consent form and are subsequently found to be ineligible prior to Day 1, will be considered a screen failure. The reason for screen failure will be recorded on the appropriate Case Report Form. In addition, only the CRFs related to the following assessments should be completed: informed consent, demography, and inclusion/exclusion criteria. The CRF for adverse events (AEs) should be completed for any Serious Adverse Events (SAEs) that occurred during the screening period. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data.

If the subject fails to be randomized, the IRT should be notified within 2 days of the screen fail that the subject was not randomized. Subjects who are randomized and fail to start treatment, e.g. subjects randomized in error, will be considered as mis-randomized. The reason for mis-randomization will be recorded on the appropriate Case Report Form.

8.2 Subject demographics/other baseline characteristics

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

Demographic and baseline characteristic data to be collected on all subjects include: age, sex, race, ethnicity, source of patient referral, relevant medical history/current medical condition present before signing informed consent where possible, diagnoses and not symptoms will be recorded. Prior therapy for Sjögren's Syndrome will also be recorded.

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

8.3 Efficacy

Clinical efficacy measurements related to primary and secondary objectives are outlined below.

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

8.3.1 EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI)

ESSDAI (Section 16.4) is a validated disease outcome measure for Sjögren's Syndrome that will be applied to the study subjects. The instrument contains 12 organ-specific domains contributing to disease activity. For each domain, features of disease activity are scored in 3 or 4 levels according to their severity. These scores are then summed across the 12 domains in a weighted manner to provide the total score. The domains (weights) are as follows: constitutional (3), lymphadenopathy (4), glandular (2), articular (2), cutaneous (3), pulmonary (5), renal (5), muscular (6), PNS (5), CNS (5), hematological (2), and biological (1). The maximum possible score is 123.

To calculate ESSDAI, all 12 organ domains must be individually assessed at every scheduled timepoint (from screening visit till end of study). Domain assessments will be entered into a tablet (provided by a central vendor) and ESSDAI score will be calculated by the software. At screening, the ESSDAI subscore from 8 pre-selected domains listed in the inclusion criterion #7, will be calculated to determine patient's eligibility.

For assessments not listed in the protocol as mandatory tests but which may be needed to estimate ESSDAI, including radiography, high resolution computer tomography (HRCT), lung function test (DLCO, FVC), estimated glomerular filtration rate (eGFR), electromyography (EMG), muscle (or any other) biopsy, it is at the investigator's discretion to have these assessed based on the signs and symptoms of the patient so to provide correct ESSDAI readout.

8.3.2 Physician Global Assessment Scale (PhGA)

The physician's global assessment scale is used for the Investigator to rate the disease activity of their patient using 100 mm VAS ranging from "no disease activity" (0) to "maximal disease activity" (100).

To enhance objectivity, the physician must not be aware of the specific patient's patient reported outcome assessments, when performing his own assessment on that patient. Therefore this assessment must be done prior to viewing the patient's reported outcomes.

8.3.3 EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI)

ESSPRI is an established disease outcome measure for Sjögren's Syndrome (Seror et al 2011). It consists of three of domains of dryness, pain and fatigue. The subject can assess severity of symptoms they experience on a single 0-10 numerical scale for each of the three domains. The ESSPRI score is defined as mean of scores from the three scales: (dryness + pain + fatigue) /3. ESSPRI will be applied to the study subjects at screening, baseline and during study treatment as per study assessment schedule (Table 8-1).

8.3.4 FACIT-Fatigue

The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-F v4) is a short, 13-item, easy-to-administer tool that measures an individual's level of fatigue during their usual daily activities over the past week. The level of fatigue is measured on a 5-point Likert scale (0 = not at all, 1 = a little bit, 2 = somewhat, 3 = quite a bit, 4 = very much) Webster et al 2003.

8.3.5 EQ5D

EQ-5D is a standardized instrument which measures the health-related quality of life. The EQ-5D consists of a descriptive system and the EQ VAS scale.

The descriptive system comprises five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. This can be used as a quantitative measure of health outcome that reflects the patient's own judgement. The scores on these five dimensions can be presented as a health profile or can be converted to a single summary index number (utility) reflecting preferability compared to other health profiles.

The EQ VAS records the patient's self-rated health on a vertical visual analogue scale with 0 representing 'Worst imaginable Health State' and 100 'Best imaginable Health State'.

