Galápagos

CLINICAL STUDY PROTOCOL (CSP)

Project Number:	GLPG1690
Study Number:	GLPG1690-CL-204
Study Title:	A Phase 2a randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy, safety, and tolerability of orally administered GLPG1690 for 24 weeks in subjects with systemic sclerosis

Development Phase:	2a	**Status:**	Final
CSP Version:	5.00	**Date:**	28-Apr-2020
Amendment:	3		
EudraCT No.:	2018-001817-33		
CT.gov No.:	NCT03798366		
IND No.:	140691		
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium		
Study Physician:	[redacted] MD		
General Protocol			

EMERGENCY CONTACT INFORMATION

In case of a **serious adverse event (SAE), a Special Situation** (see Section 9.1.6), 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 SAE or pregnancy, as follows:

[redacted]

Fax #: [redacted]

or

E-mail: [redacted]

In case of medical **questions** during the course of the study, the investigator must contact the contract research organization (CRO) Medical Monitor. For urgent medical/safety questions, the investigator can contact the safety hotline.

CRO Lead Medical Monitor:

[redacted]

Contact Safety Hotline:

EMEA: [redacted]

North America: [redacted]

Sponsor Contact Number:

[redacted]

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CLINICAL STUDY PROTOCOL HISTORY

CSP / Amendment #	Date	Main Rationale General / Country Specific
Amendment 3 / CSP Version 5.00	28-Apr-2020	To implement the urgent safety measures (USM) to mitigate the impact of the current COVID-19 pandemic for the participating systemic sclerosis patients. These were detailed in the USM letter dated 08 April 2020 and sent to investigators, Competent Authorities, Ethics Committees, and Institutional Review Boards. General
Amendment 2 / CSP Version 4.00	31-Jul-2019	Update of information based on Investigator Brochure Edition 6 (28-Jun-2019), incorporation of changes in CSP Version 1.00 for [redacted] corrections of errors and clarifications General
CSP [redacted] Version 1.00	12-Mar-2019	First country specific CSP (Version 1.00) created for [redacted] based on General CSP Version 3.00. [redacted] Country Specific: [redacted]
Amendment 1 / CSP Version 3.00	13-Nov-2018	Revision of subject exclusion criteria General
CSP Version 2.00	20-Aug-2018	Minor edits General
CSP Version 1.00	31-Jul-2018	Initial Protocol Version General

SUMMARY OF CHANGES

Amendment 3 (28-Apr-2020)
The overall reason for this amendment: To implement the urgent safety measures (USM) to mitigate the impact of the current COVID-19 pandemic for the participating systemic sclerosis patients. These were detailed in the USM letter dated 08 April 2020 and sent to investigators, Competent Authorities, Ethics Committees, and Institutional Review Boards. The objective of these USMs is to reduce the risk of infections for the study subjects by increasing the flexibility of study visits and thereby avoid exposure risk during the pandemic. The measures apply specifically to subjects who are unable or unwilling to perform on-site study procedures due to the COVID-19 pandemic.
The changes made to CSP GLPG1690-CL-204 Version 4.00 (31 Jul 2019), are listed below, with a brief rationale of each change and the applicable sections.
For any subjects who, due to any COVID-19-related reason, cannot attend the final visit in the treatment period, Visit 9 (24 weeks), within the time window of ±4 days, the window for the visit may be increased to ±28 days. The subject should continue the intake of Investigational Medicinal Product (IMP) until Visit 9 (ultimately until Week 28). For the rollover of a subject into the GLPG1690-CL-206 Open-Label Extension study, a complete, on-site rollover visit is required. If Visit 9 cannot be conducted on site within the extended window of Week 24 +28 days, the subject will be given the opportunity to rollover into the Open-Label Extension study until Week 32. In this case, the subject will however be off study medication and not receive IMP between Week 28 to 32. The Visit 9/rollover assessments should be performed at this on-site visit, [redacted] If the rollover visit cannot be scheduled before Week 32, the subject will continue in the follow-up period of GLPG1690-CL-204 with a first follow-up visit 4 weeks after last IMP administration. **Applicable Sections**: Section 4.1 Overall Clinical Study Design Section 6.1 Timing of assessments Section 6.11 Schedule of Activities
If Visit 9 needs to be postponed until after Week 24, regular phone calls at Week 24 and every 14 days thereafter should be implemented to evaluate the subject's safety until a visit can take place on site. In addition, if any of the follow-up visits cannot be performed on site, a phone call to evaluate the subject's safety should be performed. The information to be collected during these phone calls is detailed in the USM letter and summarized in the protocol Section 6.6. **Applicable Sections**: Section 6.1 Timing of events Section 6.6 Safety assessments Section 6.11 Schedule of activities
When Visit 9 needs to be postponed beyond Week 24, a Direct-to-Patient (DTP) shipment of one additional IMP kit may be implemented to cover the prolongation of treatment (by up to 28 days). Urine pregnancy tests to perform the monthly pregnancy test at home until follow-up visit 1 (if applicable) and treatment or follow-up diary cards should also be shipped to the subject to cover the longer period between on-site visits. **Applicable Sections:** Section 5.3 Packaging, labelling, and distribution Section 6.1 Timing of events Section 6.6 Safety assessments

Amendment 2 (31-July-2019)
The overall reason for this amendment: Update of information based on Investigator Brochure Edition 6 (28-Jun-2019), incorporation of changes to address changes in CSP Version 1.00 for [redacted], corrections of errors and clarifications.
The changes made to the CSP GLPG1690-CL-204 Version 3.00 (13 Nov 2018), are listed below, with a brief rationale of each change and the applicable sections.
The changes made in CSP [redacted] Version 1.00 (12-Mar-2019) have been implemented, with the exception of the change to Inclusion Criterion 8 regarding body mass index (BMI), which was modified in the CSP for [redacted]. In this General CSP Version 4.00, Inclusion Criterion 8 remains unchanged (BMI 18-35 kg/m²) except in [redacted], where a BMI of 18-30 kg/m² applies. **Applicable Sections**: Section 4.5.1 Inclusion Criteria All other changes as detailed in the separate table below for CSP [redacted] Version 1.00 (12-Mar-2019)
The current Investigator's Brochure is now Edition 6.00 (28-Jun-2019). The information on GLPG1690 has been updated. **Applicable Sections**: Section 2 Introduction Section 4.4 Potential risks and Benefits Section 5.1 Identity of the Investigational Medicinal Product Section 4.5.3.2 Prior and Concomitant Medications
[redacted] In addition, the objective and endpoint definitions were aligned. **Applicable Sections**: Summary Section 3.3 Other Objectives Section 4.3.3. Other Endpoints [redacted]
The period of time prior to the treatment period during which subjects may not take excluded medications has been clarified. **Applicable Sections**: Section 4.5.2 Exclusion Criteria

The period of time prior to screening during which subjects' medications should be stable has been clarified. Bosentan has been added to the list of excluded medications, and hydroxychloroquine to the list of medication known to prolong QT interval (to be used with caution). The prohibition of B-cell depleting agents has been broadened to "other monoclonal antibodies". **Applicable Sections**: Section 4.5.3.2 Prior and Concomitant Medications Appendix 2 Known Strong CYP3A4 Inducers and Potent P-gp Inducers Appendix 5 Medication Known to Prolong QT interval
The list of clinical laboratory tests has been revised – Mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration have been added to the hematology parameters. – Creatine kinase has been added to the serum chemistry parameters. – Ketone have been added to the urinalysis parameters **Applicable Section:** Section 6.6.2 Clinical laboratory evaluations
The ECG parameter QTcB will not be derived. **Applicable Section:** Section 6.6.5 12-lead Electrocardiogram
[redacted]
An interim analysis at Week 16 is no longer planned. The sponsor decided that an interim analysis is no longer required. A clarification has been added that the primary analysis of efficacy will be performed at Week 24, at the end of the double-blind treatment period. **Applicable Sections**: Section 4.6.2 Blinding and Unblinding Section 7 Statistical Methods New section – Section 7.3.2. Primary Analysis Renumbered section - Section ~~7.3.2~~ 7.3.3 Interim Analysis

CSP [redacted] Version 1.00 (12-Mar-2019)
The overall reason for this amendment: [redacted]
The changes made to the CSP GLPG1690-CL-204 Version 3.00, (13-Nov-2018), are listed below, reflecting a brief rationale of each change and the applicable sections.
The information on fertility has been updated with the results of nonclinical male and female fertility studies in rats. The recommendation for males to store sperm before taking part in the study has been removed, and replaced with guidance for male subjects to withdraw if they intend to father a child. **Applicable Sections:** Section 4.4 Potential Risks and Benefits Section 4.5.3.1.2 Precautions for Sexual Intercourse: Male subjects
It is clarified that all adverse events (AEs) will be collected until the subject's last follow-up Visit. **Applicable Sections**: Section 4.1 Overall Clinical Study Design Section 6.6.1 Adverse Events Section 6.11 Schedule of Activities Section 7.3.5 Analysis of Safety Data
The specific liver function test (LFT) threshold at Visit 2 was removed; the LFT criteria for treatment discontinuation apply to all study visits. **Applicable Sections**: Section 4.5.4. Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal, and Study Termination
A urine pregnancy test was added at Visit 2 (Day 1) and Follow-up Visit 1. **Applicable Sections**: Section 4.5.1 Inclusion Criteria Section 4.5.3.1.1 Precautions for Sexual Intercourse: Female subjects Section 6.11 Schedule of Activities
Inclusion criterion 8 regarding body mass index (BMI) was modified to include subjects with BMI 18-30 kg/m^2 in the study. **Applicable Sections**: Section 4.5.1 Inclusion Criteria

Minor edits and administrative updates throughout the protocol. **Applicable Sections**: Title Page Section 2.2.1 Clinical Safety Signature Page – Sponsor Appendix 2

Amendment 1 (13-Nov-2018)
The overall reason for this amendment: Subject exclusion criteria were revised to comply with the [redacted] Law and facilitate subject recruitment.
The changes made to the CSP GLPG1690-CL-204 Version 2.00, {20-aug-2018}, are listed below, reflecting a brief rationale of each change and the applicable sections.
Rationale: The protocol was updated to revise the definition of abnormal renal function in exclusion criterion 19. The initial exclusion criterion was too stringent for this patient population. The change is not expected to affect subjects' safety. **Applicable Sections**: 4.5.2 Exclusion Criteria
Rationale: The protocol was updated to add an exclusion criteria 30 to comply with the [redacted] **Applicable Sections**: 4.5.2 Exclusion Criteria
Rationale: The procedure for collection of informed consent of a patient unable to read and/or write was amended to comply with the [redacted] **Applicable Sections**: 10.4.2 Informed Consent
Rationale: The protocol was updated to delete Appendix 1 with normal ranges for vital signs and ECG parameters. The clinical significance of vital signs and ECG assessments is to be at the investigator's discretion. **Applicable Sections**: Appendix 1

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ACR	American College of Rheumatology
AE	adverse event
ALAT	Latin American Thoracic Association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
ATS	American Thoracic Society
ATX	autotaxin
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BCRP	breast cancer resistance protein
b.i.d.	twice daily
BMI	body mass index
BW	body weight
cGvHD	chronic graft-versus-host disease
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
[redacted]	[redacted]
COVID-19	Coronavirus disease
CRF	case report form
[redacted]	[redacted]
CRO	contract research organization
CSP	clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTGF	connective tissue growth factor
CYP	cytochrome P450
DBP	diastolic blood pressure
DTP	direct to patient
ECG	electrocardiogram
ED	early discontinuation

eGFR	estimated glomerular filtration rate
[redacted]	[redacted]
ENPP	ectonucleotide pyrophosphatase/phosphodiesterase
EoS	end of the study
ERS	European Respiratory Society
ET-1	endothelin-1
EU	European Union
EULAR	European League Against Rheumatism
FC	fold change
[redacted]	[redacted]
[redacted]	[redacted]
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice(s)
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
[redacted]	[redacted]
HIV	human immunodeficiency virus
HMA	Heads of Medicines Agencies
[redacted]	[redacted]
IB	investigator's brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IL-x	interleukin x
IMP	investigational medicinal product
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IWRS	interactive web response system
JRS	Japanese Respiratory Society
LFT	liver function test
LPA	lysophosphatidic acid

LPC	Lysophosphatidylcholine
LPD	lysophospholipase D
LS	least square
[redacted]	[redacted]
MATE	multi drug and toxin extrusion transporter
MCID	Minimal Clinically Important Difference
MMF	mycophenolate mofetil
MMRM	mixed-effects model for repeated measures
mRSS	modified Rodnan skin score
NOAEL	no observed adverse effects level
NOEL	no observed effect level
[redacted]	[redacted]
PDE	Phosphodiesterase
P-gp	P-glycoprotein
[redacted]	[redacted]
PLA	phospholipase A
PLC	phospholipase C
[redacted]	[redacted]
q.d.	once daily
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcV	QT interval corrected for heart rate using Van de Water's formula
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCTC	Scleroderma Clinical Trials Consortium
[redacted]	[redacted]
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
[redacted]	[redacted]
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factor β
[redacted]	[redacted]
TNF	tumor necrosis factor
ULN	upper limit of normal
[redacted]	[redacted]

WOCBP	women of childbearing potential

Definition of Terms

BMI	Weight (kg) / (height [m])^2
QTcF	QTcF = QT / RR$^{1/3}$

1. SUMMARY

Objectives:

Primary Objective

– To evaluate the efficacy of GLPG1690 as evaluated by modified Rodnan skin score (mRSS) compared to placebo over 24 weeks for the treatment of subjects with systemic sclerosis

Secondary Objective

– To evaluate the safety and tolerability of GLPG1690 compared to placebo over 24 weeks in the treatment of subjects with systemic sclerosis

Other Objectives

Design:

This is a randomized, double-blind, parallel-group, placebo-controlled, multi-center, Phase 2a study designed to evaluate the efficacy, safety, and tolerability of a 600 mg once daily (q.d.) oral dose of GLPG1690 administered over 24 weeks in adult subjects with a confirmed diagnosis of systemic sclerosis. A total of approximately 30 subjects will be randomized in a 2:1 ratio to receive GLPG1690 600 mg q.d. or matching placebo q.d. (for details on sample size, refer to "Determination of Sample Size").

