Galápagos

CLINICAL STUDY PROTOCOL

Project Number:	GLPG3970		
Study Number:	GLPG3970-CL-207		
Study Title	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered GLPG3970 for 12 weeks in adult subjects with active primary Sjögren's Syndrome		
Short Study Title	A study evaluating the effects of GLPG3970 given as an oral treatment for 12 weeks in adults with active primary Sjögren's Syndrome		
Clinical Study Phase:	2a		
Status	Final		
Protocol Version:	7.0	Date:	12-May-2021
Amendment	6		
EudraCT No:	2020-003298-22	CT.gov No:	NCT04700280
IND No:	Not applicable		
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium		
Study Physician:	[redacted], MD, Senior Medical Director, Translational Medicine		
General CSP			

Confidentiality Statement

EMERGENCY CONTACT INFORMATION

In case of a **serious adverse event (SAE)**, a special situation (see Section 11.1.6) or in case of **pregnancy** during the clinical study, the investigator must report this immediately, and under no circumstances later than 24 hours following the knowledge of the event as follows:

E-mail: [redacted]

or

[redacted] SAE Fax #: [redacted]

In case of medical questions during the course of the study, the investigator must contact the contract research organization (CRO) medical monitor or if unavailable, his/her back-up, the sponsor medical leader for all scientific, protocol and investigational product (IP) related questions, and the sponsor translational medicine leader for all safety related questions:

CRO Medical Monitor

IQVIA Medical Emergency Contact Center

Phone: [redacted] (EU)
[redacted] USA)
[redacted] (alternative number)

Sponsor medical leader

[redacted], MD
Phone: [redacted]
E-mail: [redacted]

Sponsor translational medicine leader

[redacted], MD
Phone: [redacted]
E-mail: [redacted]

Sponsor contact number:

[redacted]

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CLINICAL STUDY PROTOCOL HISTORY

Clinical Study Protocol (CSP)/Amendment #	Date	Main Rationale General/Country-Specific
CSP Version 1.0	21-Sep-2020	Initial CSP Version General
Amendment 1, CSP Version 2.0	8-Dec-2020	Updated to include more details on the Physiologically-Based Pharmacokinetic (PBPK) modeling data to support the tablet formulation.
Amendment 2, CSP Version 3.0	6-Jan-2021	A protocol amendment created upon request of the [redacted] updating the exclusion criteria, prohibited medications section, and extending the follow-up period to 4 weeks.
Amendment 3, CSP version 4.0	21-Jan-2021	Protocol amended in response to a follow up request by the [redacted] to further adapt the exclusion criteria.
Amendment 4, CSP version 5.0	8-Feb-2021	Protocol amended in response to questions from the [redacted]
Amendment 5, CSP version 6.0	4-Mar-2021	Protocol amended in alignment with the newly identified potential risk of QT prolongation
Amendment 6, CSP version 7.0	12-May-2021	Protocol amended to closer monitor the new potential risk of QT prolongation

CSP=clinical study protocol

SUMMARY OF CHANGES

Amendment 6 (12-May-2021)
The overall reason for this amendment: This protocol was amended to closer monitor the new potential risk of QT prolongation. In addition, some clarifications on the eligibility process were included.
The changes made to the CSP GLP3970-CL-207 Version 6.0, 4-Mar-2021, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: The protocol has been updated to indicate that the investigational product (IP) will be administered in a fasted state at Visit 1 (Day 1) and in a fed state (together with a meal) at all other dosing days. **Applicable sections:** 1, 6.3.3, 7.2, 8.11
Rationale: The process to determine the eligibility of a subject has been clarified. **Applicable sections:** 1, 6.1, 6.2, 6.4, 8.3
Rationale: The protocol has been updated to include additional electrocardiograms (ECGs) and a pharmacokinetic (PK) sample at Visit 1 (Day 1) to closer monitor the newly identified potential risk of QT prolongation. In addition, the "within 3 hours" predose time window has been removed for all assessments. **Applicable sections:** 6.3.2, 8.1, 8.5.5, 8.9, 8.11
Rationale: At Visit 3, a predose blood sampling [redacted] was added to assess the [redacted] **Applicable sections:** 8.1, 8.9, 8.11
Rationale: Minor administrative changes and alignments **Applicable sections:** 1, 5.5, 6.2, 6.3.2, 6.4, 7.2, 8.1, 8.5.5, 8.10, 8.11, 11.2.1, 12.6.2

Amendment 5 (4-Mar-2021)
The overall reason for this amendment: Protocol amended in alignment with the newly identified potential risk of QT prolongation.
The changes made to the CSP GLP3970-CL-207 Version 5.0, 8-Feb-2021, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: An important potential risk of QT prolongation and associated risk mitigation measures have been added. **Applicable sections:** 5.5, 6.2, and 6.4
Rationale: Reference values for creatinine clearance have been adapted. **Applicable section:** 6.2

Rationale: Guidance for vaccine (including Covid-19 vaccines) use before and during this study have been updated. **Applicable sections:** 5.5 and 6.3.2
Rationale: Clarification was added that SARS-CoV-2 tests may be analyzed in local laboratories. **Applicable section:** 8.9
Rationale: Minor administrative changes and alignments **Applicable sections:** list of abbreviations; 1, 2, 2.2, 6.2, 8.5.5 and 8.11

Amendment 4 (8-Feb-2021)
The overall reason for this amendment: This protocol was amended in response to questions from the [redacted]
The changes made to the CSP GLP3970-CL-207 Version 4.0, 21-Jan-2020, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: The phone number of the sponsor medical leader has been changed to their mobile number since due to current regional SARS-CoV-2 restrictions, a presence at the office cannot be guaranteed. **Applicable sections:** Emergency contact information.
Rationale: A footnote has been added to the exclusion criteria to define the term elderly. **Applicable Section:** 6.2
Rationale: Wording of the exclusion criterion on vaccines has been clarified to exclude live attenuated vaccines (including live attenuated covid-19 vaccines). A new subsection "vaccines" has been subsequently added to 6.3.2 Prior and Concomitant Medication. **Applicable Sections:** 6.2 and 6.3.2
Rationale: A new exclusion criterion has been added to exclude subjects who are institutionalized by virtue of an order issued by either the judicial or the administrative authorities or have a dependency on the sponsor or investigator. **Applicable Section:** 6.2
Rationale: Wording on subject discontinuation criteria was changed from "should be discontinued" to "must be discontinued" for purposes of clarification. **Applicable Section:** 6.4
Rationale: Study stopping criteria were specified. **Applicable Section:** 6.4
Rationale: Clarification has been added that the investigator should report SARS-CoV-2 results as required by local law.

Applicable Section: 8.5.2
Rationale: [redacted].
Applicable Section: 8.7.1
Rationale: The maximum blood volume was updated from not exceeding [redacted] to not exceeding [redacted] ml due to a recalculation of total blood volumes after finalization of the laboratory manuals.
Applicable Section: 8.9
Rationale: The composition of the safety monitoring committee has been clarified.
Applicable Section: 10.1

Amendment 3 (21-Jan-2021)
The overall reason for this amendment: This is a protocol amendment created upon request of the [redacted] to further adapt the exclusion criteria.
The changes made to the CSP GLP3970-CL-207 Version 3.0, 6-Jan-2020, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: The exclusion criteria on history or presence of clinically significant ECG abnormalities has been updated to also exclude a history or presence of cardiopathy. **Applicable Section:** 6.2
Rationale: Specification of abnormal laboratory values for serum potassium concentration was added to the exclusion criterion on abnormal laboratory values for aspartate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time or partial thromboplastin time added in amendment 2. **Applicable Section:** 6.2
Rationale: Minor administrative changes. **Applicable Sections:** 1 and 6.2

Amendment 2 (6-Jan-2021)
The overall reason for this amendment: This is a protocol amendment created upon request of the [redacted] updating the exclusion criteria, prohibited medication section and extending the follow-up period to 4 weeks.
The changes made to the CSP GLP3970-CL-207 Version 2.0, 8-Dec-2020, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: An exclusion criterion was added to ensure non-eligibility of subjects with presence of any organ manifestation or life-threatening condition, or who have planned a surgery during the study.

Applicable Sections: 1 and 6.2
Rationale: The exclusion criteria regarding anticholinergic agents has been updated to exclude any medication known to cause dry mouth/dry eyes that in the opinion of the investigator are a contributing factor to the subject's dryness. **Applicable Sections**: 1, 6.2, and 6.3.2
Rationale: For sporadic use of ocular medicines in the exclusion criteria, sporadic use was defined as a course of 7 days and no more than 2 courses during the study administered 2 weeks apart. **Applicable Sections**: 1, 6.2, and 6.3.2
Rationale: An additional exclusion criterion was added specifying abnormal laboratory values for aspartate aminotransferase, alanine aminotransferase, total bilirubin, prothrombin time or partial thromboplastin time to address the [redacted] concern. **Applicable Section**: 6.2
Rationale: The follow-up period of the study was extended from 2 to 4 weeks **Applicable Sections**: 1, 5.1, 6.5.2, 8.9, and 8.11
Rationale: Minor administrative changes. **Applicable Sections**: 6.3.2 and 6.4

Amendment 1 (8-Dec-2020)
The overall reason for this amendment: The overall reason for this amendment is to include more details on the Physiologically-Based Pharmacokinetic (PBPK) modeling data to support the tablet formulation, upon request from the competent authority of the [redacted]
The changes made to the CSP GLP3970-CL-207 Version 1.0, 21-Sep-2020, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: Additional details on the PBPK modeling data are included to support the tablet formulation and to compare the previous formulations with the tablet formulation. In addition, the list of abbreviations has been updated. **Applicable Section**: 2.2

CSP=clinical study protocol

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ACR	American College of Rheumatology
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AZA	azathioprine
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve from time zero until 24 hours postdose
AUC_{tau}	area under the plasma concentration-time curve from time zero until the end of the dosing period
[redacted]	
CA	citric acid
C_{avg}	mean average concentration
CI	confidence interval
CL/F	clearance
C_{max}	maximum observed plasma concentration
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
C_{trough}	plasma trough concentration
CYP	cytochrome P450
DNA	deoxyribonucleic acid
DTP	direct to patient
EC_{50}	half maximal effective concentration
ECG	electrocardiogram
ED	early discontinuation
ESSDAI	EULAR Sjögren's Syndrome Disease Activity Index
ESSPRI	EULAR Sjögren's Syndrome Patient Reported Index

EU	European Union
EULAR	European League Against Rheumatism
FAS	Full Analysis Set
FIH	first-in-human
FSH	follicle stimulating hormone
FU	follow-up
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
GLP	Good Laboratory Practice
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HOMA-IR	homeostatic model assessment of insulin resistance
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentrations
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgM	immunoglobulin M
IL	interleukin
INR	international normalized ratio
IP	investigational product
IR	immediate release
IRB	Institutional Review Board
IVIVC	in vitro in vivo correlation
IWRS	interactive web response system
LDL	low-density lipoprotein
LFT	liver function test
LPS	lipopolysaccharide
[redacted]	[redacted]
MMF	mycophenolate mofetil
MMRM	mixed model for repeated measures
[redacted]	[redacted]

MTX	methotrexate
NOAEL	no-observed-adverse-effect-level
NSAID	non-steroidal anti-inflammatory drug
[redacted]	
PBBM	Physiologically-Based Biopharmaceutics Model
PBPK	Physiologically-Based Pharmacokinetic
PCR	polymerase chain reaction
[redacted]	[redacted]
P-gp	permeability glycoprotein
PK	pharmacokinetic(s)
Pop-PK	population pharmacokinetics
pSS	primary Sjögren's Syndrome
q.d.	once daily
QMP	Quality Management Plan
[redacted]	[redacted]
RA	rheumatoid arthritis
RBC	red blood cell
RNA	ribonucleic acid
RT-PCR	real time polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
[redacted]	[redacted]
SGF	simulated gastric fluid
SIF	simulated intestinal fluid
SIK	salt-inducible kinase
[redacted]	[redacted]
SoC	standard of care
SjS	Sjögren's Syndrome
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TB	tuberculosis
TEAE	treatment-emergent adverse event
[redacted]	

t_{max}	time to maximum plasma concentration
TMF	Trial Master File
TNFα	tumor necrosis factor alpha
ULN	upper limit of normal
[redacted]	[redacted]
Vss	volume of distribution at steady state
WOCBP	women of childbearing potential

Definition of Terms

BMI	body mass index Weight (kg) / (height [m])^2
QTcF	QT interval corrected for heart rate using Fridericia's formula: $QTcF = QT/RR^{1/3}$ RR = the interval from the onset of one QRS complex to the onset of the next QRS complex
HOMA-IR	Homeostatic model assessment of insulin resistance HOMA-IR= (fasting insulin [mU/mL] x fasting glucose [mg/dL])/405
]x, y]	Interval ranging from x to y, with x not included and y included in the interval

1. CLINICAL STUDY PROTOCOL SYNOPSIS

Title of Study

A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered GLPG3970 for 12 weeks in adult subjects with active primary Sjögren's Syndrome

Short Title of Study

A study evaluating the effects of GLPG3970 given as an oral treatment for 12 weeks in adults with active primary Sjögren's Syndrome

Phase of Development: Phase 2a

Objectives and Endpoints

Objectives	Endpoints
Primary	
– To evaluate the efficacy of GLPG3970 compared to placebo on the signs and symptoms of primary Sjögren's Syndrome (pSS).	– Change from baseline in European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) score at Week 12.
– To evaluate the safety and tolerability of GLPG3970 compared to placebo.	– Number, incidence, and severity of treatment-emergent adverse events (TEAEs).
Secondary	
– To further characterize the efficacy of GLPG3970 compared to placebo on the patient-reported signs and symptoms of pSS.	– Change from baseline in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score at Week 4, 8, and 12. – Change from baseline in ESSDAI score over time at Week 4, 8, and 12.
– To characterize the pharmacokinetics (PK) of GLPG3970.	– Observed GLPG3970 plasma trough concentrations (C_{trough}).
Other	
[redacted]	

[redacted]

Planned Number of Subjects

The study is planned to randomize 30 adult subjects in a 2:1 ratio (20 subjects planned to receive GLPG3970 and 10 subjects planned to receive placebo).

Study Design

This is a randomized, double-blind, placebo-controlled, parallel-group, multicenter study.

The study will consist of 3 study periods:

- Screening period: up to 4 weeks with 1 study visit.
- Treatment period: 12 weeks with up to 5 study visits (Days 1, 8, 29, 57, and 85).
- Follow-up (FU) period: 4 weeks with 1 study visit.

A schematic diagram of clinical study design and periods is provided below.

Study Duration

The subjects will be in the study for a duration of 20 weeks: up to 4 weeks of screening, 12 weeks of treatment, and 4 weeks of FU.

Main Criteria for Inclusion and Exclusion

Main Inclusion Criteria

- Male or female subject between 18-74 years of age (extremes included), on the date of signing the informed consent form (ICF).
- Documented diagnosis of pSS for <10 years prior to screening AND defined by the classification criteria >=4 described by the American College of Rheumatology - European League Against Rheumatism (ACR-EULAR).
- Subject has an ESSDAI score >=5 assessed on 7 domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, hematological, and biological.
- Subject has an ESSPRI score >=5.

- Subject has stimulated whole salivary flow rate of >=0.1 mL/min.
- Subject has positive serum titers of anti-SS-A/Ro and/or anti-SS-B/La antibodies.
- Subjects already on treatment should be on stable standard of care (SoC) for at least 4 weeks prior to first IP dosing.

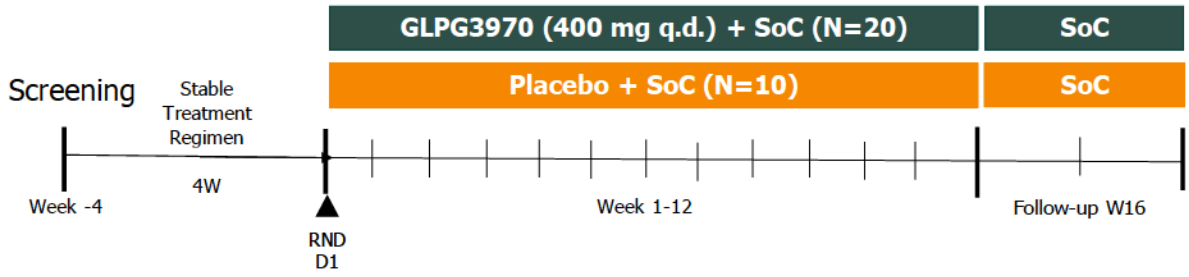
  The following SoC medications are permitted:
  - Corticosteroids <=7.5 mg/day (prednisone or equivalent); AND/OR
  - Non-steroidal anti-inflammatory drugs (NSAIDs); AND/OR
  - One single antimalarial at a stable dose (hydroxychloroquine <=400 mg/day; quinacrine 100 mg/kg/day, or chloroquine <=250 mg/day); AND/OR
  - One single immunosuppressant at a stable dose (methotrexate [MTX] <=10 mg/week or azathioprine [AZA] <=2 mg/kg/day); AND/OR
  - One single cholinergic stimulant at a stable dose (e.g. pilocarpine, cevimeline).
- Female subject of childbearing potential must have a negative highly sensitive (serum beta human chorionic gonadotropin or urine dipstick) pregnancy test.
- Female subject of childbearing potential or male subject must agree to use highly effective contraception/preventive exposure measures.