8.3.6 Appropriateness of efficacy assessments

Efficacy measures in this study are primarily based on ESSDAI (EULAR SS Disease Activity Index) measuring organ-specific disease criteria, and on ESSPRI (European League Against Rheumatism [EULAR] Sjoegren Syndrome [SS] Patient Reported Index) measuring the patient's subjective disease impact. Both instruments are widely accepted and validated, gold-standard measures of systemic and symptomatic manifestations of SjS, respectively.

ESSDAI is a systemic disease activity index that classifies disease activity in 3-4 levels, over each of 12 differentially weighted domains (biologic, hematologic, articular, glandular, cutaneous, constitutional, lymphadenopathy, renal, pulmonary, PNS, CNS and muscular). A composite weighted score provides an accurate assessment of disease activity, with a good sensitivity to change, as validated in multiple cohort studies (Seror et al 2015). The ESSPRI tool, on the other hand, is a patient reported composite score of symptoms of dryness, limb pain and fatigue evaluated on 0-10 visual analog scale, during the preceding 2 weeks (Seror et al 2011). Patient reported scores have poor sensitivity to change in disease activity, but among available tools, ESSPRI has been reported to have significantly better sensitivity. A recent prospective study reported poor correlation between systemic and patient scores, suggesting that the two indices evaluate complementary components of disease activity, therefore underscoring the importance of evaluation of both parameters to arrive at an accurate assessment of disease activity and change thereof (Seror et al 2015).

8.4 Safety

Safety assessments are specified below with the assessment schedule (Table 8-1) detailing when each assessment is to be performed.

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

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

Table 8-2 Assessments and Specifications

Assessment	Specification
Physical	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/or pelvic exams may be performed. The investigator should ask the patient for and pay attention to presence of signs and symptoms of infection. 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 blood pressure (BP) and pulse measurements. After the subject has been sitting for five minutes, with back supported and both feet placed on the floor, systolic and diastolic blood pressure will be measured using an automated validated device, with an appropriately sized cuff. Clinically notable vital signs are defined in Section 16.1.
Height and weight	Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.
Body Temperature	Measured as per local default e.g. oral or ear/tympanic measurement.

The methods for each assessment and data recording details are specified in the SOM.

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

8.4.1 Laboratory evaluations

A central laboratory will be used for analysis of all safety specimens collected. Details on the collection, shipment of samples and reporting of results by the central laboratory are provided to investigators in the central laboratory manual.

All abnormal lab results must be evaluated for criteria defining an adverse event but only reported as such if the criteria are met (please refer to Section 10.1.1). For those lab adverse events, repeated evaluations are mandatory until normalization of the result(s) or until the result is no longer considered to be clinically significant. Clinically notable laboratory findings are defined in Section 16.1.

Table 8-3 Laboratory Evaluations

Test Category	Test Name
Hematology	Hemoglobin, Hematocrit, Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC), Mean Corpuscular Volume (MCV), Red Blood Cells (RBC), White Blood Cells (WBC) plus differential count (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands), Platelets
Chemistry	Sodium, Potassium, Bicarbonate, Creatinine, Urea, Uric Acid, Chloride, Albumin, Calcium, Alkaline Phosphatase, total Bilirubin (if elevated above 1.5 times, direct and indirect Bilirubin will be differentiated), LDH, GGT, AST, ALT, Amylase, Lipase, CK, glucose, Total Cholesterol, Triglycerides; total Protein, Immunoglobulins quantitative (IgG, IgA, IgM, IgE); C-reactive Protein (CRP). Special clinical laboratory evaluations serum markers of B cell hyperactivity including but not limited to β2-microglobulin, free immunoglobulin light chains and complement (C3, C4, CH50).
Urinalysis	Urinalysis: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/hemoglobin. If positive for protein, nitrite, leucocytes and/or blood, sample will undergo microscopic analysis of WBC, RBC and casts.
Coagulation	Prothrombin time (PT), International normalized ratio [INR]), Partial thromboplastin time (PTT), Activated partial thromboplastin time (APTT)
Serology	Hepatitis serology: hepatitis B surface antigen (HBsAg), hepatitis B core antibody (anti-HBc), HBV-DNA if applicable; hepatitis C virus antibody (HCVAb); HCV-RNA if applicable (see Section 8.1.1) Human immunodeficiency virus antibody (HIV Ab)
Hepatitis monitoring	HBsAg, HBV-DNA
Pregnancy Test	Serum / Urine pregnancy test (see Section 8.4.3)

8.4.2 Electrocardiogram (ECG)

Full details of all procedures relating to the ECG collection and reporting are contained in the technical manual provided by the core laboratory.