Rationale:

There are currently no approved drugs for the treatment of systemic sclerosis, indicating a high-level unmet medical need. Available literature and preclinical pharmacology data generated by Galapagos suggest that interventions targeting the autotaxin (ATX)/lysophosphatidic acid (LPA) pathway could lead to a new class of therapy for disease modification in systemic sclerosis. GLPG1690 is currently in clinical development for the treatment of subjects with idiopathic pulmonary fibrosis (IPF). This study will assess GLPG1690 as a potential first-in-class disease-modifying drug for systemic sclerosis.

Endpoints:

Primary Endpoint

- Change from baseline in mRSS over 24 weeks

Secondary Endpoint

- Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), adverse events (AEs), and tolerability of GLPG1690 over 24 weeks

Other Endpoints

2. INTRODUCTION

For more details refer to the investigator's brochure (IB) for GLPG1690 (Edition 6, 28-Jun-2019) and relevant updates/addenda.

This clinical study will be conducted in accordance with the current International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice (ICH-GCP) Guideline E6 (see also Section 10).

Systemic Sclerosis

Systemic sclerosis (scleroderma) is a rare autoimmune disease of the connective tissue with the highest mortality rate of all rheumatic diseases. The disease has a female predominance (3:1) and a peak onset in the fourth decade of life. Systemic sclerosis has three major pathogenic components: (i) fibrosis with thickening of the skin and inner organs, (ii) inflammation, and (iii) vasculopathy. Major organs affected are the skin, the lung (pulmonary fibrosis and pulmonary arterial hypertension), the kidneys, the gastrointestinal tract, the musculoskeletal system, the retroperitoneal space, and the heart. Current treatment options for systemic sclerosis are limited and include topical skin treatments, non-steroidal anti-inflammatory drugs, steroids, and other immunosuppressants (methotrexate, mycophenolate mofetil [MMF], azathioprine, cyclophosphamide).

At present, there are no approved drugs for the treatment of systemic sclerosis, indicating a high-level unmet medical need.

The sponsor is currently pursuing the development of GLPG1690, a small-molecule autotaxin (ATX) inhibitor targeting disease-relevant signal transduction pathways, for the treatment of systemic sclerosis.

Mode of Action

GLPG1690 is a novel, potent, and selective small-molecule inhibitor of ATX.

ATX, also known as ectonucleotide pyrophosphatase/phosphodiesterase (ENPP) 2 or lysophospholipase D (LPD), is a ~120 kDa protein that belongs to the ENPP enzyme family. ATX is the only ENPP enzyme with LPD activity and is responsible for the hydrolysis of lysophosphatidylcholine (LPC) to produce the bioactive lipid lysophosphatidic acid (LPA). The term LPA covers several chemical species able to activate LPA receptors depending on the nature of the fatty acid side chain on the glycerol backbone. The most abundant LPA species in human plasma is LPA C18:2 with a fatty acid side chain of 18 carbon atoms including two unsaturated bonds (Bandoh K. et al, 2000). Literature data have identified the ATX/LPC axis as the main source of LPA in blood (Tanaka M. et al., 2006; Tsuda S. et al., 2006).

LPA acts through six different G-protein coupled receptors (LPA1-6) whereby mainly LPA1-3 have been associated with the pathogenic (pro-inflammatory and pro-fibrotic) effects of LPA. Targeting the ATX pathway by antagonizing LPA1 in a previous Phase 2a study (SAR100842) in systemic sclerosis was well tolerated and resulted in clinical improvements of skin pathologies (modified Rodnan skin score [mRSS]) and skin biomarkers, suggesting that

targeting the ATX pathway is promising in modulating skin pathologies in systemic sclerosis (Allanore T. et al., 2018).

Available literature and nonclinical pharmacology data generated by Galapagos suggest that interventions targeting the ATX/LPA pathway could lead to a new class of therapy for disease modification in systemic sclerosis.

2.1. BACKGROUND - NONCLINICAL STUDIES

2.1.1. Physical, Chemical, Pharmaceutical Properties, and Formulation

The chemical name of GLPG1690 is 2-[[2-ethyl-6-[4-[2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]piperazin-1-yl]-8-methylimidazo[1,2-a]pyridin-3-yl](methyl)amino]-4-(4-fluorophenyl)-1,3-thiazole-5-carbonitrile.

The clinical formulation used in this study is a film-coated tablet.

2.1.2. Pharmacology

2.1.2.1. Primary and Secondary Pharmacology

GLPG1690 is an ATX inhibitor (50% inhibitory concentration [IC_{50}] of 131 nM and 224 nM in biochemical assays with human enzyme and mouse enzyme, respectively). The LPA production after human plasma incubation was inhibited by GLPG1690 with an IC_{50} of 242 nM, demonstrating the low impact of plasma protein binding on the activity of the compound. The compound was selective over related enzymes like ENPP1, phosphodiesterase (PDE)4 and PDE5, and phospholipase A (PLA) and phospholipase C (PLC). Moreover, GLPG1690 showed no inhibition in a panel of kinases. In a Cerep diversity panel (98 targets including receptors and ion channels), only three targets displayed more than 50% inhibition at 10 µM, [redacted]

GLPG1690 dose-dependently inhibited the production of connective tissue growth factor (CTGF), interleukin 6 (IL-6), and endothelin-1 (ET-1) upon transforming growth factor β (TGFβ)-triggering in normal human dermal fibroblasts and in lung fibroblasts from a subject with idiopathic pulmonary fibrosis (IPF).

Pharmacokinetic (PK)/pharmacodynamic (PD) experiments in mice demonstrated an inverse relationship between LPA level and GLPG1690 concentration in plasma in vivo.

The efficacy of GLPG1690 was assessed in a murine model of chronic graft-versus-host disease (cGvHD) resembling key components of dermal and pulmonary systemic sclerosis disease manifestations by evaluating clinical scoring, dermal thickening, hydroxyproline content, and myofibroblast counts. In this model, GLPG1690 showed efficacy for skin and lung read-out parameters similar to that of nintedanib.

2.1.2.2. Safety Pharmacology

The safety pharmacology package conducted to investigate the potential effect of GLPG1690 on cardiovascular, respiratory, and central nervous systems did not show any biologically relevant effects.

2.1.3. Nonclinical Pharmacokinetics and Product Metabolism

The absolute oral bioavailability was moderate in rodents (25% to 36%), low in monkeys (14%), and high in dogs (102%).

GLPG1690 was highly bound to plasma proteins: 99.1% in human and 97.9-99.6% in rat, dog, mouse, rabbit, and monkey.

Overall, GLPG1690 did not extensively distribute into tissues as shown by the low volume of distribution at steady state (V_{ss}) ranging from 0.35 L/kg in the mouse to 0.55 L/kg in the monkey. In rat, [^{14}C]-GLPG1690 was widely distributed throughout the body. Highest concentrations of radioactivity were observed in contents of the gastrointestinal (GI) tract, glandular tissues, liver, and uveal tract. Some affinity was observed of GLPG1690 and/or metabolites for melanin-containing tissues, like uveal tract and meninges.

After oral administration, drug-related material is excreted mainly in feces in rat (about 90% or greater). In bile duct-cannulated rats, about 50% of orally administered radioactivity was recovered in bile.

Upon repeated once daily (q.d.) oral dosing of GLPG1690, no significant accumulation was observed in plasma, except in male rats (20 mg/kg/day) and dogs (50/65 mg/kg/day at Week 39). Gender differences in PK profiles were observed in rats but not in dogs.

The total plasma clearance of GLPG1690 was low in mice, rats, monkeys, and dogs, ranging between 3% and 23% of the hepatic blood flow. Therefore, GLPG1690 is expected to undergo a low first-pass effect after oral dosing.

The primary cytochrome P450 (CYP) enzyme involved in GLPG1690 metabolism was CYP3A4. In vitro metabolism studies in hepatocytes revealed 26 potential metabolites. Metabolites formed in human hepatocytes were all present to a similar or higher extent in rat and/or dog hepatocytes, the animal species selected for toxicity studies.

An in vitro study with GLPG1690 in human hepatocytes showed no clinically relevant induction of human CYP2B6 and CYP2C enzymes. Weak induction of CYP1A2 and CYP3A4, cannot be excluded at a GLPG1690 dose of 600 mg in human, with a maximal decrease of around 30% in the exposure of a sensitive probe substrate for both CYP enzymes.

An in vitro study with GLPG1690 in human liver microsomes indicated no clinically relevant inhibition of the majority of CYP enzymes. Weak competitive reversible inhibition of CYP2C8 and CYP3A4/5 cannot be excluded at a GLPG1690 dose of 600 mg in human, with a maximal increase of approximately 1.7- and 1.5-fold, respectively in the exposure of a sensitive probe substrate.

GLPG1690 demonstrated a strong time-dependent, irreversible inhibition potential against CYP2C8-mediated metabolism. This could likely lead to a pronounced interaction with a

sensitive CYP2C8 probe substrate (increased exposure) if co-administered with a GLPG1690 dose of 600 mg in human.

No interaction of GLPG1690 is expected with renal uptake transporters, organic cation transporter (OCT)2, organic anion transporter (OAT)1 and OAT3 and hepatic efflux transporters P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP). For the hepatic uptake transporters OATP1B1, OATP1B3, and OCT1, and the multi drug and toxin extrusion (MATE) efflux transporters MATE1 (hepatic/renal) and MATE2K (renal), a clinical interaction with GLPG1690 cannot be ruled out, however substantial interactions are not anticipated. For the intestinal efflux P-gp and BCRP transporters and the hepatic efflux bile salt export pump transporters an interaction cannot be ruled out.

2.1.4. Toxicology

2.1.4.1. General Toxicology

A comprehensive toxicology program has been conducted with GLPG1690. This program includes Good Laboratory Practice (GLP) oral repeat-dose toxicity studies of up to 26 weeks in rats and 39 weeks in dogs, embryo fetal development studies in rats and rabbits, fertility studies in male and female rats, non-TgrasH2 mice preliminary studies, preliminary carcinogenicity studies, and *i* vivo and in vitro genotoxicity studies. Additional toxicology studies conducted include phototoxicity studies and dose range-finding studies in rats and dogs.

In rats, no GLPG1690-related mortality was observed. The dose-limiting adverse effects consisted of reduced food consumption and markedly decreased body weight (BW) gain at 1,000 mg/kg/day in the 4-week toxicity study, histopathological changes in the testes with reduced sperm parameters at ≥130 mg/kg/day in the 13- and 26-week GLP studies, and the presence of vacuolated alveolar macrophages, with alveolar amorphous material and perivascular inflammatory cell infiltration in the lungs of females in the 26-week GLP study. The no observed adverse effects level (NOAEL) values in rats were set at 40 and 130 mg/kg/day in males and females, respectively, in the 26-week GLP study.

In repeat oral dose toxicity studies in dogs, the dose-limiting effects corresponded to decreased white blood cell count and food consumption, emesis and BW loss, associated with poor clinical conditions at doses ≥100 mg/kg/day in the 13- and 39-week GLP studies, respectively. QT prolongation (in 4-, 13-, and 39-week studies), which was considered non-adverse, were also observed in repeat oral dose toxicity studies in dogs. Additional adverse findings in dogs consisted of adverse altered sperm parameters and inflammatory cell infiltrates in the liver and minimal bile duct hyperplasia at 150/100 mg/kg/day (in the 13-week GLP toxicity study) and QT prolongation (in 4-, 13- and 39-week studies). The NOAEL value in dogs was set at 50/65 mg/kg/day in the 39-week GLP study.

Male and female fertility studies in rats showed that there were no effects of GLPG1690 on mating performance, fertility, or reproduction in either male or female rats at the different dose levels tested. As the effects on sperm and testis proved reversible and had no functional impact on animal fertility parameters, the risk of an impact on male fertility in adult subjects is considered low. In males, the no observed effect level (NOEL) for mating performance and fertility was set at 400 mg/kg/day and the NOAEL for sperm changes was determined at 40 mg/kg/day; the latter is in line with previous studies (i.e.13 week rat study). In females, the NOEL for mating performance and fertility was considered to be 120 mg/kg/day.