Main Exclusion Criteria

- Secondary Sjögren's syndrome according to the ACR-EULAR (2016) classification.
- History or presence of unstable condition not related to Sjögren's Syndrome that, in the opinion of the investigator, could constitute an unacceptable risk when taking the IP or interfere with the interpretation of data.
- Subject has any active systemic infection within 2 weeks prior to first IP dosing, or poorly controlled chronic cardiac, pulmonary, or renal disease.
- Subject has a known or suspected history of or a current immunosuppressive condition, or a history of opportunistic infections (e.g. human immunodeficiency virus [HIV] infection, histoplasmosis, listeriosis, coccidiodmycosis, pneumocystosis, aspergillosis).
- Subject has a chronic hepatitis B virus (HBV) infection, as defined by persistent HBV surface antigen (HBsAg) positivity. Subject has hepatitis C virus (HCV) infection, as defined by positive HCV antibody at screening and detectable HCV viremia. Subjects with positive HCV antibody must undergo reflex HCV ribonucleic acid (RNA) testing, and subjects with HCV RNA positivity will be excluded. Subjects with positive HCV antibody and negative HCV RNA are eligible.
- Subject testing positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection as detected at screening based on real time polymerase chain reaction (RT-PCR) or at baseline based on immunoglobulin M (IgM) immunoassay, or subjects who have been in contact with SARS-CoV-2 infected individuals in the 2 weeks prior to first dosing of IP. Subjects presenting any signs or symptoms of SARS-CoV-2 infection, as detected prior to first IP dosing following careful physical examination (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, etc). In addition, any other locally applicable standard diagnostic criteria may also apply to rule out SARS-CoV-2 infection.

- Subject has taken any disallowed therapies:
  - Mycophenolate mofetil (MMF) within a week prior to screening.
  - Cyclosporine/Tacrolimus within a week prior to screening.
  - Cyclophosphamide within 6 months prior to screening.
  - Ocular medicines (e.g. topical cyclosporine, topical NSAIDs/corticosteroids) for at least 4 weeks prior to screening, except for a sporadic use.
  - Biologics such as, but not limited to, rituximab, abatacept, and any other unapproved biologic within 6 months prior to screening.
  - Plasmapheresis within 12 weeks prior to screening.
  - Plasma exchange within 12 weeks prior to screening.
  - Intravenous immunoglobulin (IVIG) therapy within 24 weeks prior to screening.
  - Other prohibited medications within 2 weeks or 5 half-lives, whichever is longer prior to first IP dosing.
- Concurrent use of anticholinergic agents or any other medication known to cause dry mouth/dry eyes that, in the opinion of the investigator, are a contributing factor to the subject's dryness and/or use of anticholinergic agents not contributing to this dryness, if not stable at least 4 weeks prior to screening.
- Subject has a history of tuberculosis (TB) diagnosis or evidence of active or latent infection with *Mycobacterium tuberculosis*.
- Subject has a history of lymphoma or any malignancy within the past 5 years prior to screening with the exception of excised and curatively treated non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of cervix which is considered cured with minimal risk of recurrence.
- Subject has severe organ manifestation or life-threatening condition, or has planned a surgery during the study.

Treatment and Treatment Schedule



Investigational Product, Dosage, and Mode of Administration

GLPG3970 will be provided as a film-coated tablet containing 200 mg of the active pharmaceutical ingredient G1567970 (G1567970 is the compound code for GLPG3970). A dose of 400 mg (2 x 200 mg tablets) q.d. will be taken orally.

GLPG3970 will be administered in a fasted state at Visit 1 (Day 1) and in a fed state (together with a meal) at all other dosing days.

Matching placebo tablets will also be provided.

Statistical Analysis

Safety Analysis

All safety analyses will be performed using the Safety Analysis Set, consisting of all randomized subjects who received at least 1 dose of IP. All safety data collected on or after the first dose of IP administration up to the last contact after the last dose of IP, unless specified otherwise, will be summarized by treatment group according to the IP received. Clinical safety will be addressed by assessing adverse events (AEs), laboratory assessments, physical examinations, vital signs, and 12-lead electrocardiograms (ECGs).

Efficacy Analysis

All efficacy analyses will be performed using the Full Analysis Set, consisting of all randomized subjects who have received at least 1 dose of IP.

The signal detection methodology described by Frewer et al. will be used to provide further insight into the treatment effect of GLPG3970 over placebo, and will support scenario analyses. A mixed model for repeated measures (MMRM) (ESSDAI) will be used to compare treatment groups, with a 90% confidence interval (CI) of the treatment difference at Week 12.

Continuous efficacy endpoints, including the primary endpoint: MMRM to compare treatment groups, with a 90% CI of the treatment difference at each time point.

Binary efficacy endpoints will be presented with a 90% exact CI of the treatment difference at each time point.

PK Analysis

Descriptive statistics will be done on C_{trough} plasma levels for GLPG3970. Observed plasma C_{trough} for GLPG3970 will be reported in the clinical study report (CSR).

All observed GLPG3970 plasma concentrations will be analyzed using a population PK (pop-PK) approach to characterize the PK profile of GLPG3970. This analysis will provide simulated pop-PK parameters for GLPG3970, such as clearance (CL/F) and volume of distribution at steady state (Vss), and their associated variability, as well as individual estimates of area under the plasma concentration-time curve (AUC) and, if appropriate,

maximum observed plasma concentration (C_{max}). The results from the pop-PK analysis will be reported separately from the CSR.

[redacted]

2. INTRODUCTION

Sjögren's Syndrome (SjS) is a slowly progressive systemic chronic autoimmune disorder characterized by lymphocytic infiltration of exocrine glands causing lacrimal and salivary gland dysfunction. Clinical presentation varies from mild symptoms such as dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia), arthralgia, and chronic fatigue, to severe systemic symptoms, involving multiple organ systems (1). In more than 30% of cases, extra-glandular systemic disease manifestations can develop, such as arthritis, nephritis, cytopenia, pneumonitis, vasculitis, and neurological complications. Furthermore, subjects suffering from SjS have a marked increased risk of lymphoma (2,3). Disabling fatigue and loss of working productivity negatively affect the patient's quality of life (QoL). The disease may occur as a primary form (primary Sjögren's Syndrome [pSS]) or as a secondary form associated with other conditions (most commonly rheumatoid arthritis [RA] and systemic lupus erythematosus [SLE]). The estimated prevalence is 0.06% worldwide. It is known to affect perimenopausal women more frequently than men and more frequently and more severely Caucasians than other races (1,3).

Although disease pathogenesis has not yet been fully elucidated, substantial data has demonstrated that abnormal autoimmune responses involve innate and adaptive immunity, possibly triggered by viral infections and hormonal factors in genetically predisposed individuals. Salivary gland epithelial cells, alongside cluster of differentiation 4 (CD4+) T-lymphocytes and also B-lymphocytes, activated and/or stimulated by interferons and other cytokines may thus trigger and maintain chronic immune activation resulting in a vicious cycle of autoimmunity. Furthermore, a range of autoantibodies can be present in SjS (anti-SSA/Ro and anti-SSB/La antibodies, rheumatoid factor, cryoglobulins, anti-nuclear antibodies), complicating the presentation (4,5). There is also a potential role of immune factors that influence central nervous system (CNS) behavior with an impact upon efferent neuronal pathways that stimulate secretory glands (6). In addition to immune mechanisms, several non-immune factors may be involved in the pathogenesis (5).

Currently, there is no cure, nor an efficacious systemic immunomodulatory agent for the treatment of pSS. The goals of therapy in patients with pSS are symptom palliation, prevention of complications, management of systemic manifestations, and glandular and lymphoproliferative disease. The treatment of sicca symptoms alone, without glandular enlargement or other organ involvement, generally does not require systemic therapy other than secretagogues (pilocarpine, cimeviline). Steroids and typical disease-modifying antirheumatic drugs (DMARDs) have often limited efficacy, and there is no pharmacological intervention against the fatigue. Hence, the unmet medical need for more-effective treatment options is significant. Novel biological therapies may directly intervene with the pathophysiology of the syndrome and thus improve glandular and extraglandular manifestations of pSS (7,8). Oral, small-molecule inhibitors of intracellular kinases might bring therapeutic benefit in a wide range of inflammatory diseases, including pSS (9).

GLPG3970 has a dual mechanism of action with the potential to improve upon the currently available treatments, via the induction of immunoregulatory mechanisms in addition to its anti-inflammatory properties. GLPG3970 is an oral, selective, small-molecule serine/threonine salt-

inducible kinase (SIK) 2 and 3 inhibitor. These kinases provide a molecular switch in the control of pro- and anti-inflammatory cytokine production. Inhibition of these targets blocks the production of pro-inflammatory cytokines such as tumor necrosis factor alpha [TNFα], interleukin [IL]-12, and increases IL-10 levels, which has a tolerogenic role, by skewing macrophages and dendritic cells toward regulatory and tolerogenic phenotypes.

For more details refer to the latest version of the investigator's brochure (IB) and its relevant updates/addenda.

This clinical study will be conducted in compliance with this clinical study protocol (CSP), the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) Guideline E6, and applicable local ethical and legal requirements (see also Section 12).

2.1. Background - Nonclinical Studies

2.1.1. Nonclinical Pharmacokinetics

[redacted]

2.1.2. Safety Pharmacology

[redacted]

[redacted]

2.1.3. General Toxicology

[redacted]

2.1.4. Genotoxicity

[redacted]

2.1.5. Embryo-Fetal Development Toxicity

[redacted]

2.1.6. Phototoxicity

[redacted]

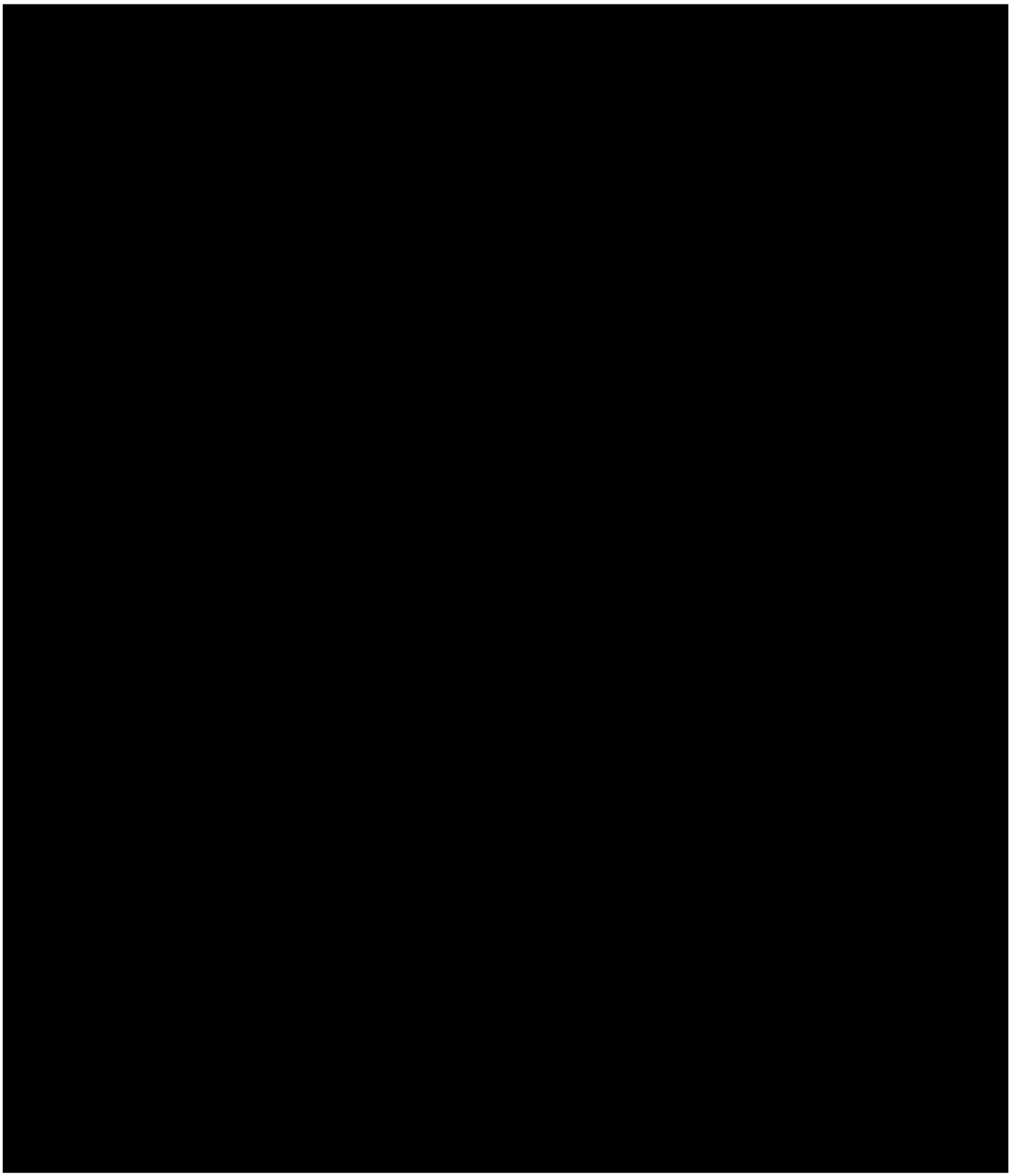
2.2. Background - Clinical Studies

GLPG3970-CL-101 is an ongoing first-in-human (FIH) study conducted in healthy male subjects and subjects with psoriasis. In healthy volunteers, single ascending doses up to 500 mg q.d. and multiple ascending dosing up to 400 mg q.d. (oral solution, fasted conditions), as well as the

relative bioavailability of an initial exploratory solid formulation (capsules filled with mini-tablets) and the effect of food on the PK with both formulations have been completed, while the part in subjects with psoriasis is ongoing. The single and multiple ascending parts of the study were randomized, double-blind, and placebo-controlled to evaluate the safety, tolerability, pharmacokinetics (PK) [redacted] of GLPG3970 in adult healthy male subjects. The single ascending dose part evaluated GLPG3970 in the dose range 10 mg to 500 mg and in the multiple ascending dose part doses of 100 mg q.d., 250 mg q.d., and 400 mg q.d were evaluated over a period of 14 days.

Administration of GLPG3970 was well tolerated. No deaths, serious treatment-emergent adverse events (TEAEs), or TEAEs leading to study drug discontinuation were reported. No clinically significant abnormalities related to laboratory parameters, cardiovascular safety (electrocardiogram [ECG]), vital signs, or physical examination were reported.

[redacted]



[redacted]

Additional PK and safety data, as well as the compositions of the formulations are described in the latest version of the IB and its relevant updates/addenda.

3. CLINICAL STUDY OBJECTIVES

3.1. Primary Objectives

- To evaluate the efficacy of GLPG3970 compared to placebo on the signs and symptoms of pSS.
- To evaluate the safety and tolerability of GLPG3970 compared to placebo.

3.2. Secondary Objectives

- To further characterize the efficacy of GLPG3970 compared to placebo on the patient-reported signs and symptoms of pSS.
- To characterize the PK of GLPG3970.

3.3. [redacted]

[redacted]

[redacted]

4. ENDPOINTS

4.1. Primary Endpoints

- Change from baseline in European League Against Rheumatism (EULAR) Sjögren's Syndrome Disease Activity Index (ESSDAI) score at Week 12.
- Number, incidence, and severity of TEAEs.

4.2. Secondary Endpoints

- Change from baseline in EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) score at Week 4, 8, and 12.
- Change from baseline in ESSDAI score over time at Week 4, 8, and 12.
- Observed GLPG3970 C_{trough}.

4.3. [redacted]

[redacted]

5. INVESTIGATIONAL PLAN

5.1. Clinical Study Design

This is a Phase 2a, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the efficacy, safety, tolerability, PK, [redacted] of orally administered GLPG3970 for 12 weeks in adult subjects with active pSS.

One dose level of GLPG3970 will be evaluated in 30 subjects who will be randomized 2:1 to receive GLPG3970 (400 mg [2 x 200 mg] q.d.) or matching placebo, respectively.

The study will consist of 3 study periods:

- Screening period: up to 4 weeks with 1 study visit. During the Screening visit, subjects will be selected based on the eligibility criteria. Subjects already on treatment will remain on a stable standard of care (SoC) treatment (see Section 6.1) during the study.
- Treatment period: 12 weeks with up to 5 study visits (Days 1, 8, 29, 57, and 85). At any time during the course of the study, phone calls or unscheduled visits can be added if deemed necessary by the investigator. Subjects will receive GLPG3970 or placebo q.d.
- Follow-up (FU) period: 4 weeks with 1 study visit. Subjects remain on stable SoC treatment, if applicable.

The subjects will be in the study for a duration of 20 weeks: up to 4 weeks of screening, 12 weeks of treatment, and 4 weeks of FU.

A schematic diagram of clinical study design and periods is provided in Figure 2.

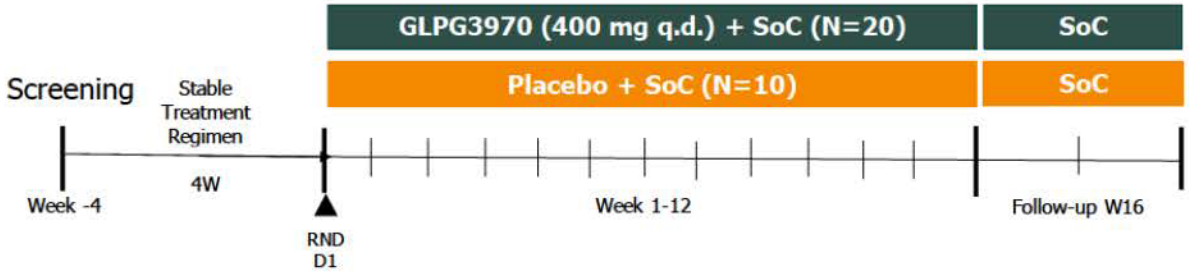


Figure 2: Schematic Diagram

For detailed information regarding dosage form, packaging, and labeling of the IP refer to Section 7.2, "Dosage and Administration" and Section 7.3, "Packaging, Labeling and Distribution".

5.2. Start and End of Study Definitions

The study start is defined when the first informed consent form (ICF) is signed. The end of the study is reached when the last FU visit, as planned according to the Schedule of Activities (Section 8.11), for the last subject is performed.

5.3. Clinical Study Design Rationale

This is a first exploration of GLPG3970 in subjects with active pSS to evaluate the efficacy, safety, tolerability, PK profile [redacted]

The double-blind, randomized, parallel-group design is a standard design for a first study in subjects with active pSS.

[redacted]

Treatment duration of 12 weeks is considered adequate in order to explore the efficacy, safety, tolerability, PK, [redacted] in a study testing GLPG3970 for the first time in subjects with active pSS, and may support the future design of efficacy and safety studies in this population.