Standard 12-lead ECGs must be recorded after 10 minutes rest in the supine position according to the ECG investigator manual. See Section 1.2 of the SOM for recommendation on the ordering of assessments. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

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

- Day 1: before administration of the first dose of study medication
- Week 4 and Week 24: before administration of study medication and 1h after administration of the study medication (study medication will be taken at the study site; ECG recording will be accompanied by taking samples for PK analysis (see Section 8.5.3)).

Single 12-lead ECGs will be recorded at Screening, Week 2, Week 8, Week 12, Week 16, Week 20 and EOS.

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

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

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

8.4.3 Pregnancy Commercially Confidential Information

All pre-menopausal women who are not surgically sterile will have pregnancy testing. Serum pregnancy test will be done at Screening and EOS and for remaining visits urine pregnancy test can be performed. Additional pregnancy testing might be performed if requested by local requirements. A positive urine test requires immediate interruption of study drug and needs to be confirmed with a serum test. If positive, the subject must be discontinued from the study treatment. Highly effective method of birth control must be used for women of child-bearing potential (see exclusion criteria definitions, Section 5.2).

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

Commercially Confidential Information

8.4.4 Appropriateness of safety measurements

The safety assessments selected are standard for this indication/subject population.

8.5 Additional assessments

Commercially Confidential Information

Commercially Confidential Information

Commercially Confidential Information

8.5.2 Other Assessments

Commercially Confidential Information

Commercially Confidential Information

8.5.3 Pharmacokinetics

PK samples will be collected at the visits and time points defined in the assessment schedule (Table 8-1). Follow instructions outlined in the laboratory manual regarding sample collection, numbering, processing and shipment.

Commercially Confidential Information

PK samples (blood) will be obtained in all subjects and at all dose levels. They will be evaluated in all subjects, except the placebo group.

Commercially Confidential Information

Concentrations will be expressed in mass per volume units (ng/mL) and will refer to the free base.

Commercially Confidential Information

For standard PK abbreviations and definitions see the list provided at the beginning of this protocol. The following PK parameters will be determined from the blood concentration time data using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.4 or higher): Cmax, Tmax, AUC.

Commercially Confidential Information

The PK of LOU064 will be characterized at Week 4 and Week 24 across all treatment arms.

Commercially Confidential Information

Proposed sampling schedule and rationale is given in Table 8-4. Detailed PK sampling schedule is given in Table 8-1.

Table 8-4 PK sampling schedule

Time	Sample	Comment
Day 1	no PK assessment	Commercially Confidential Information
Week 4	Pre-dose, 0.5h/1h/2h/3h/4h/post-dose	Early Steady-state "full" PK profile baseline PK assessment, which allows synchronization of parallel cardiovascular investigations, which may be driven by initial high blood exposures (Cmax) at the primary endpoint/interim analysis
Week 24 (last day, last dose	Pre-dose, 0.5h/1h/2h/3h/4h/post-dose	Assess steady-state + intra-subject variability + putative time dependent effects on PK, CCI

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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's decision
- Pregnancy

- Use of prohibited treatment as per recommendations in the prohibited treatment section (Section 6.2.2)
- Any situation in which study participation might result in a safety risk to the subject, e.g. required surgical interventions associated with a risk of clinically significant bleeding
- Following emergency unblinding
- Emergence of the following AEs:
  - AEs including severe or serious 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)
  - Platelets < 75 000/mm^3
  - Any other laboratory abnormalities that in the judgment of the investigator, taking into consideration the subject's overall status, prevents the subject from continuing participation in the study
  - Patient received a live virus vaccination during the study

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

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 9.1.2). **Where possible, they should return for the assessments** indicated in the assessment schedule (Table 8-1). If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the subject/pre-designated contact as specified in the lost to follow-up section (Section 9.1.3). This contact should preferably be done according to the study visit schedule (Table 8-1).