In reproductive embryofetal development studies with GLPG1690 in rats and rabbits, major external, visceral, and skeletal abnormalities were seen in fetuses of both species as well as increased incidences of post-implantation losses. In rats, the maternal and developmental NOAELs were determined at 60 mg/kg/day and 10 mg/kg/day, respectively. In rabbits, the maternal and developmental NOAELs were determined at 15 mg/kg/day and 5 mg/kg/day, respectively.

GLPG1690 showed no genotoxic effects in vitro or in vivo.

GLPG1690 showed a phototoxic potential in vitro. However, this potential has not been confirmed in an in vivo study in female pigmented Long-Evans rats, investigating the phototoxic effects on the eyes and the skin. No evidence of cutaneous or ocular phototoxicity was noted at doses of 100 and 300 mg/kg.

2.2. BACKGROUND - CLINICAL STUDIES

2.2.1. Clinical Safety

In clinical pharmacology studies, GLPG1690 has been administered to 85 healthy subjects as single doses (dose range: 20 to 1500 mg), to 96 healthy subjects in repeated doses (dose range: 100 to 1000 mg for either 7 or 14 days).

Administration of GLPG1690 in these Phase 1 studies was considered safe and well tolerated. No deaths, other serious treatment-emergent adverse events (TEAEs), TEAEs leading to IMP discontinuation, or clinically significant abnormalities related to laboratory parameters, electrocardiogram (ECG), vital signs, or physical examinations were reported during any of these Phase 1 studies. GLPG1690 was well tolerated and all TEAEs were at most moderate in severity.

Administration of oral doses of GLPG1690 600 mg q.d. as a capsule for 12 weeks in 17 subjects with IPF was well tolerated (Phase 2a study GLPG1690-CL-202). No deaths were reported. Serious TEAEs were experienced by one subject in the GLPG1690 600 mg q.d. group (cholangiocarcinoma, led to permanent discontinuation) and by two subjects in the placebo group (atrioventricular block second degree in one subject, led to permanent discontinuation; and lower respiratory tract infection, urinary tract infection, and acute kidney injury in the other subject).

None of these serious TEAEs were considered related to IMP. No notable differences were observed in the incidences of treatment-emergent abnormalities between subjects with IPF treated with GLPG1690 600 mg q.d. or placebo. The majority of TEAEs were mild to moderate in severity. No clinically significant abnormalities related to laboratory parameters, electrocardiogram (ECG), vital signs, or physical examinations were reported.

2.2.2. Clinical Efficacy

Following 12 weeks of treatment in subjects with IPF in study GLPG1690-CL-202, on-site forced vital capacity (FVC) spirometry performed at screening, baseline, Weeks 1, 2, 4, 8, and 12 (or at early discontinuation [ED], if applicable), and at follow-up (2 weeks after the last IMP intake) showed that FVC values remained stable in the majority of subjects taking GLPG1690 600 mg q.d.

2.2.3. Clinical Pharmacokinetics

GLPG1690 formulated as a liquid suspension was rapidly absorbed with a median time to maximum observed plasma concentration (t_{max}) of 0.5 to 2 hours. Steady-state exposure of GLPG1690 increased approximately (slight over proportionality) in proportion with the dose between 300 to 1,000 mg total daily dose. Excretion of unchanged GLPG1690 in human urine was low (<1.8% in 24 hours) and rapid. There was no impact on the urinary 6-β-OH-cortisol/cortisol ratio after repeated dosing suggesting a lack of CYP3A4 induction by GLPG1690.

Given as tablet, food decreased the rate of absorption of GLPG1690 but there was no clinically relevant difference in the bioavailability of GLPG1690. A higher between-subject variability was observed in fasted state, with four subjects out of 12 having 5- to 10-fold lower exposure than the other subjects. The rate of elimination was not impacted by food. The overall mean terminal elimination half-life ($t_{1/2}$) after a single dose as tablets was approximately 11 hours.

GLPG1690 exposure is reduced up to 90% by the strong CYP3A4/potent P-gp inducer rifampin (by 6.0- and 9.3-fold for C_{max} and area under the plasma concentration-time curve from time 0 to 24 h [AUC_{0-24h}], respectively). Exposure of GLPG1690, as measured by the area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0-\infty}$), was 3- and 4 fold greater when administered in combination with itraconazole (a strong CYP3A4 and potent P-gp inhibitor) and voriconazole (a strong CYP3A4 inhibitor, but non-P-gp inhibitor), respectively, than when as administered alone. Maximum exposure (C_{max}) of GLPG1690 increased slightly following administration of GLPG1690 in combination with itraconazole or voriconazole compared with administration of GLPG1690 only (C_{max} values were 1.4-fold greater following administration in combination with itraconazole or voriconazole). This increase is unlikely to be clinically significant. GLPG1690 can therefore be classified as a moderately sensitive substrate of CYP3A4 as it demonstrated an increase in AUC of ≥2 to <5-fold with strong index inhibitors.

The PK of GLG1690 was similar between Caucasian and Japanese healthy male subjects. The PK of GLPG1690 in subjects with IPF was not markedly different from those observed in healthy subjects at the same dose level.

2.2.4. Clinical Pharmacodynamics

After a single administration of GLPG1690, a significant dose-dependent percentage reduction of LPA C18:2 was observed in plasma. This effect started from 0.5 hours after IMP intake, reached a plateau, and was sustained over time up to 24 hours after IMP intake. Multiple q.d. or b.i.d. ascending doses resulted in a similar effect on LPA C18:2. A strong reduction in LPA C18:2 levels was already observed at Day 14 before IMP intake, pointing to a sustained effect over 14 days.

The sustained effect on LPA C18:2 was also confirmed by area under the effect-time curve (AUEC) for the percentage reduction from baseline and maximum effect (expressed as a percentage reduction from baseline) (E_{max}).GLPG1690 induced a fast and sustained reduction in plasma LPA C18:2 levels in subjects with IPF, indicative for target engagement. At the follow-up visit, the mean LPA C18:2 level was back to baseline levels, indicating that the inhibitory effect of GLPG1690 on the target is reversible.

3. CLINICAL STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

- To evaluate the efficacy of GLPG1690 as evaluated by mRSS compared to placebo over 24 weeks for the treatment of subjects with systemic sclerosis

3.2. SECONDARY OBJECTIVE

- To evaluate the safety and tolerability of GLPG1690 compared to placebo over 24 weeks in the treatment of subjects with systemic sclerosis

3.3. OTHER OBJECTIVES

4. INVESTIGATIONAL PLAN

4.1. OVERALL CLINICAL STUDY DESIGN

This is a randomized, double-blind, parallel-group, placebo-controlled, multi-center, Phase 2a study designed to evaluate the efficacy, safety, and tolerability of a 600 mg q.d. dose of orally administered GLPG1690 over 24 weeks in approximately 30 adult subjects with a confirmed diagnosis of systemic sclerosis.

At Day 1/Visit 2 (baseline), subjects will be randomized in a 2:1 ratio to GLPG1690 600 mg q.d. taken as three film-coated tablets of 200 mg, or matching placebo q.d. administered for 24 weeks in addition to background treatment as defined in Section 4.5.3.2, "Prior and Concomitant medications".

A schematic diagram of the clinical study design, procedures, and stages is provided in Figure 1.

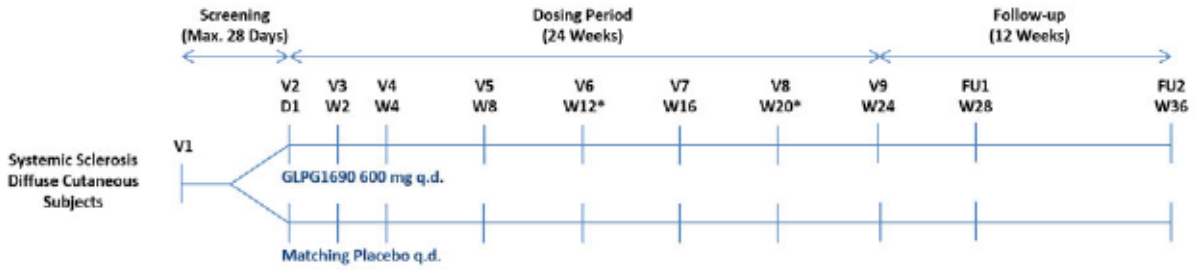


Figure 1: Schematic Study Overview

D=Day, FU=Follow-up, V=Visit, W=Week.
* This will be a phone call to assess safety (no clinical study center visit).

For the in- and exclusion criteria please refer to Section 4.5.1, "Inclusion Criteria" and Section 4.5.2, "Exclusion Criteria".

The subjects will visit the clinical study center at screening/Visit 1 (Day -28 to Day -1), Day 1/Visit 2 (baseline), Day 15 (Week 2/Visit 3), Day 29 (Week 4/Visit 4), Day 57 (Week 8/Visit 5), Day 113 (Week 16/Visit 7), Day 169 (Week 24/Visit 9), and, if applicable, the ED visit. At Weeks 12 (Visit 6) and 20 (Visit 8), a phone call will be made to assess safety. In addition, a follow-up visit will be planned 4 weeks after the last administration of IMP (Day 197 [Week 28]) (i.e. Follow-up Visit 1) and a second follow-up visit will be planned 12 weeks after the last administration of IMP (Day 253 [Week 36]) (i.e. Follow-up Visit 2). Additional unscheduled visits are allowed for any safety assessments if clinically indicated (see Section 6.2).

For any subjects who, due to any COVID-19-related reason, cannot perform Visit 9 (Week 24), within the time window of ±4 days, the window for the visit may be increased to ±28 days.

Each subject will be in the study for up to approximately 40 weeks (up to 4 weeks of screening, 24 weeks of treatment, and 12 weeks of follow-up). Covid-19 mitigation measures may increase the time in the study up to approximately 44 weeks.

For detailed info regarding dosage form, packaging, and labeling of the IMP, please refer to Section 5.2, "Dosage and Administration" and Section 5.3, "Packaging, Labeling, and Distribution".

The end of the study (EoS) is reached when the last visit of the last subject is performed.

Open-label Extension

Subjects who completed the Week 24 visit will be offered treatment with GLPG1690 in an optional open-label extension, provided regulatory and Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approvals for such an extension is granted. In this case, the follow-up visits are not performed for these subjects. This extension is described in a separate protocol, Study GLPG1690-CL-206.

For the rollover of a subject into the GLPG1690-CL-206 study, a complete rollover visit, at Visit 9 of this study (GLPG1690-CL-204), is required.

If Visit 9 cannot be conducted on site within the extended window of Week 24 +28 days, due to any COVID-19-related reason, the subject will be given the opportunity to complete an on-site visit and rollover into the Open-Label Extension study until Week 32. The Visit 9/rollover assessments should be performed at this on-site visit, [redacted]. The subject will however be off study medication and not receive IMP between Week 28 to 32. If the subject decides not to rollover to GLPG1690-CL-206, and the on-site visit can be conducted in the window Week 32 ±7 days after initial IMP start in GLPG1690-CL-204, the on-site visit should be considered to be Follow-up visit 1.

If the rollover visit cannot be scheduled before Week 32, the subject will continue in the follow-up period of GLPG1690-CL-204 with a first follow-up visit 4 weeks after last IMP administration.

4.2. CLINICAL STUDY RATIONALE

Systemic sclerosis is a chronic and progressive disease with the highest morbidity and mortality among all autoimmune diseases without any approved drug, indicating a high unmet medical need for the development of novel disease-modifying therapies.

In vitro and in vivo studies indicate an essential role for ATX, an enzyme with LPD activity responsible for the production of the pro-inflammatory/pro-fibrotic mediator LPA, in systemic sclerosis: ATX mRNA expression is significantly increased in systemic sclerosis skin biopsies compared to controls. In response to LPA, systemic sclerosis-derived dermal fibroblasts produce significant amounts of IL-6 that has been involved in systemic sclerosis pathogenesis. Two preclinical studies using independent skin fibrosis models (bleomycin and sclerodermatous cGvHD models) demonstrated a high level of target engagement and efficacy upon ATX inhibition. Moreover, GLPG1690 dose-dependently inhibited the production of the fibrogenic mediator CTGF by human dermal fibroblasts upon TGFβ-triggering. Overall, inhibition of ATX has the potential for a triple mechanism of action in systemic sclerosis: (i) inhibition of pro-fibrotic LPA, (ii) inhibition of pro-inflammatory IL-6 (ATX-IL-6 loop), and (iii) inhibition of angiogenic ET-1, thereby addressing all three major pathogenic components of systemic sclerosis (described in Section 2.1.2).

GLPG1690 is currently in clinical development for the treatment of patients with IPF. This study will assess GLPG1690 as a potential first-in-class disease-modifying drug for systemic sclerosis.