GLPG3970 is aiming to restore immune homeostasis in chronic inflammatory diseases through modulation of the immune system by altering the balance between effector and regulatory immune cells in the direction of tolerance. GLPG3970 may therefore also potentially decrease disease activity of pSS through induction of immunoregulatory mechanisms in addition to its anti-inflammatory properties. This is supported by nonclinical data obtained in various experimental models of autoimmune diseases. These data support the rationale for clinical evaluation of GLPG3970 in subjects with active pSS.

The use of a placebo arm in this type of design is widely regarded as the standard for testing the efficacy of new treatments. Subjects in the placebo arm can also be on stable SoC treatment since it is considered unethical to create a placebo group that will receive no treatment, if treatment is available.

5.4. Dosing Rationale

The dose of 400 mg q.d. GLPG3970, which was safe and well tolerated in healthy subjects, will be used in this study (see also Sections 2.1.3 and 5.5). [redacted]

5.5. Potential Risks and Benefits

GLPG3970 has been studied in a nonclinical setting (Section 2.1) in GLP studies in rat and dogs for a duration up to 13 weeks, and is being studied in a FIH study (Section 2.2) where the single ascending dose part has been completed up to the dose of 500 mg and the multiple ascending dose part up to 400 mg q.d. GLPG3970. Study GLPG3970-CL-207 is the first study where GLPG3970 is being administered to subjects with active pSS.

[redacted]

[redacted]

In the healthy volunteers part of study GLPG3970-CL-101, single doses of 10 to 500 mg GLPG3970 and repeated doses of 100 mg q.d., 250 mg q.d., 400 mg q.d. GLPG3970 administered for 14 days to healthy subjects were well tolerated. No death or SAE occurred during the study and no TEAEs led to study drug discontinuation. For more details refer to Section 2.2 and the latest version of the IB and its relevant updates/ addenda.

The most important potential risks based on in vitro and nonclinical studies, and the healthy volunteer part of study GLPG3970-CL-101 are: QT prolongation, hemato-lymphoid system toxicity, gastrointestinal toxicity, and risks related to fertility and pregnancy (see Section 2.1). Serious infections, including opportunistic infections and tuberculosis (TB) are also considered important potential risks based on the mechanism of action of the IP.

Specific for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections, risk minimization measures have been implemented in this protocol, in order to prevent recruitment of subjects with active infection and to allow prompt intervention, in case a subject is presenting with signs and symptoms of SARS-CoV-2 infection.

GLPG3970 has a novel dual mechanism of action, which is intended to restore the balance of the immune system by reducing several mediators of inflammation and by improving immune-regulatory mechanisms that may be impaired in autoimmune diseases such as, for example, pSS, RA, psoriatic arthritis, and inflammatory bowel disease. This may weaken the immune response and can potentially increase subject's vulnerability to develop infections (e.g. opportunistic infections, SARS-CoV-2, etc.). Careful monitoring and reporting of signs and symptoms is therefore required, to enable prompt medical evaluation and pharmacological or clinical intervention.

Immunomodulatory therapies may affect subjects' immune response to vaccines, including Covid-19 vaccines. Available evidence suggests that routine vaccination is effective with most degrees of disease-related immune dysfunction and associated therapies. However, in absence of specific data on Covid-19 vaccination, and without an agreed correlate of protection for SARS-CoV-2, non-live vaccines should be administered according to local regulations.

The population targeted in the study focuses on subjects with active pSS. The dual mechanism of action of GLPG3970 has the potential to reduce the expression of pro-inflammatory cytokines upregulated in pSS and to induce the expression of immunoregulatory cytokines, thus offering the possibility of restoring homeostasis of the immune system. Subjects in the study may or may not derive benefit from administration of GLPG3970.

Risk Mitigation

Mitigation measures have been taken to ensure safety of the subjects targeting population selection, dose, concomitant medications, and safety surveillance on certain laboratory parameters [redacted]. Information on important safety risks is included in the latest version of the IB.

In the forthcoming study, subjects' risk will be minimized by implementing conservative eligibility criteria, by standard laboratory tests, and by collecting TEAEs throughout the study. Any potential negative effects of GLPG3970 will be carefully assessed through regular physical assessments and laboratory monitoring that will happen at every visit. Laboratory alerts will be set up for the study in order to early inform the study investigator and the sponsor on highly abnormal laboratory values (severity Grade 3 and above). A Safety Monitoring Committee will monitor unblinded data.

- [redacted]
- The selection of the dose proposed for this study lies within the exposure safety limits, defined based on nonclinical safety and toxicity studies, and exposures previously shown to be safe and well tolerated in healthy male subjects.
- [redacted]

Subjects at risk of TB, human immunodeficiency virus (HIV) positive subjects, subjects testing positive for HBV or HCV, and subjects tested positive for SARS-CoV-2 are excluded from the study.

Given this study will be performed during a SARS-CoV-2 pandemic, appropriate measures should be taken to minimize the risk of SARS-CoV-2 infection for subjects participating in the study as well as study site personnel. Local guidelines to prevent SARS-CoV-2 infection should be adhered to and a leaflet will be made available for subjects detailing the SARS-CoV-2 safety measures to be taken.

In case a randomized subject is not able to attend a scheduled study visit on site due to SARS-CoV-2 travel restrictions, a phone call or a televisit may be conducted. It is strongly recommended to conduct planned study assessments for the applicable visit as per protocol as much as possible. If possible and if local regulations allow and the subject agrees, trained study staff or trained personnel are encouraged to collect study assessments at the study subject's home or a local facility if social distancing and hygiene rules can be applied.

Only staff trained in conducting the protocol planned assessments are authorized to perform home or local facility visit assessments and the alternative arrangements need to be adequately documented. Direct to Patient (DTP) shipments are possible, if needed. Subjects presenting with signs and symptoms of infection, including SARS-CoV-2 infection, should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and SARS-CoV-2 testing should be performed.

5.6. Estimands

ICH draft guidance E9(R1) *"Statistical Principles for Clinical Trials: Addendum: Estimands and Sensitivity Analysis in Clinical Trials"* specifies that a central question for drug development and licensing is to quantify treatment effects: how the outcome of treatment compares to what would have happened to the same subjects under different treatment conditions (e.g. had they not received the treatment or had they received a different treatment). Intercurrent events need to be considered in the description of a treatment effect on a variable of interest because both the value of the variable and the occurrence of the event may depend on treatment. The definition of a treatment effect, specified through an estimand, should consider whether values of the variable after an intercurrent event are relevant, as well as how to account for the (possibly treatment-related) occurrence or non-occurrence of the event itself. More formally, an estimand defines in detail what needs to be estimated to address a specific scientific question of interest. A description of an estimand includes 4 attributes.

Indicated in italic are the attributes in the GLPG3970-CL-207 study for the primary estimand:

1. The population, that is, the patients targeted by the scientific question:
   Patients with active pSS, defined through appropriate inclusion/exclusion criteria to reflect the targeted patient population for approval. Full Analysis Set (FAS), defined as all randomized subjects who have received at least 1 dose of IP.
2. The variable (or endpoint), to be obtained for each patient, that is required to address the scientific question:
   Change from baseline in ESSPRI score at Week 12.
3. The specification of how to account for intercurrent events to reflect the scientific question of interest:
   Early treatment discontinuation (any reason) is handled using the hypothetical strategy. Other intercurrent events (e.g. major protocol violations, intake of prohibited medication, lack of compliance) are handled using the treatment policy strategy (i.e. they are ignored).
4. The population-level summary for the variable which provides, as required, a basis for a comparison between treatment conditions:

Least square mean obtained using mixed model for repeated measurements (MMRM). For further details, see the study statistical analysis plan (SAP).

Together these attributes describe the primary estimand, defining the treatment effect of interest.

The design of the GLPG3970-CL-207 study targets this estimand as it is a randomized parallel-group study where every attempt is made to collect all measurements throughout the study.

Details on sensitivity analyses for the primary estimand or secondary estimands will be in the SAP.

6. CLINICAL STUDY POPULATION

6.1. Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Male or female subject between 18-74 years of age (extremes included), on the date of signing the ICF.
2. Documented diagnosis of pSS for <10 years prior to screening AND defined by the classification criteria >=4 described by the American College of Rheumatology - European League Against Rheumatism (ACR-EULAR) (10).
3. Subject has an ESSDAI score >= 5 assessed on 7 domains: constitutional, lymphadenopathy, glandular, articular, cutaneous, hematological, and biological.
4. Subject has an ESSPRI score >= 5.
5. Subject has stimulated whole salivary flow rate of >=0.1 mL/min.
6. Subject has positive serum titers of anti-SS-A/Ro and/or anti-SS-B/La antibodies.
7. Subjects already on treatment should be on stable SoC for at least 4 weeks prior to first IP dosing.
   The following SoC medications are permitted:
   - Corticosteroids <=7.5 mg/day (prednisone or equivalent); AND/OR
   - Non-steroidal anti-inflammatory drugs (NSAIDs); AND/OR
   - One single antimalarial at a stable dose (hydroxychloroquine <=400 mg/day; quinacrine 100 mg/kg/day, or chloroquine <=250 mg/day); AND/OR
   - One single immunosuppressant at a stable dose (methotrexate [MTX] <=10 mg/week or azathioprine [AZA] <=2 mg/kg/day); AND/OR
   - One single cholinergic stimulant at a stable dose (e.g. pilocarpine, cevimeline).
8. Subject must be able and willing to comply with the CSP requirements and must sign and date the ICF as approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), prior to any screening evaluations.
9. Subject must be able and willing to comply with restrictions on prior and concomitant medication (as described in Section 6.3.2).
10. Female subject of childbearing potential must have a negative highly sensitive (serum beta human chorionic gonadotropin or urine dipstick) pregnancy test.

11. Female subject of childbearing potential or male subject must agree to use highly effective contraception/preventive exposure measures (as described in Section 6.3.1).
12. Subject must have a body mass index (BMI) between 18-32 kg/m², inclusive.

13.1 Subject must be medically stable on the basis of physical examination, medical history, vital signs, 12-lead ECG, and clinical laboratory tests performed prior to first IP dosing. If there are abnormalities, they should be consistent with the underlying illness in the study population or considered not to be clinically significant in the opinion of the investigator.

6.2. Exclusion Criteria

Subjects meeting one or more of the following criteria cannot be selected for this clinical study:

1. Secondary Sjögren's syndrome according to the ACR-EULAR (2016) classification (10).
2. History or presence of unstable condition not related to Sjögren's Syndrome that, in the opinion of the investigator, could constitute an unacceptable risk when taking the IP or interfere with the interpretation of data.
3. Subject has any active systemic infection within 2 weeks prior to first IP dosing, or poorly controlled chronic cardiac, pulmonary, or renal disease.
4. Subject has a known or suspected history of or a current immunosuppressive condition, or a history of opportunistic infections (e.g. HIV infection, histoplasmosis, listeriosis, coccidiodmycosis, pneumocystosis, aspergillosis).
5. Subject has a chronic hepatitis B virus (HBV) infection, as defined by persistent HBV surface antigen (HBsAg) positivity. Subject has hepatitis C virus (HCV) infection, as defined by positive HCV antibody at screening and detectable HCV viremia. Subjects with positive HCV antibody must undergo reflex HCV ribonucleic acid (RNA) testing, and subjects with HCV RNA positivity will be excluded. Subjects with positive HCV antibody and negative HCV RNA are eligible.

6.1 Subject testing positive for SARS-CoV-2 infection as detected at screening based on real time polymerase chain reaction (RT-PCR) or at baseline based on immunoglobulin M (IgM) immunoassay, or subjects who have been in contact with SARS-CoV-2 infected individuals in the 2 weeks prior to first dosing of IP. Subjects presenting any signs or symptoms of SARS-CoV-2 infection, as detected prior to first IP dosing following careful physical examination (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, etc.) (11,12). In addition, any other locally applicable standard diagnostic criteria may also apply to rule out SARS-CoV-2 infection.

7.3 Subject has taken any disallowed therapies.

- Mycophenolate mofetil (MMF) within a week prior to screening.
- Cyclosporine/Tacrolimus within a week prior to screening.
- Cyclophosphamide within 6 months prior to screening.
- Ocular medicines (e.g. topical cyclosporine, topical NSAIDs/corticosteroids) for at least 4 weeks prior to screening, except for a sporadic use.
- Biologics such as, but not limited to, rituximab, abatacept, and any other unapproved biologic within 6 months prior to screening.
- Plasmapheresis within 12 weeks prior to screening.

- Plasma exchange within 12 weeks prior to screening.
- Intravenous immunoglobulin (IVIG) therapy within 24 weeks prior to screening.
- Other prohibited medications within 2 weeks or 5 half-lives, whichever is longer, prior to first IP dosing, as listed in Section 6.3.2.

8.1 Concurrent use of anticholinergic agents or any other medication known to cause dry mouth/dry eyes that, in the opinion of the investigator, are a contributing factor to the subject's dryness and/or use of anticholinergic agents not contributing to this dryness, if not stable for at least 4 weeks prior to screening (see Section 6.3.2).

9. Subject has a history of TB diagnosis or evidence of active or latent infection with *Mycobacterium tuberculosis*.
   - Positive QuantiFERON-TB Gold test result at screening, AND/OR
   - Chest radiograph (posterior anterior view) taken within 12 weeks prior to screening, read by a qualified radiologist or pulmonologist, with evidence of current active TB or inactive TB.
10. Investigator or other study staff or relative thereof who is directly involved in the conduct of the study.
11. Subject has any condition or circumstances that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures and requirements (e.g. active alcohol or drug abuse).
12. Subject has a known hypersensitivity to IP ingredients or history of a significant allergic reaction to IP ingredients as determined by the investigator.
13. Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (e.g. compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.

14.2 Subject has presence or sequelae of gastrointestinal, liver, kidney (creatinine clearance <60 mL/minute, using the Cockcroft-Gault formula: if calculated result is <60 mL/minute, a 24-hour urine collection can be done), or other conditions known to interfere with the absorption, distribution, metabolism, or excretion of drugs.

15. Subject has a history of lymphoma or any malignancy within the past 5 years prior to screening with the exception of excised and curatively treated non-metastatic basal cell carcinoma or squamous cell carcinoma of the skin or carcinoma in situ of cervix which is considered cured with minimal risk of recurrence.
16. Subject concurrently participates or participated in a drug, drug/device, or biologic investigational research study within 3 months or 5 half-lives of the IP, whichever is longer, prior to the first dose.

17.2 Subject has a history or presence of cardiopathy, or clinically significant abnormalities detected on 12-lead ECG of either rhythm or conduction e.g. repeated demonstration of a QTcF >450 ms detected on the 12-lead ECG or a history of additional risk factors for TdP (e.g. heart failure, family history of long QT syndrome, hypokalemia and other electrolyte disorders). A first-degree atrioventricular block will not be considered as a significant abnormality.

18. History of organ or bone marrow transplant.
19. Female subject is pregnant or breast feeding or intending to become pregnant or breastfeed during the study.

20.1 Subject was vaccinated with a live attenuated vaccine within 60 days prior to screening.
21.1 Subject has severe organ manifestation or life-threatening condition, or has planned a surgery during the study.
22.2 Subject has any of the following laboratory abnormalities:

- aspartate aminotransferase (AST) >2 times the upper limit of normal (ULN)
- alanine aminotransferase (ALT) >2 times the ULN
- total bilirubin >2 times the ULN
- prothrombin time or partial thromboplastin time > ULN.
- serum potassium concentration <3.5 mmol/L

23. Subject is institutionalized by virtue of an order issued by either the judicial or the administrative authorities or has a dependency on the sponsor or investigator.

6.3. Prohibition and Restrictions

6.3.1. Precautions for Sexual Intercourse

Highly effective contraceptive measures for both males and females of childbearing potential must be documented in the source documents.

6.3.1.1. Female Subjects

Female subjects are considered of non-childbearing potential if they meet one of the following criteria:

– No menses for 12 or more months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.
– Permanently surgically sterile (bilateral oophorectomy, i.e. surgical removal of ovaries, bilateral salpingectomy, or hysterectomy, i.e. surgical removal of uterus).

All other female subjects are considered to be of childbearing potential (WOCBP) and must use one of the following highly effective methods of birth control prior to the first dose of IP, during the clinical study and for at least 35 days after the last dose of IP:

– Combined (estrogen and progesterone containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation plus a barrier method.
– Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation plus a barrier method.
– Intrauterine device.
– Intrauterine hormone-releasing system.
– Bilateral tubal occlusion.

- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

Periodic abstinence (e.g. calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only, and lactational amenorrhea method are not acceptable as methods of contraception.

In case a WOCBP has a vasectomized partner, provided that partner is the sole sexual partner of the WOCBP clinical study participant and that the vasectomized partner has received medical assessment of the surgical success, then she is not required to use an additional form of contraception.

Within these limits, the specific forms of contraception employed are left to the discretion of the subject, the investigator, and/or the subject's physician.

The safety of GLPG3970 during breastfeeding is unknown. Nursing women are not allowed to take part in this clinical study.

6.3.1.2. Male Subjects

Non-vasectomized male subjects with female partners of childbearing potential must be willing to use a condom from the time of the first dose of IP, during the clinical study, and for at least 7 days after the last dose of IP, in addition to having their female partner use one of the following forms of contraception:

- Intrauterine device.
- Intrauterine hormone-releasing system.
- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
- Progesterone-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable).

Sexual abstinence defined as refraining from heterosexual intercourse is considered a highly effective contraceptive measure only if it is the preferred and usual lifestyle of the subject. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study.

Periodic abstinence (e.g. calendar, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a clinical study, withdrawal, spermicides only, and lactational amenorrhea method are not acceptable methods of contraception.

In a case where the female partner of a male subject has undergone documented surgical sterilization that was performed more than 1 year before screening, then the subject is not required to use an additional form of contraception.

Vasectomized male subjects with female partners of childbearing potential are not required to use an additional form of contraception providing that surgical sterilization has been successful (documented azoospermia by semen analysis).