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 (see Section 6.6.3).

9.1.1.1 Replacement policy

Subjects will not be replaced on study.

Commercially Confidential Information

9.1.2 Withdrawal of informed consent

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

- Does not want to participate in the study anymore, and
- Does not want any further visits or assessments, and
- Does not want any further study related contacts

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.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. However, subjects still retain the right to object to the further use of personal data. 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 discontinuation. A final evaluation at the time of the subject's study discontinuation should be made as detailed in the assessment table (Table 8-1).

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

9.1.3 Lost to follow-up

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

9.1.4 Study stopping rules

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

- If an unexpected frequency (in different subjects) of similar study-treatment related SAEs are reported
- Two or more other clinically significant, severe events (in different subjects) that preclude to continue dosing and which are considered study drug related, including but not limited to
    - development of recurrent/opportunistic infection,
    - spontaneous bleeding events (except minor bleeding like self-limiting epistaxis),
    - drug related renal or liver events meeting the event criteria as detailed in Section 10.2.1 and Section 10.2.2,
    - neutropenia <1,000/microl, anemia <8g/dl, thrombocytopenia <75.000/microl,
    - Commercially Confidential Information
- 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.

The study may resume following the safety review, if the Investigator and Sponsor agree it is safe to proceed.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time for any reason. This may include reasons related to the benefit/risk assessment of participating in the study, futility outcome CCI , practical reasons (including slow enrollment), or for regulatory or medical reasons. In making the decision to terminate, Novartis will always consider the welfare and safety of subjects. 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 the date when the last subject finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision. All randomized and/or treated subjects should have a safety follow-up call conducted 30 days after last administration of study treatment (in case of early study termination and EOS visit not performed). 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 in 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 (such as e.g. Patient-reported Outcomes).

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

1. The severity grade
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease 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 i.e., its recovery status or whether it was fatal

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

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

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

Once an 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's 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 (please refer to the ICH-E2D Guidelines).

All new 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.

10.1.3 SAE reporting

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

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

1. Screen Failures (eg a subject who is screened but is not treated or randomized): SAEs occurring after the subject has provided informed consent until the time the subject is deemed a Screen Failure must be reported to Novartis/sponsor within 24-hours of learning of its occurrence.
2. Randomized OR Treated Subjects: SAEs collected between time subject signs ICF until 30 days after the subject has discontinued or stopped study treatment

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

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

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

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

10.1.4 Pregnancy reporting

If a female trial participant becomes pregnant, the study treatment must be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. 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 Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported. Information will be collected at three time points after the estimated date of delivery and for a period of 12 months.

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 CRF irrespective of whether or not associated with an AE/SAE and reported to 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 Dosing CRF (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 Section 10.1.1, Section 10.1.2 and Section 10.1.3.

10.2 Additional Safety Monitoring

10.2.1 Liver safety monitoring

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

Please also refer to Section 16.2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-2 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 Section 16.2.

- Repeat liver chemistry tests (ALT, AST, Total Bilirubin (TBL), PT/INR, ALP and GGT) to confirm elevation. These liver chemistry repeats will be performed using the central laboratory. If results will not be available from the central laboratory, then the repeats can also be performed at a local laboratory to monitor the safety of the subject. If a liver event is subsequently reported, any local liver chemistry tests previously conducted that are associated with this event should have results recorded on the appropriate eCRF.
- If the initial elevation is confirmed, close observation of the subject will be initiated
- Discontinuation of the investigational drug (refer to Section 9.1.1), 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.

10.2.2 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the course of the study period:

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

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

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events as defined in Table 16-3 in Section 16.3 should be monitored and followed up by the investigator or designated trial staff as summarized in Table 16-4.

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 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 World Health Organization (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.

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

Subjects will fill in their electronic/paper diary data at home. The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis.

Randomization codes and data about all study treatment (s) dispensed to the subject and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor who will also manage the database. The data will be sent electronically to Novartis 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/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. 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 CRFs 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 CRFs 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

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The final analyses will be conducted after all subjects have finished the study. Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

Summary statistics for continuous variables will include N, mean, standard deviation, minimum, lower quartile, median, upper quartile, maximum. Summary statistics for discrete variables will be presented as the number and percent of patients in each category.