As described in Section 2.2, results from a GLPG1690 Phase 1 first-in-human study (GLPG1690-CL-101) generated promising PD results (target engagement, LPA reduction) and indicated that GLPG1690 was generally safe and well tolerated in a population of healthy subjects. Moreover, safety, PK, and PD properties were successfully evaluated in a Phase 2a study in subjects with IPF (GLPG1690-CL-202). In a previous Phase 2a study (SAR100842), targeting the ATX pathway in systemic sclerosis by antagonizing LPA1 was well tolerated and resulted in clinical improvements of skin pathologies (mRSS) and skin biomarkers, suggesting that targeting the ATX pathway is promising in modulating skin pathologies in systemic sclerosis (Allanore T. et al., 2018).

When viewed in combination, these preclinical and clinical studies strongly suggest that interfering with ATX by GLPG1690 in systemic sclerosis is a promising novel disease-modifying approach.

4.2.1. Dose Rationale

A dose of GLPG1690 600 mg q.d. for oral administration has been selected to be evaluated in this Phase 2a study.

This selection is based on the effective dose tested in a Phase 2a study in subjects with IPF (GLPG1690-CL-202) and on the observations made on efficacy, PD, PK, safety, and tolerability in the same study, where GLPG1690 was evaluated as monotherapy versus placebo, as well as on the Phase 1 results in the healthy-subject study (GLPG1690-CL-101).

A population PK and PK/PD model was developed to describe the exposure-response relationships of GLPG1690 and LPA C18:2 as PD biomarker. Subsequent simulations suggest that the anticipated therapeutic dose of 600 mg leads to 88% (range: 86%-89%) LPA C18:2 reduction at steady state. Predicted concentrations at a dose of 600 mg q.d. were above the LPA C18:2 IC_{50} for 100% of the dosing interval.

4.2.2. Clinical Study Design Rationale

This is a randomized, double-blind, parallel-group, placebo-controlled, multi-center, Phase 2a 24-week study in subjects with systemic sclerosis. The randomized double-blind study design was chosen because it is the most rigorous method to generate high-quality scientific data and there is no approved alternative treatment available for comparison. A placebo-controlled study contains internal evidence of assay sensitivity (i.e. when a difference is demonstrated, it is interpretable without reference to external findings), measures absolute safety and efficacy (i.e. it measures the total pharmacologically mediated effect of treatment), is very efficient (i.e. can measure treatment effects with a smaller sample size compared with any other type of controlled study) and minimizes the effect of subject and investigator expectations (ICH E10, 2000). The 2:1 randomization to GLPG1690 avoids unnecessary exposure of subjects to placebo and is typical for Phase 2a studies in systemic sclerosis. The subject eligibility criteria are typical for patient studies in early progressive diffuse cutaneous systemic sclerosis. Based on current European League Against Rheumatism (EULAR) and Scleroderma Clinical Trials Consortium (SCTC) recommendations, background treatment is allowed as defined in Section 4.5.3.2, “Prior and Concomitant Medications”. The study duration (24 weeks) was chosen based on experience with previous clinical studies in diffuse systemic sclerosis with a similar mode of action and similar clinical endpoints. The 12-week follow-up period was chosen based on experience with a previous clinical study targeting LPA1 in order to assess the occurrence of flares after IMP discontinuation in subjects with systemic sclerosis compared to placebo.

4.3. ENDPOINTS

Based on in-house and external preclinical data as well as regulatory experience from previous Phase 2 and Phase 3 studies in systemic sclerosis, mRSS is chosen as primary endpoint. mRSS is a validated outcome measure used in numerous clinical studies in systemic sclerosis and has a defined Minimal Clinically Important Difference (MCID). mRSS is valuable for the evaluation of new treatments for systemic sclerosis as it not only reflects the skin disease component but also inner organ fibrosis in a noninvasive manner.

Since safety and tolerability profiles may differ between indications (i.e. IPF and systemic sclerosis), safety and tolerability are included as secondary endpoint. [redacted]

4.3.1. Primary Endpoint

- Change from baseline in mRSS over 24 weeks

4.3.2. Secondary Endpoint

- Incidence of TEAEs, serious adverse events (SAEs), AEs, and tolerability of GLPG1690 over 24 weeks

4.3.3. Other Endpoints

[redacted]

4.4. POTENTIAL RISKS AND BENEFITS

There are currently no approved drugs for the treatment of systemic sclerosis, indicating a high-level unmet medical need.

GLPG1690 is the first ATX inhibitor in clinical development for the oral treatment of IPF.

Fertility/Embryotoxicity

The risk of treatment with GLPG1690 in adult subjects is primarily related to fertility, pregnancy, and lactation. GLPG1690 induced reversible microscopic findings in the seminiferous tubules in the 13-week oral toxicity studies as well as reversible (complete or partial) changes in sperm parameters in rats and dogs, respectively.

Male and female fertility studies showed that there are no effects of GLPG1690 on mating performance, fertility, or reproduction (litter size and embryofetal survival) in either male or female rats at the dose levels tested. However, there are no human data on the effect of GLPG1690 on fertility. As the effects on sperm and testis proved reversible and had no functional impact on animal fertility parameters, the risk of an impact on male fertility in adult subjects is considered low.

GLPG1690 showed teratogenic effects in both rats and rabbits, with induction of major external, skeletal, and visceral abnormalities at doses >10 mg/kg/day (rats) and >5 mg/kg/day

(rabbits). No data have been generated in lactating women and on excretion in milk. In view of the teratogenic effects seen in animals and limited knowledge of the possible effects of GLPG1690 on lactation at this stage of development, GLPG1690 should not be given to pregnant or lactating women. In addition, highly effective contraceptive measures/preventive exposure measures should be taken by women of childbearing potential (WOCBP) and by men to prevent pregnancy and to avoid the risk of exposure of the embryo or fetus. Detailed information on contraceptive measures is given in Section 4.5.3.1.

QT Interval Prolongation

The potential effect of GLPG1690 on QT interval prolongation is not fully known. Consequently, subjects with long QT syndrome or QTcF >450 ms during screening will be excluded. The chronic use or initiation of medication known to prolong the QT interval needs to be evaluated on a case-by-case basis. Periodic ECG recording and monitoring with central reading will be implemented for the duration of the study. A list intended as guidance for the investigator is provided in Appendix 5.

Drug-drug Interaction

For potential concomitant medication interactions, specific monitoring and guidance will be implemented during the study (refer to Section 4.5.3.2).

Clinical Studies

GLPG1690 has been evaluated in several clinical pharmacology studies and in the GLPG1690-CL-202 study with subjects with IPF. Administration of GLPG1690 was generally safe and well tolerated. In the GLPG1690-CL-202 study, FVC values remained stable in the majority of subjects on GLPG1690 600 mg q.d. (+8 mL mean change from baseline) when administered for 12 weeks (refer to Section 2.2).

Special Populations

As there is limited clinical experience with GLPG1690 so far, the IMP should not be administered to subjects with moderate to severe renal impairment or hepatic impairment.

Refer to the IB for GLPG1690 (Edition 6, 28-Jun-2019) and relevant updates/addenda for additional information on the safety of the IMP.

4.5. CLINICAL STUDY POPULATION

4.5.1. Inclusion Criteria

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

1. Able and willing to comply with the protocol requirements and to sign the informed consent form (ICF) as approved by the IEC/IRB, prior to any screening evaluations.
2. Male and female subjects ≥18 years at the time of consent who meet the American College of Rheumatology (ACR)/EULAR 2013 diagnostic criteria (Van den Hoogen F. et al., 2013) for systemic sclerosis with diffuse cutaneous involvement (according to LeRoy's criteria) and ≤5 years since the onset of the first systemic sclerosis manifestation other than Raynaud's phenomenon.
3. mRSS >10 at screening.
4. Active disease at screening, as defined by:
   - Worsening of skin thickening (≥2 mRSS points) as assessed by mRSS measured at screening versus a previous mRSS assessment made within 6 months prior to screening, or
   - New areas of skin involvement within 6 months prior to screening as documented by physician note, or
   - New-onset systemic sclerosis with symptoms or signs other than Raynaud's phenomenon within 2 years prior to screening, or
   - ≥1 tendon friction rub (palpated in the finger flexors or extensors, wrist flexors or extensors, olecranon bursa, shoulders, knees, anterior or posterior ankles with active motion).
5. Subject must be able and willing to comply with restrictions on prior and concomitant medication as described in Section 4.5.3.2.
6. Criterion modified per amendment.
   6.1 Female subjects of childbearing potential must have a negative serum pregnancy test at screening and a negative urine pregnancy test at the baseline visit.
7. Female subjects of childbearing potential or male subjects with female partners of childbearing potential must be willing to comply with the contraceptive methods described in Section 4.5.3.1 prior to the first dose of the IMP, during the clinical study, and for at least 90 days after the last dose of the IMP for male subjects and 30 days after the last dose of the IMP for female subjects.
8. A body mass index (BMI) between 18–35 kg/m^2, inclusive, at screening.
   Criterion modified per amendment for [redacted] only.
   8.1 A body mass index (BMI) between 18–30 kg/m^2, inclusive, at screening.
9. Judged to be in good health by the investigator based upon the results of a medical history, physical examination, vital signs, 12-lead ECG, and fasting clinical laboratory safety tests. Clinical laboratory safety test results must be within the reference ranges or test results that are outside the reference ranges need to be considered non-clinically significant in the opinion of the investigator.

4.5.2. Exclusion Criteria

Subjects meeting one or more of the following criteria cannot be enrolled in this clinical study:

1. Known hypersensitivity to IMP ingredients or history of a significant allergic reaction to any drug as determined by the investigator, such as anaphylaxis requiring hospitalization.
2. Breastfeeding female or subject intending to become pregnant or breastfeed.
3. History of or a current immunosuppressive condition (e.g. human immunodeficiency virus [HIV] infection, congenital, acquired).
4. Criterion modified per amendment.
   - 4.1. Positive blood testing for hepatitis B surface antigen or hepatitis C virus (antibody, confirmed by hepatitis C virus RNA positivity). Note: Subjects with a resolved hepatitis A at least 3 months prior to screening can be screened.
5. Criterion modified per amendment.
   - 5.1. History of malignancy within the past 5 years (except for carcinoma in situ of the uterine cervix, basal cell carcinoma of the skin that has been treated with no evidence of recurrence, prostate cancer medically managed through active surveillance or watchful waiting, and squamous cell carcinoma of the skin if fully resected and ductal carcinoma in situ).
6. Criterion modified per amendment.
   - 6.1. Clinically significant abnormalities, in the opinion of the investigator, detected on ECG at screening of either rhythm or conduction, QTcF >450 ms, or a known long QT syndrome.
7. Underwent major surgery within 3 months prior to the baseline visit or have major surgery planned during the study period.
8. Criterion modified per amendment.
   - 8.1. Unstable cardiovascular, pulmonary, or other disease (other than systemic sclerosis-related), in the opinion of the investigator, within 6 months prior to the baseline visit (e.g. coronary heart disease, heart failure, stroke).
9. Previous or planned hematopoietic stem cell transplantation.
10. Subjects on phototherapy within 6 weeks prior to the baseline visit.
11. Severe pulmonary disease with FVC ≤45% of predicted within 6 months prior to the baseline visit.
12. Chronic or ongoing active infectious disease, including tuberculosis (requiring hospitalization or systemic treatment within 4 weeks prior to the baseline visit).
13. Criterion modified per amendment.
   - 13.1. Taking medication known to be a substrate mainly metabolized by CYP2C8 (Appendix 1) within 4 weeks or 5 half-lives of the drug (whatever is longer) prior to the baseline visit.
14. Criterion modified per amendment.
   - 14.1. Taking medication known to be strong inducers of CYP3A4 and also including St. John's Wort (Appendix 2) within 4 weeks or 5 half-lives of the drug (whatever is longer) prior to the baseline visit.
15. Criterion modified per amendment.
   - 15.1. Taking medication known to be strong inhibitors of CYP3A4 (Appendix 3) within 4 weeks or 5 half-lives of the drug (whatever is longer) prior to the baseline visit.

16. Criterion modified per amendment.
    16.1. Taking medication known to be potent inducers of P-gp (Appendix 2) within 4 weeks or 5 half-lives of the drug (whatever is longer) prior to the baseline visit.
17. Criterion modified per amendment.
    17.1. Taking medication known to be potent inhibitors of P-gp (Appendix 4) within 4 weeks or 5 half-lives of the drug (whatever is longer) prior to the baseline visit.
18. Abnormal liver function test (LFT) at screening, defined as aspartate aminotransferase (AST), and/or alanine aminotransferase (ALT), and/or bilirubin, and/or alkaline phosphatase >2x upper limit of normal (ULN). Retesting is allowed once.
19. Criterion modified per amendment.
    19.1. Abnormal renal function at screening, defined as estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Retesting is allowed once.
20. Hemoglobin level <10 g/dL at screening. Retesting is allowed once.
21. Concurrent participation or participation in a drug, drug/device, or biologic investigational research study within 5 half-lives of the IMP (or within 8 weeks when half-life is unknown) prior to the baseline visit, or prior participation in an investigational antibody study within 6 months prior to the baseline visit.
22. Gastrointestinal involvement (e.g. unable to swallow) preventing oral administration of IMP.
23. Subjects diagnosed with:
    - Systemic sclerosis sine scleroderma, or
    - Localized scleroderma, or
    - Eosinophilic fasciitis, eosinophilia myalgia syndrome.
24. Diagnosis of another connective tissue disorder by ACR criteria.
25. History of diverticulosis requiring antibiotic treatment or any other gastrointestinal condition that might predispose to perforations.
26. Investigator or other study staff or relative thereof who is directly involved in the conduct of the study.
27. Significant blood loss (including blood donation [>450 mL]), or transfusion of any blood product within 12 weeks prior to the baseline visit.
28. Active drug or alcohol abuse (more than 3 glasses of wine or beer or equivalent/day) within 2 years prior to first IMP intake.
29. Any other clinical condition or circumstances that in the opinion of the investigator may make a subject unsuitable for inclusion or unable to complete the study or comply with study procedures and requirements.
30. A history of being admitted to an institution under an administrative or court order, if applicable by local legislation.

