CLINICAL STUDY PROTOCOL

Project Number:	GLPG1690	Study Number:	GLPG1690-CL-206
Protocol version:	2.00	Date:	8-Jan-2020
Amendment:	1		
Study Title	A multicenter, open-label extension study to evaluate the long-term safety, tolerability and efficacy of orally administered GLPG1690 in subjects with systemic sclerosis		
Status	Final	Development Phase:	2
EudraCT No:	2019-001279-34	CT.gov No:	NCT03976648
IND No	140691		
Sponsor:	Galapagos NV, Generaal De Wittelaan L11 A3, 2800 Mechelen, Belgium		
Medical Leader:	[redacted], MD		
General Protocol			

Confidentiality Statement

EMERGENCY CONTACT INFORMATION

In case of a **serious adverse event (SAE)**, a special situation (see Section 8.1.6) 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:

Contact Safety Hotline:
EMEA: [redacted]
North America: [redacted]

Sponsor contact number:
[redacted]

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[redacted]

CLINICAL STUDY PROTOCOL HISTORY

Clinical Study Protocol (CSP) / Amendment #	**Date**	**Main Rationale** **General / Country-Specific**
CSP Version 1.00	30-Jan-2019	Initial Protocol Version General
CSP Version 1.00 updated	09-Apr-2019	Addition of EudraCT number and protocol clarifications General
Amendment 1, CSP Version 2.00	08-Jan-2020	Extension of the duration of the study [redacted] General

SUMMARY OF CHANGES

Amendment 1 (08-Jan-2020)
The overall reason for this update: Extension of the duration of the treatment period from 52 weeks to 104 weeks and [redacted]
The changes made to CSP GLPG1690-CL-206 Version 1.00 dated 09-Apr-2019, are listed below, reflecting a brief rationale of each change and the applicable sections.
The protocol was updated to extend the duration of the treatment period from 52 weeks to 104 weeks. **Applicable Sections:** Synopsis Section 3.1 Clinical Study Design Section 3.3 Clinical Study Rationale Section 3.3.2 Clinical Study Design Rationale Section 5.1 Timing of Assessments Section 5.9 Schedule of Activities
The CT.gov number has been added. **Applicable Section**: Title page
The current Investigator's Brochure is now Edition 6 (28-Jun-2019). The information on GLPG1690 has been updated. **Applicable Sections:** Section 1 Introduction Section 3.5 Potential Risks and Benefits Section 3.6.3.2 Prior and Concomitant Medications
[redacted]

[redacted] [redacted]
Events meeting the following defined criteria must be reported as a serious adverse event (SAE) and Investigational Medicinal Product (IMP) must be discontinued: • AST or ALT ≥8xULN • AST or ALT ≥3xULN 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 ≥1.5xULN or international normalized ratio [INR] >1.5) The investigations and steps to be taken by the investigator have been described in Section 3.6.4. **Applicable Sections:** Section 3.6.4 Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal and Study Termination Section 8.1.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments as Adverse Events or Serious Adverse Events
Hydroxychloroquine has been added to the list of medication known to prolong QT interval (to be used with caution) in Appendix 5, and felodipine was removed from the list of prohibited medication (Erratum 2, 27-Aug-2019). Suboxone was removed from the list of known strong cytochrome P450 (CYP) CYP3A4 inhibitors because its constituents, naloxone and bupenophine are not known to be strong inhibitors. The prohibition of B-cell depleting agents has been broadened to “other monoclonal antibodies”. Restrictions on the consumption of double-strength grapefruit juice have been added in Section 3.6.3.3. **Applicable Sections**: Section 3.6.3.2 Prior and Concomitant Medications Section 3.6.3.3 Food and Beverage Restrictions Appendix 2 Known Strong CYP3A4 Inducers and Potent P-gp Inducers Appendix 3 Known Strong CYP3A4 Inhibitors Appendix 5 Medication Known to Prolong QT interval
The ECG parameter QTcB will not be derived. **Applicable Section:** Section 5.6.5 12-lead Electrocardiogram
The protocol was updated with guidance for male subjects to withdraw if they intend to father a child. **Applicable Sections:** Section 3.5 Potential Risks and Benefits Section 3.6.3.1.2 Precautions for Sexual Intercourse: Male subjects