No sperm donation is allowed from the first dose of IP during the clinical study until 7 days after the last dose of IP.

6.3.2. Prior and Concomitant Medications

Prior and concomitant therapies taken for long-term treatment of pre-existing conditions are allowed, provided they are in accordance with the inclusion and exclusion criteria (see Section 6.1 and Section 6.2, respectively) and with the prohibitions and restrictions listed below.

In case additional concomitant medications need to be administered or dose adjustments for pre-existing conditions (except for active pSS) are needed during the study, the risk/benefit to the subject should be carefully assessed by the sponsor's medical leader and consideration given to the timing of any necessary introduction of new medications.

If during the study, the subject's condition necessitates the use of prohibited medication, the use of IP may be interrupted, preferably after consultation with the sponsor's medical leader. Re-introduction of IP can be considered after the treatment course with the prohibited medication has been stopped, and after consultation with the sponsor's medical leader.

During the study, subjects will be instructed to record any change in concomitant medication in a diary (see Section 8.8.6).

Permitted Medications

Permitted medications at screening and during the study include:

- Subjects already on treatment should be on stable SoC for at least 4 weeks prior to first IP dosing.
  The following medications are permitted:
  - Corticosteroids, at a dose of <=7.5 mg/day prednisone or equivalent (see Appendix 1 for prednisone conversion table); AND/OR
  - NSAIDs; AND/OR
  - One single antimalarial at a stable dose (hydroxychloroquine <=400 mg/day, quinacrine 100 mg/kg/day, or chloroquine <=250 mg/day); AND/OR
  - One single immunosuppressant at a stable dose (MTX <=10 mg/week or AZA <=2mg/kg/day); AND/OR
  - One single cholinergic stimulant at a stable dose (e.g. pilocarpine, cevimeline).
- Analgesics, other than NSAIDs, up to the maximum recommended doses may be used for pain if required.
- Medications prescribed for the treatment of comorbidities and which are not described as prohibited medications.

All doses should remain as stable as possible until the end of the study.

Rescue Medication

Rescue medication that is permitted for the treatment of acute episodes during the study include:

- In case of symptoms worsening, increase of disease activity or acute episodes, subjects and/or investigators will have the ability to treat accordingly in order to maintain the clinical integrity of the patients.
- The dosage of corticosteroids can be increased to 10 mg/day for 3 days and must be decreased to the previous dose (<=7.5 mg/day) within 7 days.

Prohibited Medications

Prohibited medications during the study include:

- MMF within a week prior to screening.
- Cyclosporine/Tacrolimus within a week prior to screening.
- Ocular medicines (e.g. topical cyclosporine, topical NSAIDs/corticosteroids) for at least 4 weeks prior to screening, except for a sporadic use defined as a course of 7 days and no more than 2 courses during the study administered 2 weeks apart.
- Cyclophosphamide within 6 months prior to screening.
- Biologics such as, but not limited to rituximab, abatacept, and any other unapproved biologic within 6 months prior to screening.
- Any other investigational medication within 3 months or 5 half-lives of the IP, whichever is longer, prior to first IP dosing.
- Anticholinergic agents or any other medication known to cause dry mouth/dry eyes that, in the opinion of the investigator, are a contributing factor to the subject's dryness. All medications that in the opinion of the investigator are not a major factor in causing dry mouth/dry eyes can be used but must be stable for at least 4 weeks prior to first IP dosing and kept stable during the course of the study.

Other Prohibited Medications and Dietary/Herbal Products:

The following medications should be discontinued at least 2 weeks or 5 half-lives of the drug, whichever is longer, prior to first IP dosing and throughout the study.

- [redacted]

[redacted]

Additional Guidance for the Use of Concomitant Medication:

[redacted]

- [redacted]

The lists provided in Appendix 2 through Appendix 6 are non-exhaustive.

In case of questions on concomitant medications, the contract research organization (CRO)'s medical monitor (as per study contact list) and sponsor's medical leader can be contacted.

Vaccines

Live attenuated vaccines (including live attenuated Covid-19 vaccines) are prohibited in this study from 60 days prior to screening until 6 weeks after last GLPG3970 administration. Routine household contact with persons vaccinated with live vaccine components should also be avoided.

Non-live vaccines (including any non-live Covid-19 vaccines) can be administered according to local vaccination standards whenever medically appropriate. Any vaccination administration during the study should be recorded in the eCRF as a concomitant medication; all vaccine information should be collected, including brand name, manufacturer (and lot number if available) as well as administration dates. Covid-19 vaccination status should also be recorded.

6.3.3. Food and Beverage Restrictions

During the treatment and FU period, subjects must come for the study visits in the morning. At Visit 1, 4, and 5, subjects need to come for the study visits in a fasting state (no food intake for at least 8 hours) as specified in the Schedule of Activities in Section 8.11.

At Visit 1 (Day 1), the IP will be administered in a fasted state. Breakfast will be provided to the subject 0.5-1 hour after the IP intake. Lunch should be eaten 1 hour before or after the ECG measurement at 4.5 hours postdose.

At all other dosing days (including Visit 2, 3, 4, and 5), the IP should be taken in a fed state (together with a meal). Subjects will refrain from the consumption of [redacted] beginning 48 hours prior to administration of the initial dose of IP, throughout the study until 7 days after the last IP administration.

6.3.4. Other Prohibitions and Restrictions

Intravenous immunoglobulin (IVIG) therapy will not be allowed within 24 weeks prior to screening.

6.4. Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal and Study Termination

A subject may be withdrawn from the clinical study at any time without the subject's consent if the investigator or sponsor determines that it is not in the best interest of the subject to continue

participation. In such case, the reason for withdrawal will be documented in the source documents, and the subject will be asked to complete the early discontinuation (ED) visit, and FU visit(s) for safety assessments.

Treatment with IP must be discontinued by the investigator (who may consult the sponsor's medical leader) for any of the following conditions:

- Life-threatening adverse event (AE) or a serious adverse event (SAE) that places the subject at immediate risk.
- Serious infections deemed related to study treatment by the investigator, and requiring parenteral antimicrobial therapy and/or hospitalization.
- Confirmed pregnancy or lactation.
- Subjects not meeting all inclusion criteria (e.g. ESSDAI score >=5; see also Section 6.1) and/or subjects meeting 1 of the exclusion criteria (e.g. creatinine clearance <60 mL/minute using Cockcroft-Gault formula; see also Section 6.2), as determined by the central laboratory results of Visit 1 (Day 1). Before discontinuing treatment with IP based on the Visit 1 (Day 1) central laboratory results, the sponsor's medical leader should be consulted.
- Subjects presenting with signs and symptoms of SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and report an AE/SAE as applicable. In case of suspected SARS-CoV-2 infection RT-PCR and serology tests should be performed to confirm the infection. The investigator, preferably after consultation with the sponsor's medical responsible, must discontinue the subject from the study. The subject could be tested for SARS-CoV-2 in facilities outside the study site and if so, the subject should be instructed to immediately inform the study investigator if the test is positive and test results should be shared with the investigator as soon as possible.
- Arrhythmia or conduction abnormality, including but not limited to prolonged QTcF, where the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (QTc >500 ms and/or 60 ms over baseline on at least 2 separate ECGs 5 minutes apart) or clinically significant arrhythmia of any grade.
- Liver enzyme increase (see also Appendix 15)
  - AST and/or ALT >=8x the ULN.
  - AST and/or ALT elevations >=3x ULN with signs of liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin >=2.0x ULN or international normalized ratio [INR] >1.5).
  - In addition, a dose interruption or reduction (if applicable) should be considered if AST and/or ALT >=3x ULN and <5x ULN and dosing with IP should be interrupted if AST and/or ALT >=5 and <8x ULN.

  For subjects having:
  - AST or ALT >=8xULN.
  - AST or ALT >=3xULN with signs of liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or

eosinophilia [>5%], and/or total bilirubin >=1.5xULN or INR >1.5). These cases should be reported as SAEs.

the following steps will need to be performed by the investigator:

- The site should immediately contact the subject and require the subject to discontinue IP immediately. The subject should be asked to return to the site within a 48-hour window from awareness of the result.
- A full evaluation of various causes of hepatitis should be conducted (i.e. infectious, alcohol, medications, anatomical).
- An assessment of other concomitant medications and SoC should be made. The investigator should consider to whether it is in the best interest of the subject to stop/interrupt concomitant medications and SoC treatment.
- A detailed history including relevant information on alcohol use, recreational drug use, supplement consumption, any herbal remedies, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, occupational history, blood transfusion, history of liver or allergic disease, and any other potential causes attributable to a liver insult should be collected.
- A detailed assessment of the subject's clinical condition and repeat laboratory tests for liver function test (LFT), including albumin, creatine kinase, total bilirubin (direct and indirect), gamma-glutamyl transferase (GGT), INR, and alkaline phosphatase should be done.
- Further testing for hepatitis A, B, and C, and for autoimmune hepatitis should be done. Other causes of viral hepatitis (cytomegalovirus or Epstein-Barr virus, etc) should be excluded. Liver imaging should be considered.
- Referral to a hepatologist or gastroenterologist should be requested.

Every effort should be made to keep subjects in the study and on treatment. However, the investigator, who may consult the sponsor's medical leader, can consider stopping the study treatment in case of concerns about the subject's safety, serious or severe AEs or worsening of the disease condition, which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study (e.g. rescue medication).

When study treatment is discontinued, the subject will be requested to complete the assessments of the ED visit and to return for the FU visit. Reason for discontinuation must be documented in the case report form (CRF).

Subjects will be informed prior to clinical study entry that they are allowed to withdraw from the clinical study. At any time and for any reason, a subject's participation in the clinical study may terminate at their request, without prejudice to their future medical care. The subject will be encouraged to share the reason(s) for withdrawal so this can be documented in the source documents, and to complete the ED visit and FU visit for safety assessments, but will not be obliged to do so.

Subjects who withdraw from the clinical study without contact with the site (lost-to-FU) should be contacted by the site so that their health status can be assessed and documented in the source documents. The site should make every effort to understand whether the subject is alive, including checking the medical records and contacting general practitioner or relatives, if necessary. All attempts must be documented in the source documents.

The sponsor has the right to terminate the clinical study at any time and for any reason.

The sponsor and/or investigator will discontinue the study if:

- Judged necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and ICH-GCP.

- IEC/IRB and/or RA approval or favorable opinion is withdrawn, revoked, or suspended.

In the event of study termination, the investigators and relevant authorities will be informed of the reason for clinical study termination. Please also see for reference Section 12.1.2 “Clinical Study Closure Considerations”.

6.5. Measures to Minimize Bias

6.5.1. Randomization

At screening, subjects will be assigned a subject identification number. When a subject is confirmed to be eligible for the clinical study, the subject will be randomized. Allocation of each subject to a given treatment will be done using a centralized electronic system (interactive web response system [IWRS]). Subjects will be randomized in a 2:1 ratio to GLPG3970 or placebo.

6.5.2. Blinding and Unblinding

This is a randomized, double-blind clinical study. The subjects and the entire clinical study team, including the investigators, clinical study coordinators, and sponsor personnel, except for the Safety Monitoring Committee, are blinded to treatment assignment.

Blinded and packaged medication will be provided to the site. All IP formulations will be identical in appearance, shape, smell and taste, and will be packaged in the proper proportion to assure desired dosages and maintenance of the blinding.

The blind can be broken only if the investigator deems it necessary for the safety of a subject. The investigator is encouraged to discuss considerations to break the blind with the medical leader of the study, whenever possible and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he or she feels rapid emergency unblinding is necessary, but is required to inform the sponsor in within 24 hours after unblinding has occurred.

The blind can be broken by the investigator via IWRS.

If the blind is broken for any reason during the course of the clinical study, the moment on which the blind was broken, and all other relevant information will be documented by the site. The reason for breaking the blind will be indicated and justified in the source documentation.

If an AE leads to unblinding, the AE will be given as the reason for unblinding. All subjects who are unblinded should, where possible, complete the FU visit assessments 28±3 days after last IP dosing. Any AEs will be followed until resolution.

The code-break information (via IWRS vendor) will be provided to the bioanalytical laboratory responsible for PK sample analysis, the sponsor person responsible for providing unblinded data to the Safety Monitoring Committee, the CRO responsible for the population PK (pop-PK) [redacted], and to the pharmacovigilance vendor for SAE reporting purposes.

7. INVESTIGATIONAL PRODUCTS

7.1. Identity of the Investigational Products

GLPG3970 will be supplied to the pharmacist of the study site or to the hospital pharmacy, by and under the responsibility of the sponsor, who will also provide the investigator and pharmacist (or appropriate qualified member of the clinical study staff) with appropriate certificates of analytical conformity and European Union (EU) Qualified Person release documents.

Matching placebo tablets will also be provided.

For more details on the composition of the IP refer to the latest version of the IB and its relevant updates/addenda.

7.2. Dosage and Administration

GLPG3970 will be provided as a film-coated tablet containing 200 mg of the active pharmaceutical ingredient G1567970 (G1567970 is the compound code for GLPG3970). A dose of 400 mg (2 x 200 mg tablets) q.d. will be taken orally.

At all dosing days, the IP needs to be taken q.d. at approximately the same time every morning in a fed state (together with a meal), except at Visit 1 (Day 1) when the IP will be taken in a fasted state. At Visit 1 (Day 1), breakfast will be provided to the subject 0.5-1 hour after the IP intake and lunch should be eaten 1 hour before or after the ECG measurement at 4.5 hours postdose. Subjects will be instructed to swallow the tablets of GLPG3970 or placebo as a whole with a glass of water and to not chew the drug prior to swallowing. At Visit 1 (Day 1), IP will be administered on site after predose assessments have been completed. At Visit 2, 3, 4, and 5, subjects also need to take their IP on site.

Subjects will receive tablets to take home. Instructions for dosing and storage are incorporated in the IP labels.

If a subject misses a dose (e.g. because he/she forgot to take the medication), he/she should take the missed dose within 12 hours after the planned intake time. If IP is not taken within 12 hours

after the planned time, the missed dose should be skipped. For each dose taken at home, the time, date, and number of tablets taken should be recorded in the subject's diary card.

7.3. Packaging, Labeling and Distribution

IP packages will be labeled with clinical study-specific details, including storage conditions.

All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

Each medication kit will be identified with a unique kit number. Multiple kits can be provided to a subject at each visit, providing the subject with sufficient IP to cover the period until the next scheduled visit.

The distribution of IP to the site will only occur after the required local documentation is obtained, including clinical study approval by regulatory authorities and the IECs/IRBs, documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae), and the signed and dated study agreement and financial agreement.

In case of SARS-CoV-2 travel restrictions, to ensure study subjects maintain dosing per protocol requirements during this study, special delivery services through DTP shipments of IP to the subject can be implemented. DTP should only be used in case of emergency where on site IP dispensation is not possible, and if allowed per local regulations. Local guidelines must be followed and regulatory approval or notification to authorities may be required. Agreement of the subject to receive IP at home is required prior to the shipment of IP to the subject's home. The DTP process used will be reviewed and approved by the sponsor. In case the DTP shipments originates from the investigational site, they will be coordinated by the investigational site(s) in collaboration with the local CRO without the involvement of the sponsor, to ensure clinical study integrity.

7.4. Storage

Sites are to store IP supplies in a secure area until dispensed. GLPG3970 200 mg tablets and matching placebo tablets should be stored at room temperature (below 30 °C), should not be refrigerated or frozen and should be protected from light and stored in the original packaging.

Sites will be required to monitor the storage temperature by using at least a min-max temperature-recording device and to keep a minimum to maximum temperature log, which must be completed each working day in order to establish a record of compliance with these storage conditions. The investigator will instruct subjects on how the IP should be stored at home. Storage conditions to be taken into account by the subject when taking IP home, are described in the patient leaflet.

7.5. Treatment Compliance and Drug Accountability

The investigator should discuss treatment compliance with the subject prior to the start of the study. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be

made to ensure the proper subject dose. Subjects with poor compliance will be retrained by the site. IP administration as indicated by the subject (amounts as well as periods) will be recorded on the CRF.

The pharmacist or designated clinical study staff will maintain documentation of the total amount of IP received at the site, amount dispensed to the subject, and the amount of IP returned by the subject to the site. IP supplies for each subject will be inventoried and accounted for throughout the clinical study. At the end of the treatment period, these records will be checked against the inventory by the study monitor. All clinical supplies will be stored in locked and access controlled facilities. Subjects will record IP administration at home in a subject diary.

Subjects will return any unused IP and empty IP packages at each study visit and/or ED visit. Upon sponsor approval, all unused IP and used and/or empty IP packages are to be returned from the sites and/or any vendor involved in the clinical study supplies management activities to the agreed location (depot), if possible. All returns and destructions must be properly documented.

8. CLINICAL STUDY ASSESSMENTS

Every effort should be made to ensure that CSP-required tests and procedures are completed as described in the Schedule of Activities (see Section 8.11). To avoid inter-observer variability, every effort should be made to ensure that all safety and efficacy evaluations are completed by the same individual who made the initial baseline determinations. In case study assessments are not performed for reasons related to SARS-CoV-2 pandemic restrictions, this should be documented in the medical records and CRF.

In case a randomized subject is not able to attend a scheduled study visit on site because of SARS-CoV-2 travel restrictions, a phone call or a televisit may be conducted. It is strongly recommended to conduct planned study assessments for the applicable visit as per protocol as much as possible. If possible and if local regulations allow and the subject agrees, trained study staff or trained personnel are encouraged to collect study assessments at the study subject's home or a local facility if social distancing and hygiene rules can be applied.

Only staff trained in conducting the protocol planned assessments are authorized to perform home or local facility visit assessments and the alternative arrangements need to be adequately documented. Subjects presenting with signs and symptoms of infection, including SARS-CoV-2 infection should immediately contact the site investigator, who should inform the sponsor's medical responsible as soon as possible, and SARS-CoV-2 testing should be performed.

8.1. Timing of Assessments

The study assessments described below will be performed at time points as specified in the Schedule of Activities in Section 8.11. At Visit 1, 4, and 5, subjects need to come for the study visits in a fasting state (no food intake for at least 8 hours).