4.5.3. Prohibition and Restrictions

4.5.3.1. Precautions for Sexual Intercourse

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

4.5.3.1.1. Female subjects

In line with the Heads of Medicines Agencies (HMA)'s Clinical Trial Facilitation Group (CTFG) recommendation, 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 IMP, during the clinical study and for at least 30 days after the last dose of IMP:

- Combined (estrogen and progesterone containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation plus a barrier method[1].
- Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation plus a barrier method[1].
- 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.

WOCBP will be requested to do a monthly urine pregnancy test during the treatment period, and a urine pregnancy test at the Follow-up Visit 1. The monthly pregnancy test for Weeks 12 and 20 will be performed at home by the subject using home testing kits. The site will construct the subjects on how to use and read the pregnancy tests. The outcome must be documented on the subject diary card and the site will obtain the results during the phone call and record in the source and case report form (CRF). In case of a positive urine pregnancy test at home, the subject should immediately contact the clinical study center and the investigator

[1] As there is no current data available regarding potential interactions between IMP and hormonal contraceptives, female subjects who use hormonal contraception should supplement this with a barrier method (preferably male condom).

must report this immediately, and under no circumstances later than 24 hours after being made aware.

The safety of GLPG1690 during breastfeeding is unknown. Women who are nursing are not allowed to take part in this clinical study.

4.5.3.1.2. Male subjects

Men should be advised not to father a child while receiving treatment and must use effective contraception during and up to 90 days after treatment. Male subjects intending to father a child, should discontinue treatment with IMP and wait for at least 90 days before stopping the contraceptive measures detailed in this section.

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 IMP, during the clinical study, and for at least 90 days after the last dose of IMP, in addition to having their female partner use one of the following forms of contraception:

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

Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments is considered a highly effective contraceptive measure. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial 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 methods of contraception.

In a case where the female partner of a male participant 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 first dose of IMP, during the clinical study, and until 90 days after the last dose of IMP.

4.5.3.2. Prior and Concomitant Medications

Prior Medication

Prior medication taken up to 12 weeks prior to and during the screening period will be recorded after signing of the ICF, at Visit 1.

Concomitant Medication

Should any treatment other than the IMP be used during the course of the study, the name of the medication, the dosage, the route, the reason for medication, and the start and stop dates of administration must be recorded in the CRF until Follow-up Visit 2.

Concomitant medications taken for the long-term treatment of pre-existing conditions can continue during the study, provided they are in accordance with the in- and exclusion criteria (see Sections 4.5.1 and 4.5.2, respectively). It is required that these medications are stabilized prior to study entry (8 weeks prior to screening, or longer if $t_{1/2}$ and/or time to reach steady state of the drug requires) and preferably continue without variation of dose or regimen during the study.

In case additional concomitant medication needs to be administered or dose adjustments for pre-existing conditions need to be performed during the study, the benefit-risk to the subject should be carefully assessed and consideration given to the timing of any necessary introduction of new medications.

The following medications are prohibited within 4 weeks prior to the baseline visit and during the treatment period: warfarin, antifibrotic agents (including colchicine, minocycline, tyrosine kinase inhibitors [nilotinib, imatinib, dasatinib, nintedanib], pirfenidone), bosentan or Type 1 oral collagen. The following medications are prohibited within 3 months prior to the baseline visit and during the treatment period: steady dose of prednisone or its equivalent >10 mg/day, methotrexate >20 mg/week, azathioprine >150 mg/day, MMF >3 g/day, mycophenolic acid >2.16 g/day, leflunamide >20 mg/day. Cyclophosphamide is prohibited within 6 months prior to the baseline visit and during the treatment period, as well as the following biologics: tocilizumab or other drugs targeting IL-6/IL-6 receptor, abatacept, anti-tumor necrosis factor (TNF) drugs, rituximab, belimumab, or other monoclonal antibodies.

If during the study, the subject's condition necessitates the use of one of the abovementioned medications (excluding prednisone or its equivalent >10 mg/day), the use of IMP should be interrupted until resolution or stabilization of this condition, preferably after consultation with the contract research organization (CRO) medical monitor (as per study contact list) or sponsor's study physician (if the former is not available).

Precautions with concomitant medication known to prolong the QT interval

The use of medication known to prolong QT interval during the study needs to be based on a benefit-risk evaluation by the investigator, e.g. in the case of atrial fibrillation. In certain other situations (e.g. the initiation of macrolides or fluoroquinolones in case of a lower respiratory tract infection), when the benefit-risk evaluation necessitates the administration of medication known to or potentially prolonging QT, IMP can be interrupted as evaluated by the investigator after clinical assessment of the subject's profile, including the baseline QTcF and how this has changed over time for this specific subject. If the investigator elects to continue IMP, additional monitoring will be performed as per investigator's judgment. A nonexhaustive list of medication known to prolong QT interval is provided in Appendix 5. Note: In case QT interval prolongation is reported in a subject while receiving one of these medications, the investigator should follow the labels and Risk Evaluation and Mitigation Strategies guidance.

Precautions with other concomitant medications

At dose levels of 600 mg q.d., GLPG1690 has the potential to substantially influence the metabolism of CYP2C8 substrates and to potentially be influenced by known strong CYP3A4/potent P-gp inducers/inhibitors.

- GLPG1690 demonstrated a strong time-dependent inhibition potential against CYP2C8-mediated metabolism. Consequently, GLPG1690 should not be used concomitantly with medications primarily or solely metabolized via CYP2C8 (see Appendix 1). For other medications involving part of their metabolism pathway via CYP2C8, caution should be applied on a case-by-case basis taking into consideration the benefit-risk ratio. Statins such as fluvastatin and pitavastatin are metabolized to some degree by CYP2C8, and need to be used with caution. Other statins such as simvastatin, lovastatin, and atorvastatin are theoretically less metabolized by CYP2C8. Monitoring of LFTs and creatine kinase is implemented during the study, and guidance to the subject aligned with guidance for statins in clinical practice is therefore strongly recommended. Loperamide is also a substrate of CYP2C8, and special caution should be applied in alignment with clinical practice.
- GLPG1690 is a substrate of CYP3A4 and P-gp, and could therefore be influenced by their respective inhibitors and inducers. GLPG1690 exposure is reduced up to 90% by the strong CYP3A4/potent P-gp inducer rifampin. As a consequence, strong inducers of CYP3A4 and/or P-gp are part of the exclusion criteria and should be avoided during the study to ensure proper exposure to GLPG1690 (see Appendix 2). For inhibition, strong CYP3A4 and dual strong 3A4 and potent P-gp inhibitors have shown that GLPG1690 exposure increased by 3 to 4 fold when coadministered, therefore use of known strong CYP3A4 inhibitors and potent P-gp inhibitors is prohibited during the study (see Appendix 3 and Appendix 4). Antibiotics from the macrolide therapeutic class are excluded, unless they are used for the short-term treatment of a lower respiratory tract infection with interruption of IMP, which is restarted as soon as possible after the completion of the treatment with macrolides.

It is highly recommended that the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available) are consulted before the initiation of medication known to prolong QT interval, to be a CYP2C8 substrate, or to inhibit or induce P-gp/CYP3A4.

In certain situations, when the benefit-risk evaluation necessitates the administration of medication excluded from use during the study, the use of IMP should be interrupted until resolution or stabilization of this condition, preferably after consultation with the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available) and restarted as soon as possible.

As a rule, inclusion of subjects with stable chronic illness on stable medications which are metabolized/transported by the abovementioned CYP/transporter enzymes should be decided on a case-by-case basis if not excluded or prohibited, taking into account the medical history, concomitant medication of the subject, the therapeutic index of the medication, and safety profile.

As indicated in the study contact list, the CRO medical monitor should be contacted, or the sponsor's study physician in case the former is not available (when deemed necessary by the investigator), specifically for medication with a narrow therapeutic index and/or a risk of (un)predictable AEs.

Rescue medication

If the subject shows a worsening of his/her systemic sclerosis disease condition (e.g. acute exacerbation), all treatment options are allowed at the investigator's discretion. The decision to continue the IMP should be taken on a case-by-case basis.

4.5.3.3. Food and Beverage Restrictions

The use of St. John's Wort is prohibited during the study.

Double-strength grapefruit juice is potentially a potent CYP3A4 inhibitor and therefore should be avoided during the study.

4.5.3.4. Other Prohibitions and Restrictions

Not applicable.

4.5.4. 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 complete the ED visit and follow-up visits for safety assessments.

Treatment with IMP should be discontinued by the investigator (preferably after discussion with the CRO medical monitor, who may consult and must inform the sponsor's study physician) for any of the following conditions:

- Life-threatening AE or an 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: if a subject becomes pregnant during the study (to be confirmed by local serum pregnancy test; central measurement will also be performed), the IMP has to be stopped immediately and the subject has to be followed up until birth or otherwise termination of pregnancy. The subject needs to be unblinded immediately and repeat counseling on birth defect risk must be offered in case she was on active drug.
- 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 (QTcF >500 ms on at least two separate ECGs).
- An increase for QTcF with >60 ms change from baseline (Visit 2) or QTcF >500 ms at any ECG recording (triplicate mean or single) needs to be confirmed by an ECG recording as soon as possible from the original abnormal recording at the same visit. In case of an abnormal ECG on both of these two recordings, the investigator needs to send an immediate alert to the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available). If the ECG abnormality is before IMP intake, IMP administration will be withheld until the central reader has reviewed the ECG registration. In case of confirmation of the ECG abnormality, IMP will be discontinued for this subject.

- Increase in LFT:
  - AST or ALT ≥8x ULN.
  - AST or ALT ≥3x ULN with signs of severe 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 ≥1.5x ULN or international normalized ratio [INR] >1.5).
  - AST or ALT ≥3x ULN for more than 2 weeks.
- Clinical laboratory test suggestive of cholestasis with total serum bile acid levels >3x ULN on a sample taken in fasted state (at least 8 hours fasted). If the routine random or postprandial total serum bile acid sample is >3x ULN, then the subject should have a fasted sample taken within 1 to 5 days. The results of this test will determine whether the subject should discontinue IMP or not.

When test results need to be confirmed, the subject should return to the clinical study center and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment. In addition to repeating AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma glutamyl transferase (GGT), INR, and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, recreational drug and supplement consumption, family history, sexual history, travel history, history of contact with a jaundiced subject, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (e.g. biliary tract) may be warranted. All cases confirmed on repeat testing with no other cause for LFT abnormalities identified at the time should be considered potential Hy's Law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

Every effort should be made to keep subjects in the study and on treatment. However, the investigator can consider stopping the treatment with GLPG1690 or placebo, preferably after consultation with the sponsor's study physician, in case of concerns about the subject's safety, major protocol noncompliance, 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 return for the ED visit and follow-up visits.

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 his/her request without prejudice to his/her 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 follow-up visits for safety assessments, but will not be obliged to do so.

Subjects who withdraw from the clinical study without contact with the clinical study center (lost-to-follow-up) should be contacted by the clinical study center so that their health status can be assessed and documented in the source documents. The clinical study center should make every effort to understand whether the subject is alive, including checking the medical

records, contacting general practitioner or relatives, if necessary. All attempts must be documented in the source documents.

Subjects who discontinue IMP or the study will not be replaced.

The sponsor has the right to terminate the clinical study at any time in case of safety concerns or if special circumstances concerning the IMP or the company itself occur, making further treatment of subjects impossible. In this event, the investigator(s) and relevant authorities will be informed of the reason for clinical study termination.

4.6. MEASURES TO MINIMIZE BIAS

4.6.1. Randomization

At screening, subjects will be assigned a subject identification. 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 receive GLPG1690 600 mg q.d. or matching placebo, respectively.

For each subject at each clinical study center visit, the clinical study center will contact the IWRS for the appropriate treatment number to be assigned. The medication kit(s) will contain the relevant IMP for the period until the next clinical study center visit.

Subjects and study personnel will be blinded to the treatment assigned to the subject. Additional details on blinding and unblinding are provided in Section 4.6.2.

4.6.2. Blinding and Unblinding

This is a randomized, double-blind clinical study. The subject and the entire clinical study team, including the investigators, clinical study coordinators, and sponsor personnel are blinded to treatment assignment.