If not otherwise specified, p-values will be presented as two-sided p-values and two-sided confidence intervals will be displayed.

The baseline value is defined as the last assessment prior to first dose administration. In case the scheduled baseline assessment value is missing, the screening value if available will be used instead.

12.1 Analysis sets

CCI the following analysis sets will be used in this trial:

Full Analysis Set (FAS): comprises all subjects to whom study treatment has been assigned. Following the intent-to-treat principle, subjects will be analyzed according to the treatment assigned to at randomization and the strata they actually belong to in case of misallocation of strata during the randomization process.

Mis-randomized subjects are defined as those subjects who were mistakenly randomized into the IRT prior to the site confirming all eligibility criteria had been met and to whom no study medication was given. Mis-randomized subjects are treated as screen failures.

Unless otherwise specified, mis-randomized subjects (randomized by mistake in IRT) will be excluded from the FAS. The FAS will be used for summaries of subject disposition and analysis sets, and for all efficacy variables, unless otherwise stated.

Safety Set (SS): includes all subjects who received at least one dose of study medication. Subject will be analyzed according to treatment received and the strata they actually belong to in case of misallocation of strata during the randomization process. The safety set will be used in the analysis of all safety variables.

12.2 Subject demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for Safety Set and Full Analysis Set.

The following demographic variables and baseline disease characteristics will be summarized by treatment group:

- Gender, age, race, ethnicity, weight, height, BMI and disease duration
- ESSDAI and number of subjects per ESSDAI stratum, ESSPRI, PhGA, EQ-5D, unstimulated salivary flow, Commercially Confidential Information use of DMARDs (split by type), and percentage of subjects with history of prior biologics treatment use.

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

12.3 Treatments

Analyses of study treatment will be based on the Safety Set.

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

Prior and concomitant medication

Prior medications are defined as treatments taken and stopped prior to first dose of study treatment. Any medication given at least once between the day of first dose of randomized study treatment and the date of the last study visit will be a concomitant medication, including those which were started pre-baseline and continued into the period where study treatment is administered.

Prior and concomitant medications will be summarized in separate tables. Medications will be presented in alphabetical order, by Anatomical Therapeutic Classification (ATC) codes and grouped by anatomical main group. Tables will show the overall number and percentage of patients receiving at least one treatment of a particular ATC code and at least one treatment in a particular anatomical main group.

The number and percentage of subjects receiving systemic therapies for SjS as prior and concomitant background medication will be presented separately by preferred term.

12.4 Analysis of the primary endpoint(s)

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12.4.1 Definition of primary endpoint(s)

The following estimand framework is adopted for the primary analysis.

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- Variable of interest: Change from baseline in ESSDAI total score after 24 weeks of study drug administration. This will be defined as the Week 24 visit ESSDAI value minus the baseline ESSDAI value with negative values indicating improvement in disease status
- Treatment of interest: The randomized treatment (LOU064 or placebo) on top of allowed concomitant medication
- Intercurrent events: Regardless whether early termination from the study, interruption of study treatment, or intensified concomitant treatment (local and systemic) has occurred
- Summary measure: Difference in mean change from baseline in ESSDAI total score at Week 24 visit between placebo and LOU064

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12.4.2 Statistical model, hypothesis, and method of analysis

12.4.2.1 Repeated measures analysis

Commercially Confidential Information a repeated measures model will be fitted to the changes from baseline in ESSDAI up to Week 24 visit. The change from baseline in ESSDAI is assumed to be normally distributed.

A mixed effect model for repeated measurements (MMRM) will be fitted to the changes from baseline in ESSDAI for all time points until Week 24 visit including the following fixed factors

- treatment group
- visit
- treatment group by visit interaction
- actual stratification factor using baseline ESSDAI score <10 or ≥10
- geographic region

and baseline ESSDAI as a continuous covariate. An unstructured variance-covariance matrix will be fitted to model the dependency between repeated observations. Graphical checks on the model assumptions of normality of the data will be provided.

The mean treatment effects will be estimated at Week 24 visit.