ICF needs to be signed before any study procedure, including screening procedure, is carried out.

The sequence of study assessments during the treatment period(s) will preferably be as follows when planned at the same time point:

1. Patient Questionnaires (ESSPRI, [redacted]
2. Investigator Questionnaires (ESSDAI, [redacted]
3. 12-Lead ECG
4. Vital signs
5. Blood sampling for clinical laboratory assessments and PK
6. [redacted]
7. [redacted]
8. [redacted]

The following collection time windows apply:

- Vital signs and physical examinations: predose.
- 12-Lead ECGs (see also Section 8.5.5):
  - Visit 1: 1 triplicate ECG predose and at 4.5 hours postdose
  - Visit 1: 1 single ECG at 1.5 hours postdose and at 3 hours postdose
  - Other visits: single ECGs, see Schedule of Activities in Section 8.11
- Blood and urine sampling for clinical laboratory safety: any time predose, on the same visit day.
- Blood sampling for PK determination of GLPG3970:
  - Visit 1: within 30 minutes predose, 1 sample within [0.5-1.5 hours postdose], 1 sample within [2-2.5 hours postdose], and 1 sample at 4.5 hours postdose, immediately after the triplicate ECG
  - Visit 2, 3, and 5: within 30 minutes predose
  - Visit 4: within 30 minutes predose, 1 sample within [0.5-1.5 hours postdose], and 1 sample within [2-2.5 hours postdose]. If the postdose samples could not be collected at Visit 4, they should be collected at Visit 5. It is important that the PK [redacted] samples are collected on the same day.
- [redacted]

8.1.1. Retesting During Screening

During the screening period, 1 retest of the following assessments is allowed:

- For resting heart rate (after at least 5 min supine position) and blood pressure.
- For QuantiFERON –TB Gold test with indeterminate result (the subject is not eligible if retest result is indeterminate or positive).
- During screening or later during the study, retesting (resampling) of clinical laboratory safety tests or SARS-CoV-2 RT-PCR tests is allowed once and only for technical or transport reasons (e.g. sample hemolyzed, out of stability, late arrival at laboratory impacting sample quality, loss, or destruction of the sample before analysis).

8.1.2. Rescreening of Subjects

If a subject is a screening failure, it is allowed to rescreen the subject once, if the reason for failure is temporary and expected to resolve, as judged by the investigator. When a subject is rescreened, the subject needs to be reconsented and all screening assessments need to be repeated. The subject will be assigned a new subject number. The time in between 2 screening attempts could vary depending on the screening failure reason.

The following data will be collected for screening failure subjects: ICF signed data, demographics, failed inclusion or exclusion criteria, and AEs.

8.2. Unscheduled Visits

Additional visits can be performed at other time points for any safety assessments, if clinically indicated. These unscheduled visits and outcomes of additional assessments need to be recorded in the source and, if it is a CSP-specified assessment performed before the subject's last visit per CSP, also in the CRF.

8.3. Subject and Disease Characteristics

Subjects will be asked to attend the site for a screening assessment. After giving written informed consent, demographic data (year of birth, age, sex, ethnicity, and race) will be collected and a medical history will be taken, including pSS disease history. pSS disease history will capture at least the duration of disease, clinical symptoms, and medication used to treat the disease. A physical examination will be performed, including measurement of weight and height. The subject's diagnosis of active pSS will be confirmed based on the pSS classification criteria described by the ACR-EULAR(10).

Vital signs (systolic and diastolic blood pressure, heart rate, oral/tympanic body temperature, the same method of measuring body temperature to be used throughout the study) will be measured and a 12-lead ECG will be recorded. Subjects should rest for at least 5 minutes in the supine position before the ECG recording, blood pressure, and heart rate measurement.

The inclusion and exclusion criteria will be checked to assess eligibility for the study based on the screening assessments. At Visit 1 (Day 1), it is the responsibility of the investigator to confirm that each subject remains eligible for the study, based on the available data (including data from Visit 1 [Day 1]), before randomization and first IP dosing.

8.4. Efficacy Assessments

8.4.1. EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) Score

The ESSDAI is a systemic disease activity index to assess 12 domains (i.e. organ systems: constitutional, lymphadenopathy, glandular, articular, cutaneous, pulmonary, renal, muscular, peripheral nervous system, CNS, hematological, biological) in patients with pSS, where each of the domains is divided into 3-4 levels of activity. These scores are summed across the 12 domains in a weighted manner to provide the total score (range 0-123). A clinically meaningful reduction from baseline (>=3 points) indicates the improvement of symptoms. (Appendix 7) (13).

8.4.2. EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) Score

The ESSPRI is a patient self-reported outcome measure to assess dryness, limb pain, fatigue, and mental fatigue, where each of the domains normally reported as 0 (not at all) to 10 (extremely severe). The final ESSPRI score is the average of 3: dryness, pain, and fatigue. A clinically significant reduction from baseline (at least 1 point or 15% of the baseline value) indicates the improvement of symptoms. (Appendix 8) (13).

[redacted]

8.4.4. [redacted]

[redacted]

8.4.4.1. [redacted]

[redacted]

8.4.4.2. [redacted]

[redacted]

8.4.4.3. [redacted]

[redacted]

8.5. Safety Assessments

This section describes methods and timing for all safety assessments and recording. Additional assessments (e.g. unscheduled clinical laboratory tests or extra vital signs recordings) are allowed to ensure appropriate collection of safety data and to assess any perceived safety concerns.

8.5.1. Adverse Events

The AEs reporting period for safety surveillance begins when the subject signs the ICF and ends at his/her last FU visit. Investigators are not obliged to actively seek SAEs after the CSP-defined FU period. However, if the investigator is informed about an SAE that occurs at any time after

the subject's post-treatment FU visit and the event is deemed related to the use of IP, they should promptly document and report the event to the sponsor by using the SAE form.

Detailed definitions, reporting period, ratings and reporting requirements for AEs and SAEs are found in Section 11.

8.5.2. Clinical Laboratory Evaluations

The following clinical laboratory safety tests will be performed:

- **Hematology:**
  Hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, hemoglobin, red blood cell (RBC) count, white blood cell count, white blood cell differential count (absolute and relative), RBC differential count/ morphology (if indicated), and platelets.
- **Coagulation:**
  INR, activated partial thromboplastin time, and prothrombin time.
- **Clinical chemistry:**
  Glucose, fasted glucose, fasted insulin, hemoglobin A1c, urea, creatinine, bicarbonate, uric acid, sodium, potassium, calcium (total), reflex calcium (free/ionized only if serum calcium total is elevated), chloride, phosphorus/phosphate, AST, ALT, GGT, total bilirubin, alkaline phosphatase, alkaline phosphatase bone fraction (if total alkaline phosphatase elevated), creatinine phosphokinase, total immunoglobulin (Ig) levels, lactate dehydrogenase, albumin, total proteins, triglycerides, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), HDL/LDL ratio, high sensitivity C-reactive protein (hsCRP), lipase, and amylase.
  Homeostatic model assessment of insulin resistance (HOMA-IR) and HDL/LDL ratio will be derived from clinical chemistry parameters. An estimate of the creatinine CL based on the serum creatinine level will be calculated.
- **Urinalysis:**
  Dipstick: pH, glucose, proteins, blood, leukocytes, ketones, calcium, phosphate, and creatinine.
  Microscopic examination of the sediment for cellular elements (cylinders, erythrocytes, leukocytes), if indicated.
- **Serology/blood:**
  HBsAg (if positive, confirmed by HBV deoxyribonucleic acid [DNA] polymerase chain reaction [PCR]), HCV antibody (if positive, confirmed by reflex HCV RNA), and HIV 1 and 2 antibodies at screening. Positive hepatitis and HIV results should be reported by the investigator as required by local law.
  FSH test for females at screening to confirm menopause, if applicable.
- **Pregnancy test for females:**
  Serum beta human chorionic gonadotropin at screening (all females), urine pregnancy test (UPT) and urine dipstick (WOCBP only) at Visit 1 (Day 1 predose), at Visit 2 (Day 8 predose), at Visit 3 (Day 29 predose), Visit 4 (Day 57 predose), and at Visit 5 (Day 85 predose).

- **QuantiFERON-TB Gold test** to check for latent or active TB (at screening). TB results should be reported by the investigator as required by local law.
- **SARS-CoV-2:**
  IgM Immunoassay.
  RT-PCR from a nasal swab sample to check for SARS-CoV-2 infection at screening and RT-PCR from a nasal swab sample and serology testing at baseline, and throughout the study as needed (when SARS-CoV-2 symptoms present). The repeat RT-PCR may be performed 2-3 days prior to the baseline visit to allow for results availability prior to randomization. Positive SARS-CoV-2 results should be reported by the investigator as required by local law.

The clinical laboratory evaluations will be performed at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Reference ranges will be supplied by the central laboratory. Clinical laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Only laboratory test abnormalities judged as clinically significant by the principal investigator should be recorded as AEs. At the discretion of the investigator, when following up AEs, additional laboratory parameters may be tested, and additional samples taken.

Blood and urine sample handling and shipment instructions will be provided in a separate laboratory manual.

8.5.3. Physical Examination

Physical examinations, including weight and height (at screening), will be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). The person conducting the physical examination will document this in the subject's medical source records. Clinically significant abnormal findings should be recorded as AEs.

Particular attention should go to physical examination at all visits, to identify any potential SARS-CoV-2 related signs and symptoms, indicating potential infection (e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, etc). Subjects presenting such symptoms at screening/baseline should not be included/randomized in the study (see Section 6.2). Developing such symptoms during the study, should be managed as per Section 8.5.6.

8.5.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, heart rate, and oral/tympanic body temperature, the same method of measuring body temperature to be used throughout the study) will be recorded in a standardized manner (i.e. after the subject has rested in a supine position for at least 5 minutes) at visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Clinically significant abnormal values should be recorded as AEs.

8.5.5. 12-lead Electrocardiogram

At the time points specified in the Schedule of Activities (see Section 8.11 and also Section 8.1, "Timing of Assessments"), a 12-lead ECG will be recorded and results will be sent for central reading.

12-lead ECG recordings will be performed before blood sampling and after subjects rested for at least 5 minutes in supine position. In case an indwelling catheter is used, ECGs may be recorded after blood sampling, provided that there is at least 30 minutes between catheter insertion and the ECG recording. When catheter insertion would fail, the 12-lead ECG needs to be taken before the venipuncture and at least 30 minutes after the failed attempt. Triplicate ECGs (i.e. 3 ECGs) will be performed at Visit 1 (Day 1) predose and at 4.5 hours postdose, within a time span of 6 minutes, with an approximate 3-minute interval between ECGs. At all other timepoints, single ECGs will be taken.

The following parameters need to be recorded: heart rate, PR interval, RR interval, QRS interval, uncorrected QT interval, morphology, and rhythm analysis. QTcF will be derived. QTcF will be considered as normal if <=450 ms, while a prolongation of QTcF to >500 ms and/or an increase from baseline >60 ms will be considered a threshold of concern.

Immediately after recording, the ECGs will be reviewed by the investigator to detect clinically significant abnormalities. This immediate review during the visit needs to be documented in the subject's source. After receipt of the central report, also all flagged ECG abnormalities need to be assessed by the investigator on clinical relevance. Clinically significant abnormal findings should be recorded as AEs.

8.5.6. Other Safety Assessments

SARS-CoV-2 infection will be assessed at screening by RT-PCR and at baseline through careful physical examination to exclude any potential signs and symptoms of infection, e.g. cough, fever, headaches, fatigue, dyspnea, myalgia, anosmia, dysgeusia, anorexia, sore throat, etc.

Additional RT-PCR and serology testing will be repeated at baseline and throughout the study as needed. The repeat RT-PCR may be performed 2-3 days prior to the baseline visit to allow for results availability prior to randomization. The subject could be tested for SARS-CoV-2 in facilities outside the study site and if so, the subject should be instructed to immediately inform the study investigator if the test is positive and test results should be shared with the investigator as soon as possible.

8.6. Pharmacokinetic Assessments

Blood samples (2 mL) for the PK assessment should be collected on the visits specified in the Schedule of Activities in Section 8.11 (see also Section 8.1, "Timing of Assessments"). Samples will be obtained by venipuncture (or indwelling cannula), preferably in the forearm into tubes containing K2EDTA and will be immediately chilled (ice bath). Within 30 minutes after blood collection, the plasma will be separated in a refrigerated centrifuge at 4 °C for 10 minutes at circa 1500 g and transferred into tubes as described in the laboratory manual. The plasma samples will

be stored at approximately -60°C to -90°C at the site until shipment to the bioanalytical laboratory.

8.7. [redacted]

[redacted]

8.7.1. [redacted]

[redacted]

8.7.2. [redacted]

[redacted]

[redacted]

8.7.3. [redacted]

[redacted]

8.8. Other Assessments

8.8.1. [redacted]

[redacted]

8.8.2. [redacted]

[redacted]

8.8.3. [redacted]

[redacted]

8.8.4. [redacted]

[redacted]

8.8.5. [redacted]

[redacted]

8.8.6. [redacted]

[redacted]

Subjects will be trained on how to complete the subject diary.

8.9. Sample Management

Total Blood Volume

The total amount of blood to be taken per subject over a period of 20 weeks for scheduled laboratory parameters will not exceed [redacted] mL. This includes sampling for safety, PK, [redacted] assessments.

Blood and Urine Samples for Routine Safety Tests, Serology, SARS-CoV-2, FSH, and Pregnancy Tests

All blood and urine samples for routine safety tests, serology, FSH, and pregnancy tests will be analyzed in a central laboratory and will be destroyed after analysis. SARS-CoV-2 tests may be analyzed in local laboratories and samples will be destroyed after analysis.

Blood Samples for PK [redacted]

After the end of the study (defined in Section 5.2), all biological samples obtained during the clinical study may be stored for a maximum period of 5 years, after which the samples will be destroyed. The sample storage period will be in accordance with the IRB/IEC-approved ICF and applicable regulations (e.g. Regulatory Authority requirements).

The stored samples shall only be used by the sponsor, sponsor partners, and/or other companies contracted by the sponsor, for research related to this clinical study. Any research outside the context described in this CSP may only be conducted after approval by the IRB/IEC and Regulatory Authority and after obtaining informed consent from the subject.

[redacted]

The details of blood and sample handling and shipment instructions for all samples collected during the study will be provided in a separate laboratory manual.

[redacted]

[redacted]

8.10. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.11. Schedule of Activities

For detailed instructions on the clinical study procedures, please see referred sections and Section 8.1, "Timing of Assessments".

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1]						FOLLOW-UP PERIOD
Study Visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[2]**	**Follow-up Visit**
Study Week	**-4 to -1**	**Baseline**	**1**	**4**	**8**	**12**		
Study Day (D) ± Days	**-28 to -1**	**1**	**8±1**	**29±2**	**57±2**	**85±2**	**Early treatment discontinuation**	**28 ± 3 after last IP dosing**
Informed consent	✓							
Inclusion/exclusion criteria	✓	✓						
Demographics	✓							
Medical history	✓							
Physical examination	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs	✓	✓	✓	✓	✓	✓	✓	✓
Body weight and height[3]	✓	✓	✓	✓	✓	✓	✓	✓

[1] On dosing days, all assessments are to be performed predose, unless otherwise specified.
[2] Subjects who discontinue treatment early will be requested to return for an ED visit and to return for a FU visit 28 ± 3 days after last IP administration.
[3] Height only to be measured at screening.

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1]						FOLLOW-UP PERIOD
Study Visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[2]**	**Follow-up Visit**
Study Week	**-4 to -1**	**Baseline**	**1**	**4**	**8**	**12**		
Study Day (D) ± Days	**-28 to -1**	**1**	**8±1**	**29±2**	**57±2**	**85±2**	**Early treatment discontinuation**	**28 ± 3 after last IP dosing**
12-lead ECG[4]	✓	Predose, 1.5h, 3h, 4.5h postdose[4]	Predose	Predose	Predose	Predose	✓	✓
QuantiFERON-TB Gold test	✓							
SARS-CoV-2 RT-PCR test[5,6]	✓	✓	As needed					
SARS-CoV-2 serology test[5,6]		✓	As needed					
Randomization		✓						
Blood collection								
– Safety (hematology, coagulation, chemistry)	✓	✓[7]	✓	✓	✓[7]	✓[7]	✓	✓
– Safety (HBV, HCV, HIV serology)	✓							

[4] At Visit 1 (Day 1), triplicate ECGs will be recorded predose and at 4.5 hours postdose. At all other timepoints, single ECGs will be taken.
[5] RT-PCR from a nasal swab sample at screening and RT-PCR from a nasal swab sample and serology testing at Visit 1 (Day 1), and as needed when subject presents signs and symptoms of SARS-CoV-2 infection.
[6] SARS-CoV-2 RT-PCR and serology tests can (optionally) be sampled by a nurse at the subject's home 2-3 days before Visit 1 (Day 1).
[7] Fasted glucose, fasted insulin, and HOMA-IR only at Visit 1, 4, and 5.