Blinded and packaged medication will be provided to the clinical center. The placebo formulation will match the active formulation in size, color, shape, and appearance. All IMP formulations (active and placebo) 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 CRO medical monitor (as per study contact list) or the sponsor's study physician (in case the former is not available), 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 CRO medical monitor and the sponsor in a timely fashion after unblinding has occurred.

The blind can be broken by the investigator via IWRS.

Code-break information (via IWRS vendor/randomization list) will be provided to the bioanalytical laboratory responsible for plasma drug determination sample analysis, and to the sponsor pharmacovigilance lead for SAE reporting purposes.

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. IDENTITY OF THE INVESTIGATIONAL MEDICINAL PRODUCT

The IMPs (GLPG1690 and placebo) will be supplied to the clinical study center, by and under the responsibility of the sponsor, who will also provide the investigator with European Union (EU) Qualified Person release documents.

GLPG1690 will be provided as film-coated tablets for oral use, containing 200 mg G451990 each (G451990 is the compound code for GLPG1690). The placebo will be provided as matching film-coated tablets for oral use.

A full list of excipients used in the film-coated tablet formulation is available in the IB for GLPG1690 (Edition 6, 28-Jun-2019) and relevant updates/addenda.

5.2. DOSAGE AND ADMINISTRATION

The following dose will be used:

- 600 mg GLPG1690 q.d. (as three GLPG1690 film-coated tablets of 200 mg).
- Placebo q.d. (as three placebo film-coated tablets).

The IMP is to be taken q.d. around the same time every day with food (e.g. breakfast, small meal, or a snack) or after food intake; taking into account the timing of the planned visits, with a maximum of 2 hours between the food intake and IMP intake. Subjects will be instructed to swallow the tablets as a whole with a glass of water and to not chew the IMP prior to swallowing. On clinical study center visit days, the IMP will be administered at the clinical study center after predose assessments have been completed.

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 and within 2 hours of food intake. If the IMP is not taken within 12 hours after the planned time, the missed dose should be skipped.

5.3. PACKAGING, LABELING, AND DISTRIBUTION

The film-coated tablet for oral use will be packaged in blisters. IMP packages will be labeled with clinical study-specific details.

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. A multiple of kits will be provided to the subject at each clinical study center visit, providing the subject with sufficient tablets to cover the period until the next scheduled clinical study center visit.

If subjects, due to any COVID-19-related reason, cannot attend Visit 9 (Week 24) within the time window of ±4 days, the window for the visit may be increased to ±28 days (Section 6.1). If Visit 9 is postponed beyond Week 24, a Direct-to-Patient (DTP) shipment of one additional IMP kit may be implemented to cover the treatment prolongation of up to 28 days.

If Visit 9 is not conducted in the extended (±28 days) window, i.e. after Week 28, no further IMP will be provided to the subject, and the subject will not take any IMP after Visit 9 (i.e. ultimately Week 28).

The distribution to the clinical study center will only occur after the required local documentation is obtained including clinical study approval by Competent 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.

5.4. STORAGE

Clinical study centers are to store all drug supplies in a secure, locked area with limited access below 30°C, protected from light, until dispensed. Clinical study centers will be required to monitor the storage temperature by using at least a calibrated minimum-maximum 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 IMP should be stored at home.

5.5. TREATMENT COMPLIANCE AND DRUG ACCOUNTABILITY

For each dose taken at home, the date and number of tablets taken should be recorded on the subject diary card (see Section 6.4 for additional information). Any interruption or change in treatment (together with the reason for change) should be documented on the subject diary card.

The pharmacist or designated clinical study personnel will maintain a log of the total amount of IMP received at the clinical study center, the amount dispensed to the subject, and the amount of IMP returned by the subject to the clinical study center. IMP 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 facilities.

Subjects will return any unused IMP and empty IMP packages at each clinical study center visit. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure proper subject dosing. Subjects with poor compliance will be retrained by the clinical study center. Upon sponsor approval, all unused IMP and empty IMP packages will be destroyed at the clinical study center. If destruction by the clinical study center is not possible or the destruction process is found unacceptable by the sponsor, the IMP should be returned to the drug supplier/drug depot as appropriate.

At each clinical study center visit, clinical study center staff will review treatment compliance by assessing the number of returned IMP.

6. CLINICAL STUDY ASSESSMENTS

Every effort should be made to ensure that clinical study protocol (CSP)-required tests and procedures are completed as described in the Schedule of Activities (see Section 6.11). 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.

6.1. TIMING OF ASSESSMENTS

The study assessments will be undertaken at time points as specified in the Schedule of Activities in Section 6.11. A window of ±2 days is allowed for Visits 3 and 4, a window of ±4 days is allowed for all visits during the treatment period after Visit 4, and a window of ±7 days is allowed for the follow-up visits. [redacted]

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

The sequence of study assessments will preferably be as shown in Table 1 (per visit). [redacted]

Alternative timing and assessment procedures for subjects who, due to any COVID-19-related reason, cannot perform the study procedures:

Visit 9 (Week 24)

- If Visit 9 (Week 24) cannot be conducted within the time window of ±4 days, the visit window can be extended to ±28 days (i.e. can be extended or shortened up to 28 days) to enable conduct of the visit on site. [redacted]
- If Visit 9 is performed after Week 24, additional IMP may be required. This may be shipped by the site directly to the subject as detailed in Section 5.3.
- For the rollover of a subject into the GLPG1690-CL-206 Open-Label Extension study, a complete, on-site rollover visit is required. If Visit 9 cannot be conducted on site within the extended window of Week 24 +28 days, the subject will be given the opportunity to rollover into the Open-Label Extension study until Week 32. The subject will however be off study medication and not receive IMP between Week 28 to 32. The Visit 9/rollover assessments should be performed at this on-site visi[redacted]
- If the rollover visit cannot be scheduled before Week 32, the subject cannot rollover and will continue in the follow-up period of GLPG1690-CL-204 with a first follow-up visit 4 weeks after last IMP administration.
- The follow-up visits need to be scheduled in relation to the last dose of IMP. Follow-up visit 1 should be 28 days ±7 days after the last IMP administration, and Follow-up visit 2 should be 84 days ±7 days after the last IMP administration.

Phone calls

- If Visit 9 is conducted after Week 24, additional regular phone calls at Week 24 and every 14 days thereafter should be implemented until an on-site Visit 9 can take place, or until Week 32, to evaluate the subject's safety.
- In addition, if any of the follow-up visits cannot be performed on site, a phone call to evaluate the subject's safety should be performed on the date of the visit.

– The information to be collected during these phone calls is detailed in Section 6.6.

Table 1 Timing of Assessments

EVENT	SCR	TREATMENT PERIOD							FOLLOW-UP	
Study Visit	**1**	**2**	**3**	**4**	**5**	**7**	**9**	**ED[a]**	**FU1**	**FU2**
Before IMP intake										
[redacted]										
2. ECG (triplicate)[b]	✓[c]	✓	✓							
3. ECG (single)[b]						✓	✓	✓	✓	
4. Blood sampling for clinical laboratory tests	✓[c,d]	✓	✓	✓	✓	✓	✓	✓	✓	
[redacted]										
After IMP intake										
7. ECG (triplicate) (between 2-3 hours after IMP intake)		✓	✓							
[redacted]										

FU=follow-up, SCR=screening.

[a] ED visit if applicable.

[b] 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.

[c] Irrespective of IMP intake.

[d] Also including blood sampling for safety, FSH, and serum pregnancy test (if applicable).

[redacted]

6.2. 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 performed before the subject's last visit per CSP, also in the CRF.

6.3. INITIAL SUBJECT AND DISEASE CHARACTERISTICS

Subjects will be asked to attend the clinical study center for a screening assessment. After giving written informed consent, demographic data (age, sex, and race), and a medical history will be taken, including questions regarding medication intake. A physical examination will be performed, including measurement of weight and height.

Vital signs (systolic and diastolic blood pressure [SBP and DBP], heart rate, tympanic body temperature, and respiratory rate) will be measured and a 12-lead triplicate 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. All screening tests will be reviewed to confirm eligibility before randomization and IMP intake.

Retesting of individual screening assessment(s) that did not meet eligibility criteria is not permitted, with the following exceptions AND only in case it is still possible to randomize the subject within the per-protocol defined screening period of 28 days:

- Laboratory values for LFTs, eGFR, and hemoglobin can be retested once.
- Lost or invalid blood or urine samples.

Rescreening: in case of screening failure, subjects are allowed to be rescreened maximum two times, after signing a new ICF. Rescreening can start at least 6 weeks after the initial laboratory testing of the previous screening.

6.4. SUBJECT DIARY CARD

Subjects will be given diary cards from Visit 2 until Follow-up Visit 1 to record the following:

- From Day 1 until the last visit of the treatment period, subjects will be asked to record the date of IMP intake, the number of tablets taken for each administration, any change in intake and reason for the change, and monthly urine pregnancy test outcome (only for WOCBP, see Section 4.5.3.1.1).
- From Day 1 until Follow-up Visit 2, subjects will be asked to record changes in concomitant medication regimen, including new medicines not captured in medication history, and any other concomitant medication used as well as any emerging AE.

Subjects will be instructed to bring their diary cards and used/unused IMP to each clinical study center visit. At each clinical study center visit, review of compliance with the diary cards and subject re-training if needed, will be performed.

6.5. EFFICACY ASSESSMENTS

6.5.1. Modified Rodnan Skin Score

mRSS is an established primary outcome measure in most therapeutic studies in systemic sclerosis, based on the evidence that skin thickness serves as a surrogate for overall disease activity, severity, and mortality in systemic sclerosis. mRSS scoring will be performed at Visit 1 (screening), Visit 2 (baseline), Visits 4, 5, 7, and 9, ED (if applicable), and Follow-up Visit 1. mRSS will be assessed in a standardized manner according to published protocols by the SCTC and the World Scleroderma Foundation (Khanna D. et al., 2017) by the responsible study physician. Preferably, each subject will be assessed by the same study physician (or nurse practitioner, as acceptable according to local clinical study center setup and meeting the experience criterion defined outside the protocol) for the entire study. The 17-site mRSS will be used, with each site assessed on a scale of 0 to 3 with a maximum score of 51. For individual subjects, clinically meaningful changes in skin score (MCID) are 4.7 skin score units and/or at least 20% change in overall mRSS (Khanna D. et al., 2006). Regardless of experience, each assessor will need to undergo study-specific training and qualification to ensure consistency. In the event of a change of assessor, consistency of scoring between assessors should ideally be assessed and documented (i.e. new and previous assessor carry out scoring in parallel).

6.6. 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.

For subjects who, due to any COVID-19-related reason, cannot perform the study procedures.

If Visit 9 needs to be postponed until after Week 24, regular phone calls at Week 24 and every 14 days thereafter should be implemented to evaluate the subject's safety until a visit can take place on-site. In addition, if any of the follow-up visits cannot be performed on site, a phone call to evaluate the subject's safety should be performed.

During these phone calls, the investigator should at least discuss the following items and collect the following information as much as possible:

- subject's general condition and ongoing study medication intake
- information on any adverse events (changes of ongoing or new events)
- information on concomitant medication intake
- completion of subject diary cards and urine pregnancy test and result (monthly, if applicable) by the subject
- the possibility for local laboratory testing, vital signs, and ECG should be considered, and discussed. This local testing may occur either prior to the phone call, or as a consequence of the exchanged information, at the discretion of the investigator.

All adverse events including those based on, or identified by local testing need to be reported in the eCRF, and any SAEs should be reported within 24 hours with the SAE form.

Urine pregnancy tests to perform the monthly pregnancy test at home until follow-up visit 1 (if applicable) and treatment or follow-up diary cards will also be shipped to the patient to cover the longer period between on-site visits.

6.6.1. Adverse Events

The AEs reporting period for safety surveillance begins when the subject signs the ICF and ends at his/her last follow-up visit as defined in the Schedule of Activities (see Section 6.11).

Detailed definitions, ratings, and reporting requirements for AEs and SAEs are found in Section 9.

6.6.2. 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 count, white blood cell count, white blood cell differential count (absolute and relative), and platelets.
- Coagulation: INR, thromboplastin time, and partial thromboplastin time.
- Serum/plasma chemistry: random glucose, urea, creatinine, uric acid, sodium, potassium, calcium, chloride, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase,

lactate dehydrogenase, total serum bile acid, albumin, total proteins, triglycerides, cholesterol (total, low density lipoprotein, and high density lipoprotein), creatine kinase, and C-reactive protein.

- Urinalysis:
  - Dipstick: pH, glucose, proteins, blood, leucocytes, ketones.
  - Microscopic examination of the sediment (cylinders, erythrocytes, leucocytes) if indicated.
- Serology: hepatitis B surface antigen, hepatitis C virus antibody, and HIV-1 and HIV-2 antibodies (only 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, urine pregnancy test on a monthly basis (only for WOCBP).

The clinical laboratory evaluations will be performed at visits specified in the Schedule of Activities in Section 6.11 (see also Section 6.1, "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.

The details of blood and urine sample handling and shipment instructions will be provided in a separate laboratory manual.