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12.4.3 Handling of missing values/censoring/discontinuations

Missing baseline value

If the baseline ESSDAI total score is missing, the screening value (if available) will be used to impute the baseline value. If neither the ESSDAI total score at baseline nor the ESSDAI total score at screening can be calculated due to missing domain scores, then the baseline ESSDAI total score is calculated using combination of baseline visit domain scores (where those are not missing) and screening domain scores (where the baseline analogs are missing) if they are available, and otherwise the baseline ESSDAI total score is set to missing.

Other missing data

For post-dose time points with missing data in one of the domains of the ESSDAI, the ESSDAI total score will be set to missing.

The MMRM utilized for the primary analysis implicitly imputes missing data under a missing at random assumption. The reasonableness of this assumption will be checked during the blinded review of the data and, if necessary, further methods may be applied.

12.4.4 Sensitivity and Supportive analyses

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12.5 Analysis of secondary endpoints

For the analysis of the secondary endpoints of ESSDAI, ESSPRI, FACIT-F, EQ-5D and PhGA, the same population and a similar estimand framework as for the primary endpoint (Section 12.4.1) will be adopted. Descriptive summary statistics will include all subjects in the Full Analysis Set.

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

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Efficacy analysis CCI

The change from baseline over time for secondary efficacy endpoints (ESSDAI, ESSPRI, FACIT-F, EQ-5D and PhGA) will be presented by treatment group and visit. Summary statistics will be presented for original results and mean change from baseline, together with adjusted mean change from baseline and 95% confidence interval estimated from CCI MMRM Commercially Confidential Information . Differences in change from baseline between LOU064 treatment groups and placebo, along with associated 95% confidence intervals, will be presented by visit. Commercially Confidential Information

12.5.2 Safety endpoints

All safety endpoints (i.e. AEs, laboratory data, vital signs, and ECG) will be summarized by treatment for all subjects in the safety set.

Adverse events

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

The number (and percentage) of subjects with treatment emergent AEs (events started after the first dose of study 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 AEs, deaths, serious adverse events, and other significant AEs leading to discontinuation. A subject with multiple AEs within a primary system organ class is only counted once towards the total of the primary system organ class.

Laboratory data

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

Vital signs

Analysis of the vital sign measurements using summary statistics for the change from baseline for each post-baseline visit will be performed. These descriptive summaries will be presented by vital sign, treatment group and visit/time. Change from baseline will only be summarized for subjects with both baseline and post-baseline values. Shifts with respect to normal ranges and number and percentage of notable abnormalities will also be summarized.

ECG

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

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

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12.5.3 Pharmacokinetics

Descriptive summary statistics for PK concentration data will be provided by treatment and visit/sampling time point, Commercially Confidential Information . Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum.

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Descriptive summary statistics for pharmacokinetic parameters will be provided by treatment. Summary statistics include mean (arithmetic and geometric), SD, and CV (arithmetic and geometric), median, minimum, and maximum. An exception to this is Tmax where median, minimum, and maximum will be presented.

Table 12-1 Non-compartmental pharmacokinetic parameters

AUClast and AUC0-4h	The AUC from time zero to the last measurable concentration sampling time (tlast) (ng x h/mL). As the proposed sampling time is up to 4 hr AUClast will be equivalent to AUC0-4 hr if blood concentrations can be measured up to 4 hr
AUCtau	The AUC calculated to the end of a dosing interval (tau) at steady-state (ng x h/mL).
Cmax	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (ng/mL
Tmax	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (h)
MRT	Mean residence time of the analyte in the central compartment (h)
T1/2	The elimination half-life

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

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12.6 Analysis of exploratory endpoints

Analyses of exploratory endpoints will be performed using Full Analysis Set.

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12.7 Interim analyses

12.7.1 Timing of analyses

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12.7.2 Purpose of analyses

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12.7.3 Maintenance of study integrity

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12.7.4 Decision criteria for interim analyses

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12.8 Sample size calculation

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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 International Council for Harmonisation (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 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 investigators 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.

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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 should be done within 5 days after the first assessment based on investigator's clinical judgement. Discontinuation of the study treatment should be considered if the abnormal hematology parameter is confirmed:

Hemoglobin: < 10 g/dl

Platelets: < 75 000/mm^3

White blood cells: 3 000/mm^3

Neutrophils: < 1 500/mm^3

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

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

Notable values are defined as follows: heart rate of < 50 and > 100 bpm; systolic blood pressure of < 90 and ≥ 140 mmHg; diastolic blood pressure of < 60 and ≥ 90 mmHg.