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1]						FOLLOW-UP PERIOD
Study Visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[2]**	**Follow-up Visit**
Study Week	**-4 to -1**	**Baseline**	**1**	**4**	**8**	**12**		
Study Day (D) ± Days	**-28 to -1**	**1**	**8±1**	**29±2**	**57±2**	**85±2**	**Early treatment discontinuation**	**28 ± 3 after last IP dosing**
– Pregnancy test serum (all females)	✓							
– FSH test (WOnonCBP, non-surgical postmenopausal women)	✓							
– Blood samples for PK GLPG3970		Predose[8], 0.5-1.5h, 2-2.5h, 4.5h[9] postdose[10]	Predose[8]	Predose[8]	Predose[8], 0.5-1.5h, 2-2.5h postdose[10]	Predose[8]	✓	
[redacted]								
– [redacted]								
– [redacted]								

[8] At Visit 1, 2, 3, 4, and 5, PK sample to be taken within 30 minutes predose.
[9] At Visit 1, the PK sample collected at 4.5 hours postdose must be taken immediately after the triplicate ECG.
[10] At Visit 1, 4, and 5 subjects must come for the study visits in a fasting state (no food intake for at least 8 hours). If the postdose samples could not be collected at Visit 4, they should be collected at Visit 5. It is important that the PK [redacted] samples are collected on the same day.
[redacted]

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1]						FOLLOW-UP PERIOD
Study Visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[2]**	**Follow-up Visit**
Study Week	**-4 to -1**	**Baseline**	**1**	**4**	**8**	**12**		
Study Day (D) ± Days	**-28 to -1**	**1**	**8±1**	**29±2**	**57±2**	**85±2**	**Early treatment discontinuation**	**28 ± 3 after last IP dosing**
– [redacted]								
Urine sample								
– Safety (urine)	✓	Predose	Predose	Predose	Predose	Predose	✓	✓
– Pregnancy testing (UPT, dipstick) (WOCBP only)		Predose	Predose	Predose	Predose	Predose		
Subject diary evaluation		✓	✓	✓	✓	✓	✓	✓
ESSDAI	✓	✓		✓	✓	✓	✓	
ESSPRI	✓	✓		✓	✓	✓	✓	
[redacted]								
[redacted]								
[redacted]								

[redacted]

EVENT	SCREENING PERIOD	TREATMENT PERIOD[1]						FOLLOW-UP PERIOD
Study Visit	**S**	**1**	**2**	**3**	**4**	**5**	**ED[2]**	**Follow-up Visit**
Study Week	**-4 to -1**	**Baseline**	**1**	**4**	**8**	**12**		
Study Day (D) ± Days	**-28 to -1**	**1**	**8±1**	**29±2**	**57±2**	**85±2**	**Early treatment discontinuation**	**28 ± 3 after last IP dosing**
[redacted]								
Dispense IP		✓	✓	✓	✓			
IP administration[14]		Once daily throughout the treatment period						
AE and concomitant medication	throughout the study							

[13] [redacted]

[14] At Visit 1 (Day 1), the IP will be administered at the study site in a fasted state. Breakfast will be provided to the subject 0.5-1 hour after the IP intake. Lunch should be eaten 1 hour before or after the ECG measurement at 4.5 hours postdose. At all other dosing days (including Visit 2, 3, 4, and 5), the IP should be taken in a fed state (together with a meal).

9. STATISTICAL METHODS

All statistical methods shall be detailed in a SAP that will be finalized prior to the database lock and unblinding. All relevant data collected in this clinical study will be documented using summary tables, figures, and subject data listings.

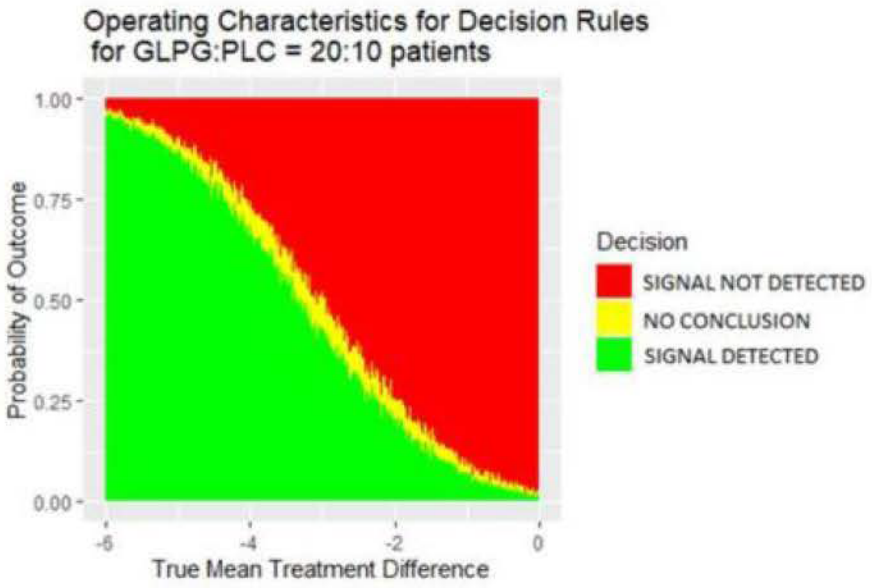
Any deviations from the CSP are to be justified in the SAP.

9.1. Determination of Sample Size

Up to 30 subjects are planned to be randomized 2:1, i.e. 20 subjects will receive GLPG3970 (400 mg q.d.) and 10 subjects will receive placebo. In case of drop-outs due to SARS-CoV-2 infection, additional subjects may be randomized on top of the planned sample size. The number of additional subjects randomized will not exceed the number of subjects dropping out of the study in relation to SARS-CoV-2. Randomization of additional subjects will be decided by the sponsor before study lock or related unblinding has occurred.

This sample size provides favorable operating characteristics for the primary efficacy endpoint (i.e. ESSDAI change from baseline at Week 12) in terms of the modified signal detection methodology (21). This methodology will be used to provide further insight into the treatment effect of GLPG3970 over placebo, and will support scenario analyses. The posterior distribution of this treatment effect will be estimated, and from this distribution probabilities of reaching at least a certain effect (delta) will be derived, e.g. a range of plausible effect size values going from as high as P (delta <=-5) to as low as P (delta <=-2). A common SD of 4 was assumed for both active and placebo arm.

Probability	Reference value	Outcome
0.852	-5	Signal detected
0.041		No conclusion
0.107		Signal not detected
0.427	-3	Signal detected
0.088		No conclusion
0.485		Signal not detected
0.205	-2	Signal detected
0.050		No conclusion
0.745		Signal not detected



9.2. Population for Analyses

9.2.1. All Screened Subjects

All subjects who signed and dated an ICF.

9.2.2. All Randomized Subjects

All screened subjects who were randomized into the clinical study.

9.2.3. Full Analysis Set

All randomized subjects who have received at least 1 dose of IP

9.2.4. Safety Analysis Set

All randomized subjects who have received at least 1 dose of IP.

9.2.5. Pharmacokinetic Analysis Set

Subset of the Safety Analysis Set for which plasma concentration data are available to facilitate development of the population PK model as described in the pharmacometric analysis plan and excluding CSP deviations which have an impact on the PK analyses.

9.2.6. [redacted]

[redacted]

9.2.7. Pharmacokinetic/[redacted] Analysis Set

Intersection of the PK[redacted] Analysis Sets.

9.3. Statistical Analyses

9.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, standard deviations (SDs) and/or standard error (as appropriate), median, minimum and maximum (for continuous variables), and the number and percentage per category (for categorical data). In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data.

Baseline is defined as the last available assessment prior to the first intake of IP. For ECG, the baseline ECG result is the mean of the last available triplicate prior to the first intake of IP.

Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 10% significance level.

9.3.2. Interim Analysis

No formal interim analysis is planned for this clinical study.

9.3.3. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for ED), CSP deviations, demographics, baseline characteristics, medical history, and concomitant therapies will be analyzed descriptively.

9.3.4. Analyses of Efficacy Parameters

Efficacy analysis will be performed on the FAS.

9.3.4.1. Analysis for Primary Efficacy Endpoint

The signal detection methodology described by Frewer et al (21) will be used to provide further insight into the treatment effect of GLPG3970 over placebo, and will support scenario analyses. See also Section 9.1.

A MMRM (ESSDAI) will be used to compare treatment groups, with a 90% confidence interval (CI) of the treatment difference at Week 12.

9.3.4.2. Analyses for Secondary and Other Efficacy Endpoints

Continuous efficacy endpoints, including the primary endpoint: MMRM to compare treatment groups, with a 90% CI of the treatment difference at each time point.

Binary efficacy endpoints: Presented with a 90% exact CI of the treatment difference at each time point.

9.3.5. Analyses of Safety Data

All safety analyses will be performed using the Safety Analysis Set (Section 9.2.4). All safety data collected on or after the first dose of IP administration up to the last contact after the last dose of IP, unless specified otherwise, will be summarized by treatment group according to the IP received. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs.

9.3.5.1. Extent of Exposure

A subject's extent of exposure to the IP will be generated from the IP administration page of the CRF. Exposure data will be summarized by treatment group. Duration of exposure to the IP will be expressed as the number of days between the first and last dose of IP, inclusive, regardless of temporary interruptions in IP administration and summarized by treatment group.

9.3.5.2. Adverse Events

Clinical and laboratory AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. System Organ Class, High-Level Group Term, High-Level Term, Preferred Term, and Lower-Level Term will be attached to the clinical database.

The following AEs will be considered as treatment-emergent adverse events (TEAEs):

Any AE with an onset date on or after the IP start date and no later than 30 days after last dose of IP, or any worsening of any AE on or after the IP start date.

Summaries (number and percentage of subjects) of TEAEs per subject by System Organ Class and Preferred Term will be provided by treatment group. TEAEs will also be summarized by causal relationship to the IP and severity. In addition, TEAEs leading to ED of the IP will be summarized and listed. Also, all SAEs, including the non-treatment-emergent SAEs, will be listed.

9.3.5.3. Clinical Laboratory Evaluations

Laboratory assessments will be analyzed descriptively. Changes from baseline and treatment-emergent shifts according to normal ranges and CTCAE grades will be presented as well. Analyses will be done per treatment group.

9.3.5.4. Physical Examinations

Only abnormal post-baseline physical examination results will be listed, when available.

9.3.5.5. Vital Signs

Vital signs will be analyzed descriptively. Changes from baseline will be presented as well. Analyses will be done per treatment group.

9.3.5.6. 12-Lead Electrocardiogram

A descriptive analysis will be done for the 12-lead ECG. Changes from baseline will be presented as well. Frequency analyses of abnormalities based on actual values and on changes from baseline will be presented as well. Analyses will be done per treatment group.

9.3.6. Pharmacokinetic Analyses

GLPG3970 plasma concentrations will be listed and predose concentrations (C_{trough}) will be summarized descriptively and reported in the CSR.

All observed GLPG3970 plasma concentrations will be analyzed using a population PK approach to characterize the PK profile of GLPG3970. This analysis will provide simulated pop-PK parameters for GLPG3970, such as clearance (CL/F) and Vss, and their associated variability, as well as individual estimates of AUC and, if appropriate, C_{max}. The results from the pop-PK analysis will be reported separately from the CSR.

[redacted]

9.3.7. [redacted]

[redacted]

9.3.8. Analysis of Other Assessments

Not applicable.

9.3.9. Additional Statistical Considerations

Not applicable.

10. DATA MONITORING

10.1. Safety Monitoring Committee

A Safety Monitoring Committee independent from the study will review unblinded data during the course of the study. This Committee will include a physician with experience in drug development, a biostatistician, and a safety physician. External medical experts (such as an expert in the field of pSS and an infectious diseases expert) may be included to support data interpretation. The Committee will review unblinded safety data and assess any potential safety issues arising during the conduct of the clinical study, including (but not limited to) any potential issues in the context of the SARS-CoV-2 pandemic. The process is described in a separate 'Safety Monitoring Committee Charter'.

11. SAFETY REPORTING

11.1. Definitions of Adverse Events, Serious Adverse Events, and Special Situations

11.1.1. Adverse Events

An AE is any untoward medical occurrence, new or worsening of any pre-existing condition, in a clinical study subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g. an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related. AEs may also include pre- or post-treatment complications that occur as a result of CSP-specified procedures, worsening of the targeted disease, overdose, drug abuse/misuse reports, or occupational exposure. Pre-existing conditions that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

11.1.2. Serious Adverse Events

An SAE is defined as an AE that:

- Results in death.
- Is life-threatening (Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly / birth defect.
- Is medically significant (medical and scientific judgment should be exercised in deciding whether other situations should be considered serious 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 in the definition above).

11.1.3. Unlisted (Unexpected) Adverse Events/ Reference Safety Information

An AE is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For an IP, the expectedness of an AE will be determined by whether or not it is listed in the reference safety information part of the IB.

11.1.4. Adverse Events of Special Interest

Not applicable.

11.1.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events

Laboratory abnormalities without clinical significance based on the investigator's judgment are not considered AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) or other abnormal (clinical study-specific) assessments (e.g. ECG, radiography, vital signs) that require medical or surgical intervention, are associated with signs and/or symptoms, and/or lead to IP interruption, modification or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 11.1.1 and 11.1.2, respectively. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis is to be reported (e.g. anemia instead of decreased hemoglobin).

The following liver enzyme elevations must be reported as SAEs:

- AST or ALT >=3xULN with signs of liver damage (total bilirubin >2xULN OR INR >1.5, and/or with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%]).

11.1.6. Special Situations

Special situations are situations that have a possible impact on the safe use of the IP. These situations might be or might not be associated with AEs.

- Pregnancy.
- Overdose with IP.
  An overdose of IP is defined as the administration of a quantity of the IP given per administration or cumulatively, which is above the dose of IP given during this study.
- Medication error with IP.
  A medication error with IP is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.
- Product complaint or quality defect of IP.
  Product complaint or quality defect of IP is defined as complaints or defects of the IP arising from potential deviations in the manufacture, packaging, or distribution of the IP.

- Abuse or misuse of IP.
  Abuse of IP is defined as the persistent or sporadic, intentional excessive use of the IP, which is accompanied by harmful physical or psychological effects.
  Misuse of IP is defined as a situation where the IP is intentionally and inappropriately used not in accordance with the product information.
- Drug interaction or food interaction with IP.
  A drug interaction with IP is defined as a situation in which there is evidence or a suspicion that the IP interacts with another drug when both are administered together.
  A food interaction with IP is defined as a situation in which there is evidence or a suspicion that the IP interacts with a food when taken together.
- Occupational exposure to IP.
  Occupational exposure to IP is defined as an exposure to the IP as a result of one's professional or non-professional occupation.

11.2. Assessment of Adverse Events and Serious Adverse Events

The investigator is responsible for assessing AEs and SAEs for causality and severity. This is the basis for the sponsor's final review and confirmation of accuracy and completeness of event information and causality assessments.

11.2.1. Action Taken Regarding Investigational Product (if Applicable)

The action taken must be described by choosing from:

- Dose not changed: In case no action is taken regarding the IP.
- IP permanently discontinued: In case a subject is permanently discontinued from treatment or withdrawn from the study by the investigator (who may consult the sponsor's medical leader).
- IP temporarily discontinued: In case the IP is temporarily discontinued by the investigator (who may consult the sponsor's medical leader).
- Not applicable: Other situations (e.g. in case an AE started after the last IP administration).

11.2.2. Assessment of Causality

The investigator is responsible for assessing the causal relationship to IP(s) administration or study procedures (e.g. invasive procedures such as venipuncture) based on her/his clinical judgment. The following decision choice will be used by the investigator to describe the causality assessment between the reported event or laboratory test abnormality and the IP.

- **Unrelated:**
  Time relationship to IP intake is improbable. Related to other etiologies such as concomitant medications or subject's clinical state.
- **Unlikely:**
  Time relationship to IP intake is improbable (but not impossible). Concomitant disease or other drugs provide plausible explanations.
- **Possible:**
  Time relationship to IP intake is reasonable. Event or laboratory test abnormality could also be explained by disease or other drugs. Information on IP withdrawal may be lacking or unclear.
- **Probable:**
  Time relationship to IP intake is reasonable. Unlikely to be attributed to concurrent disease or other drugs. Response to withdrawal is clinically reasonable and rechallenge not required.
- **Certain:**
  Time relationship to IP intake is plausible. Cannot be explained by concomitant disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactory, if ethical and necessary.

It should be emphasized that ineffective treatment (worsening of the disease) should not be considered as causally related in the context of AE reporting.

11.2.3. Assessment of Severity

The severity of AEs should be graded using the CTCAE version current at the time of assessment. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 2.

Table 2: Grading of AE Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death-related AE

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

For AEs associated with laboratory abnormalities, the event should be graded on the basis of the clinical severity in the context of the underlying conditions; this may or may not be in agreement with the grading of the laboratory abnormality. This is upon the investigator's assessment.

If there is a change in intensity (worsening or improvement) of an AE, it must be recorded.

11.2.4. Outcome

Each AE must be rated by choosing among:

- Recovered/resolved;
- Recovered/resolved with sequelae;
- Recovering/resolving;
- Not recovered/not resolved;
- Fatal;
- Unknown.

11.3. Investigator Requirements and Instructions for Reporting Adverse Events, Serious Adverse Events, Pregnancies, and Other Special Situations to the Sponsor

11.3.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at the subject's last FU visit (the last FU visit after the last dose of IP). In this period, all new AEs,

regardless of cause or relationship, derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questioning (such as "How do you feel?") need to be recorded in the source and in the CRF.

In case an AE is ongoing at the time of the last FU visit, the investigator needs to follow up on the subject until AE resolution or reasonable stabilization and to document in the subject's source documentation. No related updates or additional data on the AE should be reported in the CRF.

If a subject is documented as lost-to-FU, ongoing/unknown outcome AEs will not be followed-up.

If the AE meets the criteria for seriousness, the SAE form must be completed and sent to the sponsor within 24 hours (see Section 11.3.2).

11.3.2. Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The subject will remain under observation as long as medically indicated. Appropriate laboratory tests will be performed until all parameters return to normal or are otherwise explained or stable.

All SAEs, whether or not deemed IP-related, must be recorded on the SAE form and in the CRF. The investigator must report each SAE immediately, and under no circumstances should this exceed 24 hours following the knowledge of the SAE, as is indicated on page 2 under "Emergency Contact Information".

The SAE form should at least contain identifiers of the subject and the reporter, SAE term and statement of relatedness to the IP, and at a later stage if not yet available within 24 hours, the form needs to be completed with a clearly written narrative describing signs, symptoms, and treatment of the event, diagnostic procedures, as well as any relevant laboratory data and any sequelae.

FU and outcomes should be reported and documented in the source documents for all subjects that experience an SAE. It is important that the information provided on the SAE form matches the information recorded on the CRF for the same event.