6.6.3. Physical Examination

Physical examinations 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 6.11. The person conducting the physical examination will document this in the subject's medical records. Clinically significant abnormal findings should be recorded as AEs. Height and weight will only be recorded at screening.

6.6.4. Vital Signs

Vital signs (SBP, DBP, heart rate, respiratory rate, and body temperature) will be recorded in a standardized manner (i.e. after the subject has rested in a supine position for 5 minutes) at visits specified in the Schedule of Activities in Section 6.11. Clinically significant abnormal values should be recorded as AEs.

6.6.5. 12-lead Electrocardiogram

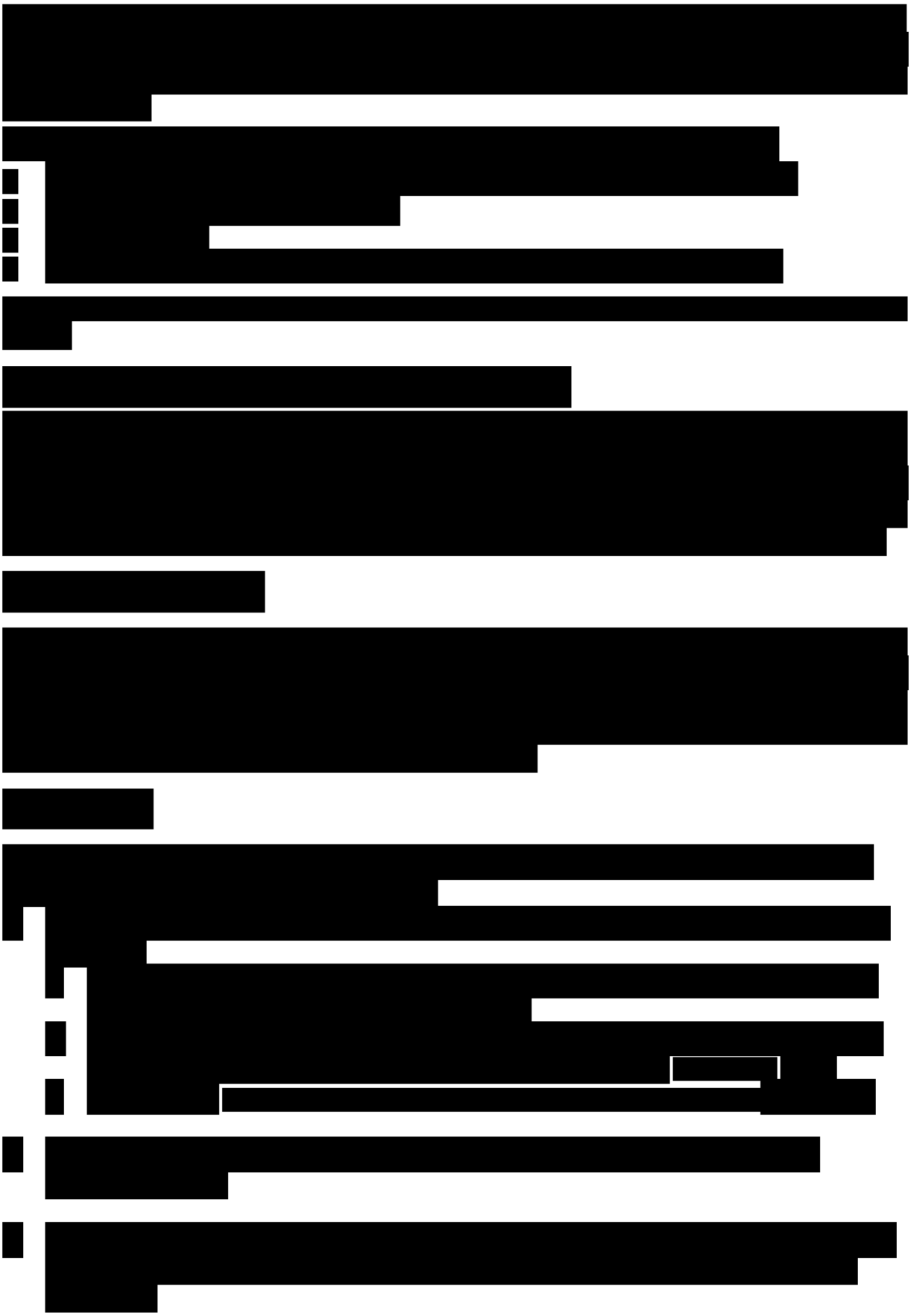
At the time points specified in the Schedule of Activities (see Section 6.11) a 12-lead ECG will be recorded and results will be sent for central reading. Triplicate ECGs will be performed irrespective of IMP intake at Visit 1 (screening), within 30 minutes before IMP intake and between 2 to 3 hours after IMP intake at Visit 2 (baseline) and Visit 3. A single ECG will be performed within 30 minutes before IMP intake at Visits 7 and 9, and irrespective of IMP intake at ED (if applicable) and Follow-up Visit 1. The ECG must be taken after subjects rested for at least 5 minutes in the 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 will be performed preferably within a time span of 6 minutes, with an approximate 2-minute interval between ECGs. Parameters to be recorded include the following: heart rate, PR interval, QRS interval, uncorrected QT interval, morphology, and rhythm analysis. QTcF will be considered as normal if ≤450 ms, while a prolongation of QTcF to ≥500 ms or an increase from baseline >60 ms will be considered a threshold of concern. Immediately after recording, the ECG will be reviewed by the investigator on 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 values should be recorded as AEs.

[redacted]

6.9. OTHER ASSESSMENTS

[redacted]



[redacted]

6.10. SAMPLE MANAGEMENT

Blood and Urine Samples for Routine Safety Tests, Serology, FSH, and Pregnancy Tests

All blood and urine samples for routine safety tests, serology, FSH, and pregnancy test will be analyzed in a central laboratory and will be destroyed after analysis.

Blood Samples for [redacted]

After the EoS (e.g. Last Subject Last Visit), all biological samples obtained during the clinical study may be stored for a period of maximum 5 years, after which the samples will be destroyed. The sample storage period will be in accordance with the IEC/IRB-approved ICF and applicable laws (e.g. health 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 IEC/IRB and Regulatory Authority and after obtaining informed consent from the subject.

If research is performed on genetic material of the samples, then this can only be performed in context of the described CSP [redacted] and the data obtained may in no case be used for the purpose of identification or re-identification of subjects.

6.11. SCHEDULE OF ACTIVITIES

For detailed instructions on the clinical study procedures, please see referred Sections and Section 6.1, "Timing of Assessments".

EVENT	SCREENING	TREATMENT PERIOD									FOLLOW-UP [j]	
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ED[a]**	**FU1**	**FU2**
Study Day (D) or Week (W)[b] ± days (d)	**D-28 to D-1**	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W12[c] ±4d**	**W16 ±4d**	**W20[c] ±4d**	**W24[i] ±4d**		**W28 ±7d**	**W36 ±7d**
Informed consent (Section 6.3)	✓											
Inclusion/exclusion criteria (Section 6.3)	✓	✓										
Demographics (Section 6.3)	✓											
Medical history/concurrent illnesses (Section 6.3)	✓											
FSH test (Section 6.6.2)	✓											
Randomization (Section 4.6.1)		✓										
Phone call						✓		✓				
Pregnancy test [d] (Section 6.6.2)	✓	✓		✓	✓	✓	✓	✓	✓	✓	✓	
Physical examination (Section 6.6.3)	✓	✓	✓	✓	✓		✓		✓	✓	✓	
Vital signs (Section 6.6.4)	✓	✓	✓	✓	✓		✓		✓	✓	✓	
12-Lead ECG[e] (Section 6.6.5)	✓	✓	✓				✓		✓	✓	✓	
Serology (Section 6.6.2)	✓											
Clinical laboratory tests (Section 6.6.2)	✓	✓	✓	✓	✓		✓		✓	✓	✓	

EVENT	SCREENING	TREATMENT PERIOD									FOLLOW-UP[j]	
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ED[a]**	**FU1**	**FU2**
Study Day (D) or Week (W)[b] ± days (d)	**D-28 to D-1**	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W12[c] ±4d**	**W16 ±4d**	**W20[c] ±4d**	**W24[i] ±4d**		**W28 ±7d**	**W36 ±7d**
mRSS (Section 6.5.1)	✓	✓		✓	✓		✓		✓	✓	✓	
[redacted]												
Dispense subject diary		✓	✓	✓	✓		✓		✓	✓	✓	
Collect subject diary			✓	✓	✓		✓		✓	✓	✓	✓
Dispense IMP		✓	✓	✓	✓		✓					
Review IMP compliance			✓	✓	✓		✓		✓	✓		

EVENT	SCREENING	TREATMENT PERIOD									FOLLOW-UP [j]	
Study Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ED[a]**	**FU1**	**FU2**
Study Day (D) or Week (W)[b] ± days (d)	**D-28 to D-1**	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W12[c] ±4d**	**W16 ±4d**	**W20[c] ±4d**	**W24[i] ±4d**		**W28 ±7d**	**W36 ±7d**
Dose IMP (Section 5.2)		q.d. throughout the treatment period										
AE assessment (Section 6.6.1)	Throughout the study											
Concomitant medication assessment and documentation (Section 4.5.3.2)	Throughout the study											

FU=follow-up, QoL=quality of life.

[a] ED visit if applicable.

[b] Week is defined as 7 days.

[c] This will be a phone call to assess safety (no clinical study center visit).

[d] Serum pregnancy test at screening, urine pregnancy test at all other visits.

[e] Triplicate ECGs will be performed irrespective of IMP intake at Visit 1 (screening), within 30 minutes before IMP intake and between 2 to 3 hours after IMP intake at Visit 2 (baseline) and Visit 3. A single ECG will be performed within 30 minutes before IMP intake at Visits 7 and 9, and irrespective of IMP intake at ED (if applicable) and Follow-up Visit 1.

[redacted]

[i] If Visit 9 (Week 24) cannot be conducted within the time window of ±4 days, the visit window can be extended to ±28 days (i.e. can be extended or shortened up to 28 days) to enable conduct of the visit on site. If Visit 9 is conducted after Week 24, additional regular phone calls at Week 24 and every 14 days thereafter should be implemented, until an on-site Visit 9 can take place, or until Week 32, to evaluate the subject's safety. In addition, if any of the follow-up visits cannot be performed on-site, a phone call to evaluate the subject's safety should be performed on the date of the visit. The information to be collected during these phone calls is detailed in Section 6.6.

[j] The FU visits need to be scheduled in relation to the last dose of IMP. FU1 should be 28 days ±7 days after the last IMP administration, and FU2 should be 84 days ±7 days after the last IMP administration.

7. STATISTICAL METHODS

All statistical methods shall be detailed in a statistical analysis plan (SAP) that will be prepared before the Week 24 primary analysis. All relevant data collected in this clinical study will be documented using summary tables, figures, and subject data listings.

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

7.1. DETERMINATION OF SAMPLE SIZE

Sample size was based on empirical considerations. The number of subjects (30) included in this study should give reasonable precision around the estimates derived for the efficacy evaluation.

The primary endpoint of the study is the change from baseline in mRSS over 24 weeks.

Considering 20 and 10 subjects in the GLPG1690 and placebo arm, respectively, and a common standard deviation of 5 on the change from baseline in mRSS, the MCID of 4.7, and taking into account a 10% dropout, the probability to observe a treatment effect of more than 4 points is 63%.

7.2. POPULATION FOR ANALYSES

7.2.1. All Screened Subjects

All subjects who signed and dated an ICF and underwent screening assessments to check whether or not they are eligible to participate in the clinical study.

7.2.2. All Enrolled Subjects

All subjects who were found eligible to participate in the clinical study and could be randomized.

7.2.3. All Randomized Subjects

All enrolled subjects who were randomized into the clinical study.

7.2.4. Full Analysis Set

All randomized subjects who have received/used at least 1 dose of IMP.

7.2.5. Per-Protocol Set

All Full Analysis Set subjects who did not have a major protocol deviation that impacts the efficacy results (as defined in a protocol deviation plan). The determination of the per-protocol population will be finalized and documented prior to database lock and unblinding.

7.2.6. Safety Analysis Set

All randomized subjects who used at least 1 dose of IMP.

[redacted]

7.3. STATISTICAL ANALYSES

7.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, standard deviations 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. Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 5% significance level. Data may be pooled across centers and countries.

7.3.2. Primary Analysis

The primary analysis will be performed when all subjects have completed the Week 24 visit (or discontinued earlier). Every effort will be made to keep the subjects and investigators blinded to individual treatment assignments until completion of the final analysis (after the last subject has completed the last follow-up visit in this study).

7.3.3. Interim Analysis

No interim analysis is planned for the study.

7.3.4. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, and concomitant medications will be analyzed descriptively and/or listed for the Full Analysis Set (Section 7.2.4).

7.3.5. Analyses of Efficacy Parameters

All efficacy parameters will be analyzed descriptively in the Full Analysis Set (Section 7.2.4) unless otherwise specified.