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

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. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
ALT or AST		
> 8 × ULN	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 × ULN and INR > 1.5	• Discontinue the study treatment immediately • Hospitalize, if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 5 to ≤ 8 × ULN	• Repeat LFT within 48 hours • If elevation persists, continue follow-up monitoring • If elevation persists for more than 2 weeks, discontinue the study drug • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms[b]	• Discontinue the study treatment immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the 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. conmeds, med hx, lab) in the appropriate CRF	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	• Repeat LFT within 48 hours • If elevation persists, discontinue the study drug immediately • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	• Repeat LFT within the next week • If elevation is confirmed, initiate close observation of the patient	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Actions required	Follow-up monitoring
Jaundice	• Discontinue the study treatment immediately • Hospitalize the patient • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	ALT, AST, TBL, Alb, PT/INR, ALP and GGT until resolution[c] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	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 or 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+ OR Protein-creatinine **ratio** (PCR) ≥ 1g/g Cr (or mg/mmol equivalent as converted by the measuring laboratory)	• Consider causes and possible interventions • Assess serum albumin & serum total protein • Repeat assessment to confirm • Consider drug interruption or discontinuation unless other causes are diagnosed and corrected
New onset hematuria ≥ 3+ on urine dipstick	<u>Assess & document</u> • Repeat assessment to confirm • Distinguish hemoglobinuria from hematuria • Urine sediment microscopy • Assess sCr • Exclude infection, trauma, bleeding from the distal urinary tract/bladder, menstruation • Consider bleeding disorder

[+] 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

Assess, document and record in CRF • 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 CRF
Monitor patient regularly (frequency at investigator's discretion) until • Event resolution: (sCr within 10% of baseline or PCR < 1 g/g Cr, or ACR <300 mg/g Cr) or • Event stabilization: sCr level with ±10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ±50% variability over last 6 months. • Analysis of urine markers in samples collected over the course of the DIN event

16.4 Appendix 4: ESSDAI

Table 16-5 The EULAR Sjögren's syndrome disease activity index (ESSDAI): domain and item definitions and weights

Domain [weight]	Activity level	Description
Constitutional [3] Exclusion of fever of infectious origin and voluntary weight loss	No = 0 Low = 1 Moderate = 2	Absence of the following symptoms Mild or intermittent fever (37.5–38.5°C)/night sweats and/or involuntary weight loss of 5-10% of body weight Severe fever (>38.5°C)/night sweats and/or involuntary weight loss of >10% of body weight
Lymphadenopathy [4] Exclusion of infection	No = 0 Low = 1 Moderate = 2 High = 3	Absence of the following features Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/or splenomegaly (clinically palpable or assessed by imaging) Current malignant B-cell proliferative disorder
Glandular [2] Exclusion of stone or infection	No = 0 Low =1 Moderate = 2	Absence of glandular swelling Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular or lachrymal swelling Major glandular swelling with enlarged parotid (>3 cm), or important submandibular or lachrymal swelling
Articular [2] Exclusion of osteoarthritis	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active articular involvement Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min) 1–5 (of 28 total count) synovitis ≥6 (of 28 total count) synovitis

Domain [weight]	Activity level	Description
Cutaneous [3] Rate as 'no activity' stable long-lasting features related to damage	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active cutaneous involvement Erythema multiforma Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute lutaneous lupus Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis
Pulmonary* [5] Rate as 'no activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active pulmonary involvement Persistent cough or bronchial involvement^ with no radiographic abnormalities on radiography Or radiological or HRCT evidence of interstitial lung disease with no breathlessness and normal lung function test Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NYHA II) or abnormal lung function tests restricted to 70%>DL_{CO}≥40% or 80%>FVC≥60% Highly active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath at rest (NHYA III, IV) or with abnormal lung function tests DL_{CO}<40% or FVC<60%