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and available. Only subject identifiers (subject number) should appear on the copies, and all names and initials should be blackened and rendered illegible. Follow-up (FU) reports relative to the subject's subsequent course must be submitted until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

Any SAEs that occur after the post-treatment FU visit but within 30 days of the last dose of IP(s), regardless of causality, should also be reported (Emergency Contact Information on Page 2) but not entered in the CRF. Investigators are not obligated to actively seek SAEs after the CSP-defined FU period. However, if the investigator is informed about an SAE that occurs at any time

after the subjects' post-treatment FU visit and the event is deemed relevant to the use of IP(s), he/she should promptly document and report the event to the sponsor by using the SAE form.

11.3.3. Pregnancy

All initial reports of pregnancy in female subjects and pregnancies in partners of male subjects included in the clinical study must be recorded and documented in the source documents and on the pregnancy form. The investigator must report each pregnancy immediately, and under no circumstances should this exceed 24 hours following the knowledge of the pregnancy, as is indicated on page 2 under "Emergency Contact Information".

All pregnancies should be followed-up until delivery or pregnancy interruption. The investigator will contact the subject or partner of the subject after giving consent, at the expected time of delivery for FU and for information regarding the outcome of the newborn. Abnormal pregnancy and/or abnormal newborn outcomes are considered SAEs and must be reported using the SAE form.

11.3.4. Reporting of Special Situations (Other Than Pregnancy) and Adverse Events

In case a special situation is not associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form as is indicated on page 2 under "Emergency Contact Information".

In case a special situation is associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form and the associated AE should be reported as specified in Section 11.3.1.

In case a special situation is associated with an SAE, the special situation should be reported within 24 hours by using the SAE form (and not the Special Situations form) and the associated SAE should be reported as specified in Section 11.3.2.

11.4. Sponsor Reporting Requirements

Depending on relevant local legislation or regulations, including the applicable United States Federal Drug Administration Code of Federal Regulations, the EU Clinical Trials Directive (2001/20/EC) and relevant updates, and other country-specific legislation or regulations, the sponsor may be required to expedite reports of SAEs and serious adverse drug reactions or suspected unexpected serious adverse reactions (SUSARs) to worldwide regulatory authorities. The sponsor or a specified designee will notify worldwide regulatory authorities and the relevant IEC/IRB in concerned Member States of applicable SUSARs as outlined in current regulations.

Assessment of expectedness for SAEs will be determined using the reference safety information section in the IB or relevant local label as applicable.

All concerned investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any IP(s). The investigator should notify the IEC/IRB of SUSAR reports as soon

as is practical, where this is required by local regulatory authorities, and in accordance with the local institutional policy.

12. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This clinical study will be conducted in compliance with this CSP, the current ICH-GCP Guideline E6, and applicable local ethical and legal requirements.

Good Clinical Practice is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of clinical study subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki (1996 and successive amendments), and that the clinical study data are credible.

The name and address of each third party vendor (e.g. CRO) used in this study and the sponsor's study team members will be maintained in the investigator's and sponsor's files as appropriate.

12.1. Sponsor's Responsibilities

12.1.1. Regulatory Authority Approval

Prior to clinical study start, this CSP together with all relevant documentation needs to be submitted to the respective regulatory authorities for review and approval in compliance with current regulations before the study can start.

12.1.2. Clinical Study Closure Considerations

The sponsor reserves the right to close the site or end the clinical study at any time for any reason. In case of an early termination of the clinical study or temporary halt by the sponsor, the IEC/IRB should be notified according to local requirements, unless otherwise specified by the sponsor, the IEC/IRB, and/or the regulatory authorities including a detailed written explanation of the reasons for the termination/halt.

Reasons for the closure of a site may include, but are not limited to:

- Successful completion of the clinical study at the center.
- The overall required number of subjects for the clinical study has been recruited.
- Failure of the investigator to comply with the CSP, ICH-GCP guidelines, or local requirements.
- Inadequate recruitment of subjects by the investigator.

Reasons for early termination of a clinical study by the sponsor may include, but are not limited to:

- Safety concerns.
- Sufficient data suggesting lack of efficacy.

The end of clinical study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete clinical study has ended in all participating centers, in all countries. This notification will also be submitted according to local requirements of the end of the clinical study in a given country/member state.

12.1.3. Indemnification

Under the conditions of a contract concluded between investigator, site, and sponsor or designee, which shall prevail, the sponsor shall, except in case of gross negligence or willful misconduct, indemnify and hold harmless the investigator and his/her medical staff from any claim arising from the clinical study activities carried out in compliance with the CSP, sponsor's instructions, and applicable local regulations.

The investigator must notify the sponsor immediately upon notice of any claims or lawsuits.

12.1.4. Insurance

The sponsor shall maintain insurance coverage that is sufficient to cover its obligations and that is consistent with human clinical study local regulations. Provided that the subject has been treated according to the CSP and sponsor's instructions, any injury caused to a subject which is the direct result of his/her participation to the clinical study shall be covered by the sponsor's insurance, except in case of gross negligence or willful misconduct by the investigator.

12.1.5. Archiving

The sponsor will archive the content of the Trial Master File (TMF) for at least 25 years after the end of the clinical study.

12.2. Reporting

Where required by IEC/IRB per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study (see Section 12.6.1).

At the end of the clinical study, the results of the clinical study will be reported in a CSR by the sponsor. The pop-PK analysis data [redacted] data may be reported separately from the main CSR. A summary or full report, depending on the requirements, will be provided by the sponsor to the investigators, to the relevant regulatory authorities, and IECs/IRBs (if required by the applicable regulatory requirements) within 1 year, or 6 months for pediatric studies, after the end of the clinical study.

12.3. Publication

It is understood by the investigator that the sponsor shall be free to use the compound-related information, which is generated during the clinical study and may disclose it to other clinical investigators and to regulatory agencies. As a consequence, the investigator agrees to provide all clinical study results and data generated during this clinical study to the sponsor.

The investigator shall not be authorized to submit the results of this clinical study and any data for public disclosure (e.g. publication or presentation) without the prior written approval of the sponsor, which shall not be unreasonably withheld.

However, it is understood and agreed by the investigators that their results and/or findings shall not be authorized for publication prior to sponsor's publication of the overall clinical study results. The investigator agrees that prior to the publication of any results, he/she shall provide the sponsor with a draft copy of the intended publication. The sponsor shall have the right to review it and to make any comments. In accordance with generally accepted scientific collaboration principles, co-authorship with any staff member sponsor involved in the clinical study, will be discussed and mutually agreed upon before submission of any manuscript to a publisher.

12.4. Investigator's Responsibilities

12.4.1. Source Data and Data Capture

The nature and location of all source documents need to be identified and documented to ensure that all sources of original data required to complete the CRF are known and are accessible for verification by the monitor.

Source data may be directly captured from devices transferred from third partners (e.g. laboratory data) or entered manually into the CRF. The CRF completion guidelines will be provided to each site.

It is recommended that the author of an entry in the source documents should be identifiable. Following ICH-GCP guidelines, direct access to sponsor's representatives to source documents must be granted for the purpose of verifying that the data recorded on the CRF are consistent with the original source data.

12.4.2. Archiving

Unless local legislation requires archiving for a longer period, the investigator shall archive the content of the clinical investigator site file for at least 25 years after the end of the clinical study. However, the medical files of subjects shall be archived in accordance with national law.

The investigator should take measures to prevent accidental or premature destruction of these documents.

Under no circumstance shall the investigator relocate or dispose any clinical study documents before having obtained a written approval of the sponsor.

If it becomes necessary for the sponsor or the appropriate Regulatory Authority to review any documentation relating to this clinical study, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the ICF.

Any difficulty in storing original documents must be discussed with the monitor prior to the initiation of the clinical study.

After study completion, the site must notify the sponsor (PostStudySupport@glpg.com) on planned audits, archives, etc.

12.4.3. Participation Cards

If the subjects are not under 24-hour supervision of the investigator or site staff, they must be provided with a subject participation card indicating the name of the IP, the clinical study number, the investigator's name, and the site's 24-hour emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

12.5. Confidentiality

The subject will receive all information as required by the EU General Data Protection Regulation, namely the identity and contact details of the controller, the contact details of the data protection officer, the clinical research purposes, the legal basis for the processing, the recipients of the personal data, the transfer of the personal data to third countries and respective safeguards, the retention periods, the fair processing of his data, and all his/her data subject's rights. All details are listed in the ICF.

All information concerning the product and the sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential and should not be disclosed by the investigator to any third party without the sponsor's prior written approval. The investigator agrees to use this information only in accomplishing the clinical study and will not use it for other purposes.

In order to permit easy identification of the individual subject during and after the clinical study, the investigator is responsible for keeping an updated Subject Identification Code List. The monitor will review this document for completeness. However, the investigator must guarantee the subject's anonymity will be maintained. Therefore, in order to ensure subject confidentiality, the Subject Identification Code List must remain at the center and no copy will be made.

12.6. Ethical Considerations

12.6.1. Independent Ethics Committee / Institutional Review Board

This clinical study can only be undertaken after IEC/IRB approval of this CSP together with all relevant documentation. This approval document must be dated and clearly identify the clinical study and the related clinical study documents being approved, including the subject compensation programs, if applicable.

During the course of the clinical study, at least the following documents have to be submitted to the IEC/IRB, per local requirements:

- Changes to the IB
- Reports of AEs that are serious, unlisted, and associated with the IP (in compliance with IEC/IRB, per local requirements)
- CSP amendments
- ICF amendments

The IEC/IRB is responsible for continuous review of the clinical study. Where required by IEC/IRB, per local requirements, at least once a year the investigator will provide the IEC/IRB with a progress report to allow review of the clinical study. Additional progress reports should be provided according to local legal requirements. These requests and (re-)approvals, if applicable, should be documented in writing.

12.6.2. Informed Consent

The investigator or designated personnel must explain the clinical study and the implications of participation (e.g. objectives, methods, anticipated benefits, possible risks) to potential subjects according to applicable regulations prior to any clinical study-related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the clinical study at any time. They will be informed that choosing not to participate or to withdraw from the clinical study will not have an impact on the care the subject will receive for the treatment of his/her disease.

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the clinical study, the subject's consent should be appropriately recorded by means of the subject's personally dated signature and by the investigator's dated signature. In case the subject is unable to read and/or write, oral consent in the presence of at least 1 impartial witness who was also included when the affected person was being informed, may be given. The witness may not be anyone working at the site nor a member of the investigating team. The orally given consent shall be documented in writing, dated and signed by the witness. After having obtained the consent, a copy of the signed and dated ICF must be given to the subject.

If new information becomes available relevant to the subject's willingness to participate in the clinical study, the subject will be informed in a timely manner by means of an amended ICF. This

amended ICF will be signed and dated by the subject (or, if applicable, by an independent witness) and the investigator to document the willingness of the subject to continue with the clinical study.

This signed and dated amended version will be filed together with the initial signed and dated ICF.

A pregnant partner, who agrees that information will be gathered about her pregnancy and the birth, will be asked to sign a specific ICF to participate in the data collection. Data about the health of the baby will be collected if the parent(s)/legal guardian(s) agree with the data collection and sign a specific ICF.

Subjects who agree to participate in the study and who have signed informed consent, will be given the option to provide additional (and optional) informed consent for the long-term storage of additional collection of sample(s) and/or of left over samples and associated data, collected during the study, for future scientific research.

[redacted]

12.7. Data Quality Control/Assurance

12.7.1. Monitoring

Data quality will be assured through Risk-Based Monitoring, medical monitoring, and other relevant activities as described in the Data Management Plan or Medical Review Plan and monitoring plans available in the TMF. This clinical study will be monitored by sponsor representatives according to their current standard operating procedures.

To guarantee adequate protection of the subjects and to guarantee the quality of the data, the sponsor will ensure oversight of any clinical study-related duties and functions carried out on its behalf, including clinical study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

A risk-based Quality Management Plan (QMP) is prepared for the study that evaluates potential risks in relation to rights, safety, and well-being of the study subjects as well as the data integrity. The QMP describes and evaluates all involved stakeholder interfaces having potential critical impact on the above. Risks are considered at both the system level (e.g. standard operating procedures, computerized systems, personnel, and vendors) and study level (e.g. IP, study design, data collection, informed consent process, and recording).

12.7.2. Audit and Inspection

To ensure compliance with relevant regulations, an independent quality assurance representative, regulatory authorities and/or IECs/IRBs may review this clinical study. This implies that auditors/inspectors will have the right to inspect the clinical study center(s) at any time during

and/or after completion of the clinical study and will have access to the data generated during the clinical study, source documents, and subject's files. By participating in this clinical study, investigators agree to this requirement.

13. REFERENCES

1. Patel R, Shahane A. The epidemiology of Sjögren's syndrome. Clin Epidemiol. 2014 Jul 30;6:247–55.

2. Franceschini F, Cavazzana I, Andreoli L, Tincani A. The 2016 classification criteria for primary Sjogren's syndrome: what's new? BMC Med. 2017 Mar 31;15(1):69.

3. Qin B, Wang J, Yang Z, Yang M, Ma N, Huang F, et al. Epidemiology of primary Sjögren's syndrome: a systematic review and meta-analysis. Ann Rheum Dis. 2015 Nov;74(11):1983–9.

4. Huang Y, Cheng Q, Jiang C, An S, Xiao L, Gou Y, et al. The Immune Factors Involved in the Pathogenesis, Diagnosis, and Treatment of Sjogren's Syndrome [Internet]. Vol. 2013, Clinical and Developmental Immunology. Hindawi; 2013 [cited 2020 Apr 22]. p. e160491. Available from: https://www.hindawi.com/journals/jir/2013/160491/

5. Sandhya P, Kurien BT, Danda D, Scofield RH. Update on Pathogenesis of Sjogren's Syndrome. Curr Rheumatol Rev. 2017;13(1):5–22.

6. Fox RI, Fox CM. Sjögren Syndrome: Why Do Clinical Trials Fail? Rheum Dis Clin North Am. 2016;42(3):519–30.

7. Verstappen GM, van Nimwegen JF, Vissink A, Kroese FGM, Bootsma H. The value of rituximab treatment in primary Sjögren's syndrome. Clin Immunol Orlando Fla. 2017;182:62–71.

8. Vivino FB, Carsons SE, Foulks G, Daniels TE, Parke A, Brennan MT, et al. New Treatment Guidelines for Sjögren's Disease. Rheum Dis Clin North Am. 2016;42(3):531–51.

[redacted]

10. Shiboski CH, Shiboski SC, Seror R, Criswell LA, Labetoulle M, Lietman TM, et al. 2016 ACR-EULAR Classification Criteria for primary Sjögren's Syndrome: A Consensus and Data-Driven Methodology Involving Three International Patient Cohorts. Arthritis Rheumatol Hoboken NJ. 2017 Jan;69(1):35–45.

11. BMJ, B. M. (2020, May 13). British Medical Journal Best Practice. Retrieved from Coronavirus disease 2019 (COVID-19) Diagnostic guidelines. [Internet]. Available from: https://bestpractice.bmj.com/topics/en-gb/3000168/guidelines

12. BMJ, B. M. (2020, May 13). British Medical Journal Best Practice. Retrieved from Coronavirus disease 2019 (COVID-19) History and exam: [Internet]. Available from: https://bestpractice.bmj.com/topics/en-gb/3000168/history-exam

13. Seror R, Bootsma H, Saraux A, Bowman SJ, Theander E, Brun JG, et al. Defining disease activity states and clinically meaningful improvement in primary Sjögren's syndrome with

EULAR primary Sjögren's syndrome disease activity (ESSDAI) and patient-reported indexes (ESSPRI). Ann Rheum Dis. 2016 Feb;75(2):382–9.

[redacted]

17. Senchyna M, Wax MB. Quantitative assessment of tear production: A review of methods and utility in dry eye drug discovery. J Ocul Biol Dis Infor. 2008 Mar;1(1):1–6.

[redacted]

19. Shahid A, Wilkinson K, Marcu S, Shapiro CM, editors. STOP, THAT and One Hundred Other Sleep Scales [Internet]. New York: Springer-Verlag; 2012 [cited 2020 Aug 6]. Available from: https://www.springer.com/gp/book/9781441998927

[redacted]

21. Frewer P, Mitchell P, Watkins C, Matcham J. Decision-making in early clinical drug development. Pharm Stat. 2016;15(3):255–63.