7.3.5.1. Analysis for Primary Efficacy Endpoint

Change from baseline in mRSS will be presented descriptively and graphically over time by treatment group.

Change from baseline in mRSS will be analyzed using a mixed-effects model for repeated measures (MMRM). The model will include treatment and visit as fixed effects, baseline mRSS and country as covariates, and treatment-visit as interaction terms. Least square (LS) means with 95% confidence intervals (CIs) will be calculated from the model at each time point as well as difference from placebo in LS means with 95% CIs.

The number and percentage of subjects with a clinically meaningful change in skin score (as defined in Section 6.5.1) will be summarized by treatment.

Change from baseline in mRSS will also be analyzed for a series of subgroups (such as baseline characteristics and background treatment). Details will be provided in the SAP.

7.3.5.2. Analyses for Other Efficacy Endpoints

7.3.6. Analyses of Safety Data

All safety analyses will be performed using the Safety Analysis Set (Section 7.2.6). All safety data collected on or after the first dose of IMP administration up to the last contact after the last dose of IMP, unless specified otherwise, will be summarized by treatment group according to the IMP received. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs.

7.3.6.1. Extent of Exposure

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

7.3.6.2. Adverse Events

Clinical and laboratory AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities. System Organ Class (SOC), 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 AEs (TEAEs):

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

AEs reported before the start of IMP or later than 30 days after the last dose of IMP will be listed.

In addition, summaries and/or listings will be provided for the suspected symptoms/AEs of flare with an onset date on or after the IMP start date until the EoS (including information from Follow-up Visit 2).

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

7.3.6.3. Clinical Laboratory Evaluations

Laboratory assessments will be analyzed descriptively. Changes from baseline (Day 1 before IMP intake) and shifts according to normal ranges will be presented as well. Analyses will be done per treatment group.

7.3.6.4. Physical Examinations

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

7.3.6.5. Vital Signs

Vital signs will be analyzed descriptively. Changes from baseline and shifts according to normal ranges will be presented as well. Analyses will be done per treatment group.

7.3.6.6. 12-Lead Electrocardiogram

A descriptive analysis will be done for the 12-lead ECG. Changes from baseline and shifts according to normal ranges will be presented as well. Analyses will be done per treatment group.

[redacted]

7.3.9. Analysis of Other Assessments

[redacted]

[redacted]

8. DATA MONITORING

8.1. MEDICAL REVIEW

An independent medical safety review will be implemented for this clinical study. The review will be conducted by an independent blinded clinician experienced in the field of systemic sclerosis. The independent expert will review safety data and assess any potential safety issues arising during the conduct of the clinical study. This process will be described in a separate 'Independent Medical Safety Review Charter'.

9. SAFETY REPORTING

9.1. DEFINITIONS OF ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, AND SPECIAL SITUATIONS

9.1.1. 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.

9.1.2. 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).

9.1.3. Unlisted (Unexpected) Adverse Event/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 IMP, the expectedness of an AE will be determined by whether or not it is listed in the reference safety information part of the IB.

9.1.4. Adverse Events of Special Interest

Not applicable.

9.1.5. 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, lead to IMP interruption, modification, or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 9.1.1 and 9.1.2, 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).

9.1.6. Special Situations

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

- Pregnancy
- Abuse or misuse of study drug
    - Abuse of study drug is defined as the persistent or sporadic, intentional excessive use of the study drug, which is accompanied by harmful physical or psychological effects.
    - Misuse of study drug is defined as a situation where the study drug is intentionally and inappropriately used not in accordance with the product information.
- Drug interaction or food interaction with study drug
    - A drug interaction with study drug is defined as a situation in which there is evidence or a suspicion that the study drug interacts with another drug when both are administered together.
    - A food interaction with study drug is defined as a situation in which there is evidence or a suspicion that the study drug interacts with a food when taken together.
- Medication error with study drug

- A medication error with study drug is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.

- Occupational exposure to study drug

  - Occupational exposure with study drug is defined as an exposure to the study drug as a result of one's professional or non-professional occupation.

- Overdose with study drug

  - An overdose of study drug is defined as the administration of a quantity of the study drug given per administration or cumulatively, which is the intake of more than three tablets/day

- Product complaint or quality defect of study drug

  - Product complaint or quality defect of study drug is defined as complaints or defects of the study drug arising from potential deviations in the manufacture, packaging, or distribution of the study drug.

9.2. 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.

9.2.1. Assessment of Causality

The investigator is responsible for assessing the causal relationship to IMP(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 IMP.

– **Unrelated:**
Time relationship to IMP intake is improbable. Related to other etiologies such as concomitant medications or subject's clinical state.

– **Unlikely:**
Time relationship to IMP intake is improbable (but not impossible). Concomitant disease or other drugs provide plausible explanations.

– **Possible:**
Time relationship to IMP intake is reasonable. Event or laboratory test abnormality, could also be explained by disease or other drugs. Information on IMP withdrawal may be lacking or unclear.

– **Probable:**
Time relationship to IMP 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 IMP 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.

9.2.2. Assessment of Severity

The severity of AEs should be graded using the CTCAE version 5.0. 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 the table below.

Table 2 Grading of Adverse Event 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

* Activities of Daily Living (ADL) Instrumental 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.

9.2.3. Outcome

Each AE must be rated by choosing among:

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

9.3. INVESTIGATOR REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS, SERIOUS ADVERSE EVENTS, PREGNANCIES, AND OTHER SPECIAL SITUATIONS TO THE SPONSOR

9.3.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at the subject's last follow-up visit (the last follow-up visit after the last dose of IMP) as described in the Schedule of Activities (see Section 6.11). 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 follow-up visit, the investigator needs to follow 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-follow-up, 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 9.3.2).

9.3.2. 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 IMP-related, must be recorded in the CRF and on the SAE form. 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 IMP, 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.

Follow-up 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, postmortem 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 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 follow-up visit but within 30 days of the last dose of IMP(s), regardless of causality, should also be reported (Emergency Contact Information on page 2). Investigators are not obligated to actively seek SAEs after the CSP-defined follow-up period. However, if the investigator is informed about an SAE that occurs at any time after the subjects' post-treatment follow-up visit and the event is deemed relevant to the use of IMP(s), he/she should promptly document and report the event to the sponsor by using the SAE form.

9.3.3. 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 follow-up 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.

9.3.4. Reporting of Special Situations (Other Than Pregnancy) and Associated 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 9.3.1.

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 9.3.2.

9.4. 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 to worldwide regulatory agencies reports of SAEs, serious adverse drug reactions, or suspected unexpected serious adverse reactions (SUSARs). The sponsor or a specified designee will notify worldwide regulatory agencies 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 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 IMP(s). The investigator should notify the IEC/IRB of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This clinical study is conducted in accordance with the current applicable regulations, ICH-GCP Guideline E6, EU Directive 2001/20/EC and its updates, and local ethical and legal requirements.

GCP 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, 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.

10.1. SPONSOR'S RESPONSIBILITIES

10.1.1. Regulatory Approval / Notification

Prior to clinical study start, this CSP together with all relevant documentation will be submitted to the local regulatory authorities for review and approval and/or notification in compliance with local requirements.

10.1.2. Clinical Study Closure Considerations

The sponsor reserves the right to close the investigational 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 within 15 calendar days unless otherwise specified by the IEC/IRB, including a detailed written explanation of the reasons for the termination/halt.

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 within 90 days of the end of the clinical study in a given country/member state or within the timelines required by the local regulations.

Reasons for the closure of an investigational site 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.

10.1.3. Indemnification

Under the conditions of a contract concluded between investigator, site, and sponsor or designee, which shall prevail, 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.

10.1.4. Insurance

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 sponsor's insurance, except in case of gross negligence or willful misconduct by the investigator.

10.1.5. 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 10.4.1). At the end of the clinical study, the results of the clinical study will be reported in a clinical study report. A summary or full report, depending on the requirements, will be provided to the investigators, to the applicable regulatory authorities and IECs/IRBs if required by the applicable regulatory requirements within one year, or 6 months for pediatric studies, after the end of the clinical study.

10.1.6. 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. 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.

10.2. INVESTIGATOR'S RESPONSIBILITIES

10.2.1. Financial Disclosure

The disclosed financial interest of the investigators must be collected before screening of the first subject, following clinical study completion at the investigator site, and 1 year following overall clinical study completion. The investigators should promptly update this information if any relevant changes occur during this period. Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any investigator(s) added as investigational staff must complete the Investigator Financial Disclosure Form at the beginning of their participation in the clinical study. For any investigator(s) leaving the site prior to clinical study completion, an Investigator Financial Disclosure Form should be obtained at the end of their contribution to the clinical study.

10.2.2. 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 investigational 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.

10.2.3. Archiving

The investigator shall maintain the clinical study-specific documents as specified in Section 8 "Essential Documents for the Conduct of a Clinical Study" of the ICH-GCP Guidelines and as required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the IMP. These documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor.

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.

10.2.4. 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 IMP, the clinical study number, the investigator's name and a 24-hour emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

10.3. CONFIDENTIALITY

All information concerning the product and the sponsor's operations (such as patent applications, formulae, 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.

The subject will receive all information as required by the EU General Data Protection Regulation and other data privacy regulations, 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/her data, and all his/her data subject's rights. All details are listed in the ICF.

10.4. ETHICAL CONSIDERATIONS

10.4.1. Independent Ethics Committee (IEC) / Institutional Review Board (IRB)

This clinical study can only be undertaken after full approval of the CSP, ICF, any other written information given to subjects, and subject recruitment materials has been obtained from the IEC/IRB. 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 will be submitted to the IEC/IRB per local requirements:

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

CSP amendments and applicable ICF amendments must promptly be submitted to the IEC/IRB for review and approval prior to implementation of the change(s), except when necessary to eliminate an immediate hazard to the clinical study subjects, or according to local requirements.

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.

10.4.2. Informed Consent

The investigator or designated personnel must explain the clinical study and the implications of participation (e.g. objectives, methods, anticipated benefits, and 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, 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 one 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 trial 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 and health of her baby, will sign a specific ICF to participate in the data collection.

10.5. DATA QUALITY CONTROL / ASSURANCE

10.5.1. Monitoring

This clinical study will be monitored by sponsor representatives according to their current Standard Operating Procedures for the monitoring of clinical studies as described in the monitoring plan.

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).

10.5.2. 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.

REFERENCES

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APPENDICES

APPENDIX 1: KNOWN CYP2C8 SUBSTRATES

Excluded medication:

Amiodarone
Buprenorphine
Amiodaquine; Chloroquine
Repaglinide
Rosiglitazone, pioglitazone
Verapamil
Zopiclone

This list is intended as a guidance for the investigator.

APPENDIX 2: KNOWN STRONG CYP3A4 INDUCERS AND POTENT P-GP INDUCERS

Excluded medication:

Barbiturates
Carbamazepine
Glucocorticoids: steady dose of prednisone or equivalent >10 mg/day
Modafinil
Oxcarbazepine
Phenobarbital
Phenytoin
Pioglitazone
Rifabutin
Rifampin
Bosentan
St. John's Wort

This list is intended as a guidance for the investigator.

APPENDIX 3: KNOWN STRONG CYP3A4 INHIBITORS

Excluded medication:

Clarithromycin
Itraconazole
Ketoconazole
Nefazodone
Suboxone®
Telithromycin

This list is intended as a guidance for the investigator.

APPENDIX 4: KNOWN POTENT P-GP INHIBITORS

Excluded medication:

Amiodarone
Azelastine
Azithromycin – Clarithromycin – Erythromycin – Roxithromycin – Telithromycin (unless used under the condition described in Section 4.5.3.2)
Cyclosporine
Itraconazole - Ketoconazole
Tamoxifen
Verapamil

This list is intended as a guidance for the investigator.

APPENDIX 5: MEDICATION KNOWN TO PROLONG QT INTERVAL

This is based on the CredibleMeds list of medication known to prolong QT interval/cause Torsade de Pointes (Woosley RL. et al., 2018).

Medication to be used with caution:

Disopyramide
Dofetilide
Flecainide
Ibutilide
Quinidine
Sotalol
Hydroxychloroquine

This list is intended as a guidance for the investigator.

SIGNATURE PAGE – SPONSOR

Study Title: A Phase 2a randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy, safety, and tolerability of orally administered GLPG1690 for 24 weeks in subjects with systemic sclerosis

CSP Version: 5.00 **Date:** 28-Apr-2020

This clinical study protocol has been reviewed and approved by the sponsor to ensure compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

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

[redacted] MD

Study Physician	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title: A Phase 2a randomized, double-blind, placebo-controlled, multi-center study to evaluate the efficacy, safety, and tolerability of orally administered GLPG1690 for 24 weeks in subjects with systemic sclerosis

CSP Version: 5.00 **Date:** 28-Apr-2020

I, the undersigned, have read this clinical study protocol and will conduct the study as described in compliance with the clinical study protocol, in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Investigator Name	Signature	Date

Signature Page for glpg1690-cl-204-protocol 11151

Approval	[redacted]al Director Phase I Translational Medicine 28-Apr-2020 14:26:27 GMT+0000

Signature Page for glpg1690-cl-204-protocol 11151