Domain [weight]	Activity level	Description
Renal [5] Rate as 'no activity' stable long-lasting features related to damage and renal involvement not related to the disease. If biopsy has been performed, please rate activity based on histological features first	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active renal involvement with proteinuria <0.5 g/day, no haematuria, no leucocyturia, no acidosis, or long-lasting stable proteinuria due to damage Evidence of mild active renal involvement, limited to tubular acidosis without renal failure or glomerular involvement with proteinuria (between 0.5 and 1 g/day) and without haematuria or renal failure (GFR ≥60 ml/min) Moderately active renal involvement, such as tubular acidosis with renal failure (GFR <60 ml/min) or glomerular involvement with proteinuria between 1 and 1.5 g/day and without haematuria or renal failure (GFR ≥60 ml/min) or histological evidence of extra-membranous glomerulonephritis or important interstitial lymphoid infiltrate Highly active renal involvement, such as glomerular involvement with proteinuria >1.5 g/day or haematuria or renal failure (GFR <60 ml/min), or histological evidence of proliferative glomerulonephritis or cryoglobulinaemia-related renal involvement
Muscular* [6] Exclusion of weakness due to corticosteroids	No = 0 Low = 1 Moderate = 2 High = 3	Absence of currently active muscular involvement Mild active myositis shown by abnormal EMG or biopsy with no weakness and creatine kinase (N<CK≤2N) Moderately active myositis confirmed by abnormal EMG or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N) Highly active myositis shown by abnormal EMG or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)
PNS* [5]	No = 0 Low = 1	Absence of currently active PNS involvement

Domain [weight]	Activity level	Description
Rate as 'no activity' stable long-lasting features related to damage or PNS involvement not related to the disease	Moderate = 2 High = 3	Mild active peripheral nervous system involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia Moderately active peripheral nervous system involvement shown by NCS, such as axonal sensorimotor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinamic vasculitis, ganglionopathy with symptoms restricted to mild/moderate ataxia, inflammatory demyelinating polyneuropathy (CIDP) with mild functional impairment (maximal motor deficit of 4/5 or mild ataxia) Or cranial nerve involvement of peripheral origin (except trigeminal (V) neuralgia) Highly active PNS involvement shown by NCS, such as axonal sensorimotor neuropathy with motor deficit ≤3/5, peripheral nerve involvement due to vasculitis (mononeuritis multiplex, etc), severe ataxia due to ganglionopathy, inflammatory demyelinating polyneuropathy (CIDP) with severe functional impairment: motor deficit ≤3/5 or severe ataxia
CNS* [5] Rate as 'no activity' stable long-lasting features related to damage or CNS involvement not related to the disease	No = 0 Moderate = 2 High = 3	Absence of currently active CNS involvement Highly active CNS features, such as cerebral vasculitis with cerebrovascular accident or transient ischaemic attack, seizures, transverse myelitis, lymphocytic meningitis, multiple sclerosis-like syndrome with motor deficit

Domain [weight]	Activity level	Description
Haematological [2] For anaemia, neutropenia, and thrombopenia, only autoimmune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia	No = 0 Low = 1 Moderate = 2 High = 3	Absence of auto-immune cytopenia Cytopenia of auto-immune origin with neutropenia (1000<neutrophils<1500/mm3), and/or anaemia (10<haemoglobin<12 g/dl), and/or thrombocytopenia (100000<platelets<150000/mm3) Or lymphopenia (500<lymphocytes<1000/mm3) Cytopenia of auto-immune origin with neutropenia (500≤neutrophils≤1000/mm3), and/or anaemia (8≤haemoglobin≤10 g/dl), and/or thrombocytopenia (50000≤platelets≤100000/mm3) Or lymphopenia (≤500/mm3) Cytopenia of auto-immune origin with neutropenia (neutrophils <500/mm3), and/or or anaemia (haemoglobin <8 g/dl) and/or thrombocytopenia (platelets <50000/mm3)
Biological [1]	No = 0 Low = 1 Moderate = 2	Absence of any of the following biological features Clonal component and/or hypocomplementaemia (low C4 or C3 or CH50) and/or hypergammaglobulinaemia or high IgG level between 16 and 20 g/l Presence of cryoglobulinaemia and/or hypergammaglobulinaemia or high IgG level >20 g/l, and/or recent onset hypogammaglobulinaemia or recent decrease of IgG level (<5 g/l)

^ Based on the EULAR ESSDAI user guide (Seror et al 2015), an inconsistency was observed under the pulmonary domain. The description column of the low disease activity for the pulmonary domain has been modified from “persistent cough or bronchial involvement” to “persistent cough due to bronchial involvement”.

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