14. APPENDICES

Appendix 1: Prednisolone Conversion Table

Glucocorticoid Name	Dose Equivalent to 5 mg Prednisolone
Prednisone	5 mg
Betamethasone	0.6 mg
Cortisol (hydrocortisone)	20 mg
Cortisone	25 mg
Deflazacort	7.5 mg
Dexamethasone	0.75 mg
Methylprednisolone	4 mg
Methylprednisolone Acetate	4 mg
Methylprednisolone Sodium Succinate	4 mg
Paramethasone	2 mg
Prednisolone	5 mg
Triamcinolone	4 mg
Beclometasone Dipropionate	1.25 mg
Budesonide	1.5 mg
Hydrocortisone Sodium Succinate	20 mg

(Steroid Conversion Calculator)

Appendix 7: EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) Score

Domain	Activity level	Description
Constitutional *Exclusion of fever of infectious origin and voluntary weight loss*	No=0	Absence of the following symptoms
	Low=3	Mild or intermittent fever (37.5–38.5°C)/night sweats and/or involuntary weight loss of 5–10% of body weight
	Moderate=6	Severe fever (>38.5°C)/ night sweats and/or involuntary weight loss of >10% of body weight

Domain	Activity level	Description
Articular *Exclusion of osteoarthritis*	No=0	Absence of currently active articular involvement
	Low=2	Arthralgias in hands, wrists, ankles and feet accompanied by morning stiffness (>30 min)
	Moderate=4	1–5 (of 28 total count) synovitis
	High=6	≥6 (of 28 total count) synovitis

Domain	Activity level	Description
Lymphadenopathy and lymphoma *Exclusion of infection*	No=0	Absence of the following features
	Low=4	Lymphadenopathy ≥1 cm in any nodal region or ≥2 cm in inguinal region
	Moderate=8	Lymphadenopathy ≥2 cm in any nodal region or ≥3 cm in inguinal region, and/ or splenomegaly (clinically palpable or assessed by imaging)
	High=12	Current malignant B-cell proliferative disorder

Domain	Activity level	Description
Cutaneous *Rate as 'No activity' stable long-lasting features related to damage*	No=0	Absence of currently active cutaneous involvement
	Low=3	Erythema multiforma
	Moderate=6	Limited cutaneous vasculitis, including urticarial vasculitis, or purpura limited to feet and ankle, or subacute cutaneous lupus
	High=9	Diffuse cutaneous vasculitis, including urticarial vasculitis, or diffuse purpura, or ulcers related to vasculitis

Domain	Activity level	Description
CNS *Rate as 'No activity' stable long-lasting features related to damage or CNS involvement not related to the disease*	No=0	Absence of currently active CNS involvement
	Moderate=10	Moderately active CNS features, such as cranial nerve involvement of central origin, optic neuritis or multiple sclerosis-like syndrome with symptoms restricted to pure sensory impairment or proven cognitive impairment
	High=15	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	Activity level	Description
Biological	No=0	Absence of any of the following biological feature
	Low=1	Clonal component and/or hypocomplementemia (low C4 or C3 or CH50) and/or hypergammaglobulinemia or high IgG level between 16 and 20 g/L
	Moderate=2	Presence of cryoglobulinemia and/ or hypergammaglobulinemia or high IgG level >20 g/L, and/or recent onset hypogammaglobulinemia or recent decrease of IgG level (<5 g/L)

Domain	Activity level	Description
Pulmonary *Rate as 'No activity' stable long-lasting features related to damage, or respiratory involvement not related to the disease (tobacco use, etc)*	No=0	Absence of currently active pulmonary involvement
	Low=5	Persistent cough **due to** 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
	Moderate=10	Moderately active pulmonary involvement, such as interstitial lung disease shown by HRCT with shortness of breath on exercise (NHYA II) or abnormal lung function tests restricted to: 70% >DL_{CO} ≥40% or 80% >FVC≥60%
	High=15	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%

FVC, forced vital capacity; HRCT, high-resolution CT; NYHA, New York Heart Association.

Domain	Activity level	Description
Haematological *For anaemia, neutropenia, and thrombopenia, only auto-immune cytopenia must be considered Exclusion of vitamin or iron deficiency, drug-induced cytopenia*	No=0	Absence of autoimmune cytopenia
	Low=2	Cytopenia of autoimmune origin with neutropenia (1000<neutrophils<1500/mm^3), and/or anaemia (10<haemoglobin<12 g/dL), and/or thrombocytopenia (100 000<platelets<150 000/mm^3) Or lymphopenia (500<lymphocytes<1000/mm^3)
	Moderate=4	Cytopenia of autoimmune origin with neutropenia (500≤ neutrophils ≤1000/mm^3), and/or anaemia (8≤ haemoglobin ≤10 g/dL), and/or thrombocytopenia (50 000 ≤ platelets ≤100 000/mm^3) Or lymphopenia (≤500/mm^3)
	High=6	Cytopenia of autoimmune origin with neutropenia (neutrophils<500/mm^3), and/or or anaemia (haemoglobin<8 g/dL) and/or thrombocytopenia (platelets<50 000/mm^3)

Domain	Activity level	Description
Glandular *Exclusion of stone or infection*	No=0	Absence of glandular swelling
	Low=2	Small glandular swelling with enlarged parotid (≤3 cm), or limited submandibular (≤2 cm) or lachrymal swelling (≤1 cm)
	Moderate=4	Major glandular swelling with enlarged parotid (>3 cm), or important submandibular (>2 cm) or lachrymal swelling (>1 cm)

Domain	Activity level	Description
Muscular *Exclusion of weakness due to corticosteroids*	No=0	Absence of currently active muscular involvement
	Low=6	Mild active myositis shown by abnormal EMG, MRI* or biopsy with no weakness and creatine kinase (N≤CK≤2N)
	Moderate=12	Moderately active myositis proven by abnormal EMG, MRI* or biopsy with weakness (maximal deficit of 4/5), or elevated creatine kinase (2N<CK≤4N),
	High=18	Highly active myositis shown by abnormal EMG, MRI* or biopsy with weakness (deficit ≤3/5) or elevated creatine kinase (>4N)

*We decided to add this item not included in the initial version since the value of this examination for the diagnosis of myositis was not clear until recently.
EMG, electromyogram.

Domain	Activity level	Description
Renal *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	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
	Low=5	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)
	Moderate=10	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
	High=15	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 cryoglobulinemia related renal involvement

GFR, glomerular filtration rate.

Domain	Activity level	Description
PNS *Rate as 'No activity' stable long-lasting features related to damage or PNS involvement not related to the disease*	No=0	Absence of currently active PNS involvement
	Low=5	Mild active PNS involvement, such as pure sensory axonal polyneuropathy shown by NCS or trigeminal (V) neuralgia **Proven small fibre neuropathy*
	Moderate=10	Moderately active PNS involvement shown by NCS, such as axonal sensory–motor neuropathy with maximal motor deficit of 4/5, pure sensory neuropathy with presence of cryoglobulinemic 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)
	High=15	Highly active PNS involvement shown by NCS, such as axonal sensory–motor 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

*We decided to add this item not included in the initial version since the link between this entity and SS was not clear until recently.
CIPD, chronic inflammatory demyelinating polyneuropathy; NCS, nerve conduction study.

Appendix 8: EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) Score

1) How **severe** has your **dryness** been during the last 2 weeks?

No dryness	0	1	2	3	4	5	6	7	8	9	10	Maximal imaginable dryness

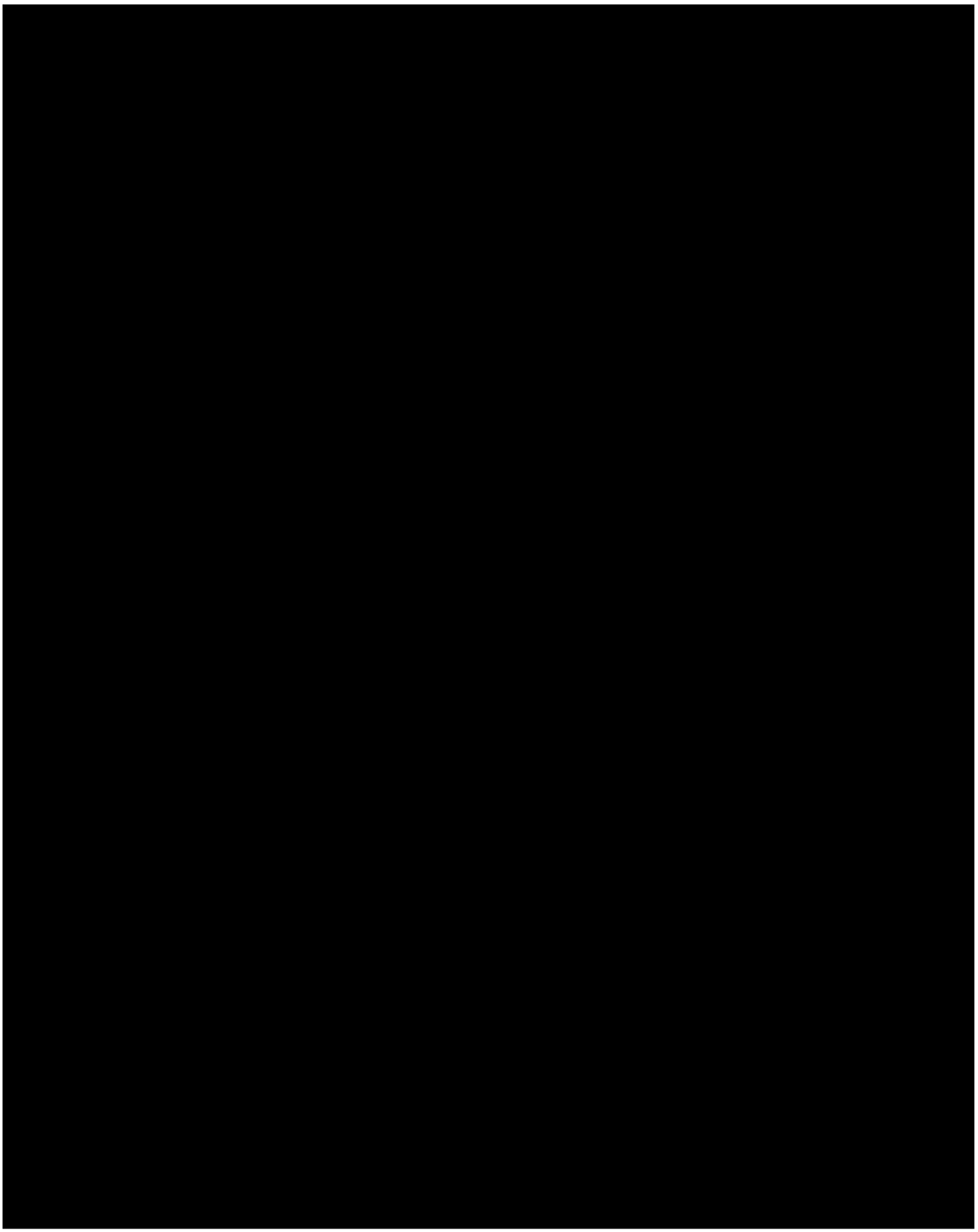
2) How **severe** has your **fatigue** been during the last 2 weeks?

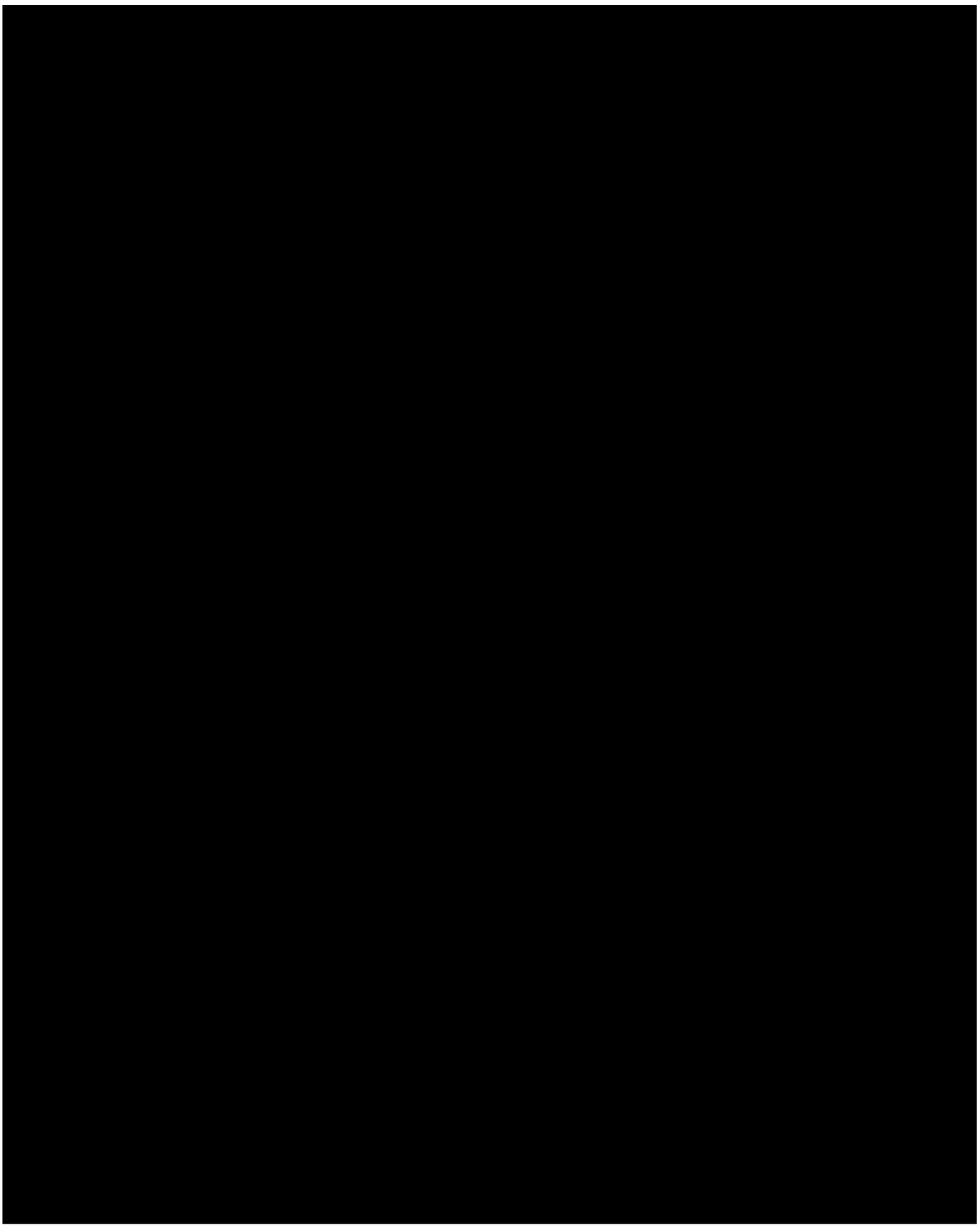
No fatigue	0	1	2	3	4	5	6	7	8	9	10	Maximal imaginable fatigue

3) How **severe** has your **pain** (joint or muscular pains in your arms or legs) been during the last 2 weeks?

No pain	0	1	2	3	4	5	6	7	8	9	10	Maximal imaginable pain

Fig. 1. The EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI). The ESSPRI score is the mean of the 3 scales.





Appendix 15: Algorithm for Elevated Liver Function Tests

<table>
<tr><td></td><td colspan="5">AST or ALT increase to</td></tr>
<tr><td>Value Range</td><td>>=1.5x to 3xULN</td><td>>=3x to <5xULN</td><td>>=5x to <8xULN</td><td>>=3xULN with signs of liver damage[1]</td><td>>=8xULN</td></tr>
<tr><td rowspan="2">IP Action</td><td>Continue as planned</td><td rowspan="2">Reduce or interrupt IP for at least 2 weeks

Close observation[2]</td><td rowspan="2">Interrupt IP for at least 2 weeks

Close observation[2]</td><td>Discontinue IP[2]</td><td>Discontinue IP[2]</td></tr>
<tr><td colspan="3">↙ ↘</td></tr>
<tr><td>After at least 2 weeks</td><td colspan="2">AST and ALT <3xULN</td><td colspan="3">AST or ALT >=3xULN</td></tr>
<tr><td></td><td colspan="2">Weekly LFTs for the first 2 weeks (biweekly for the following weeks, or more frequently at investigator's discretion)</td><td colspan="3">Discontinue IP

Report SAE and complete liver event page for any of abnormalities listed below[3]:

- AST/ALT increase >=3xULN with signs of liver damage[1]</td></tr>
</table>

[1] Signs of liver damage:
- total bilirubin >=2.0xULN OR INR >1.5, and/or
- symptoms: appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

[2] Close observation recommendations:
- Monitor 2 to 3 times per week all of the following parameters: ALT, AST, alkaline phosphatase, total bilirubin, eosinophils, INR. If local regulations allow, home visits can be performed if subjects cannot come to the clinical study center.
- Frequency of retesting can be reduced to once a week or less if abnormalities stabilize or the IP has been discontinued; however, monitoring might still be needed more frequently taking into consideration the SoC and/or changes to this.
- Based upon investigator's discretion gastroenterology or hepatology consultations, additional serology testing, imaging, and pathology assessments may be required.
- Re-query history of symptoms, prior and concurrent diseases, concomitant medication and non-prescription medicines, herbal, dietary supplements, alcohol use, recreational drug use, special diets.
- Rule out all of the following: acute viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, non-alcoholic fatty hepatitis, hypoxic/ischemic hepatitis, biliary tract disease, and cholestasis.
- Re-query exposure to environmental chemical agents.

[3] The following steps should be followed:
- The site should immediately contact the subject and require the subject to discontinue IP immediately. The subject should be asked to return to the site within a 48-hour window from awareness of the result.
- A full evaluation of various causes of hepatitis should be conducted (i.e. infectious, alcohol, medications, anatomical).
- An assessment of other concomitant medications and SoC should be made. The investigator should consider to whether is in the best interest of the subject to stop/interrupt concomitant medications and SoC treatment.
- A detailed history including relevant information on alcohol use, recreational drug use, supplement consumption, any herbal remedies, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, occupational history, blood transfusion, history of liver or allergic disease, and any other potential causes of attributable to a liver insult should be collected.

- A detailed assessment of the subject's clinical condition and repeat laboratory tests for LFT, including albumin, creatine kinase, total bilirubin (direct and indirect), GGT, INR, and alkaline phosphatase should be done.
- Further testing for Hepatitis A, B, and C, and for autoimmune hepatitis should be done. Other causes of viral hepatitis (cytomegalovirus or Epstein-Barr virus etc) should be excluded. Liver imaging should be considered.
- Referral to a hepatologist or gastroenterologist should be requested.
- These cases should be reported as SAEs.

SIGNATURE PAGE – SPONSOR

Study Title:	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered GLPG3970 for 12 weeks in adult subjects with active primary Sjögren's Syndrome		
CSP Version:	7.0	Date:	12-May-2021
Amendment	6		

This CSP has been reviewed and approved by the sponsor to ensure compliance with this CSP, the current ICH-GCP Guideline E6, and applicable local ethical and legal requirements.

[redacted] MD,

An electronic signature for the sponsor is provided at the end of the document

Medical Leader	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title:	A randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy, safety, tolerability, pharmacokinetics, and pharmacodynamics of orally administered GLPG3970 for 12 weeks in adult subjects with active primary Sjögren's Syndrome		
CSP Version:	7.0	Date:	12-May-2021
Amendment	6		

I, the undersigned, have read this CSP and will conduct the study as described in compliance with this CSP, the current ICH-GCP Guideline E6, and applicable local ethical and legal requirements.

Investigator Name	Signature	Date

Signature Page for glpg3970-cl-207-protocol 15985

Approval	[redacted] Senior Medical Director Clinical Development 12-May-2021 12:59:50 GMT+0000

Signature Page for glpg3970-cl-207-protocol43952_17185_51842