The protocol was updated to correct the Safety hotline number and e-mail address (Erratum 1, 23-Jul-2019). **Applicable Sections**: Emergency Contact Information
Minor edits and administrative updates throughout the protocol. **Applicable Sections**: List of Abbreviations and Definition of Terms Section 3.3 Clinical Study Rationale Section 3.6.3.3 Food and Beverage Restrictions Section 3.6.4 Treatment Discontinuation (Temporarily and Permanently), Subject Withdrawal and Study Termination Section 4.4 Storage Section 5.6.2 Clinical Laboratory Evaluations Section 6.3.2 Interim Analysis Appendix 2 Appendix 5

Update to Version 1.00 (09-Apr-2019)
The overall reason for this update: Addition of EudraCT number and protocol clarifications.
The changes made to CSP GLPG1690-CL-206 Version 1.00 dated 30-Jan-2019, are listed below, reflecting a brief rationale of each change and the applicable sections.
The protocol EudraCT number added **Applicable Sections**: Title page
The protocol was updated to clarify that dosing of Investigational Medicinal Product (IMP) in this study starts on the day after the Rollover visit **Applicable Sections**: Synopsis Section 3.1 Clinical Study design Section 5.8 Schedule of Activities
The list of safety laboratory parameters was updated to align with the prior GLPG1690-CL-204 study **Applicable Sections**: Section 5.6.2 Clinical Laboratory Evaluations
Clarifications have been made throughout the protocol.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

ADL	activities of daily living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
[redacted]	[redacted]
ATX	autotaxin
[redacted]	[redacted]
BCRP	breast cancer resistance protein
BW	body weight
CRF	case report form
[redacted]	[redacted]
CRO	contract research organization
CSP	clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
ECG	electrocardiogram
ED	early discontinuation
ENPP	ectonucleotide pyrophosphatase/phosphodiesterase
EoT	end of treatment
EU	European Union
FAS	full analysis set

[redacted]	[redacted]
FSH	follicle stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice(s)
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP	Good Laboratory Practice
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-6	interleukin 6
IMP	investigational medicinal product
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
LFT	liver function test
LPA	lysophosphatidic acid
LPC	lysophosphatidylcholine
LPD	lysophospholipase D
MATE	multidrug and toxin extrusion transporter
MCID	Minimal Clinically Important Difference
MMF	mycophenolate mofetil

[redacted]	[redacted]
NOAEL	no observed adverse effects level
NOEL	no observed effect level
OAT	organic anion transporting polypeptides
OCT	organic cation transporter
OLE	open-label extension
[redacted]	[redacted]
PDE	phosphodiesterase
P-gp	P-glycoprotein
[redacted]	[redacted]
q.d.	once daily
[redacted]	[redacted]
QTcF	QT interval corrected for heart rate using Fridericia's formula
SAE	serious adverse event
[redacted]	[redacted]
[redacted]	[redacted]
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed plasma concentration
ULN	upper limit of normal
WOCBP	women of childbearing potential

Definition of Terms

QTcF	QT interval corrected for heart rate using Fridericia's formula:

$$QTcF = QT/RR^{1/3}$$

PROTOCOL SYNOPSIS

Title of Study

A multicenter, open-label extension study to evaluate the long-term safety, tolerability and efficacy of orally administered GLPG1690 in subjects with systemic sclerosis.

Phase of Development: 2

Planned Number of Subjects

Up to 30 subjects may roll over from Study GLPG1690-CL-204 into this open-label extension (OLE) study.

Study Duration

Each subject will be in the study for up to 116 weeks (104 weeks of treatment and 12 weeks of follow-up).

Study Design

An open-label, multicenter, single-arm, 104-week extension study for subjects with systemic sclerosis who completed the 24-week double-blind treatment period of Study GLPG1690-CL-204.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the long-term safety and tolerability of GLPG1690 in subjects with systemic sclerosis.	Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), AEs over time.
Key Secondary	
Not applicable	

Main Criteria for Inclusion and Exclusion

Key Inclusion Criteria

- Male or female subjects who completed the 24-week treatment period of Study GLPG1690-CL-204 and who according to the investigator's judgment may benefit from long-term treatment with GLPG1690.

Key Exclusion Criteria

- Any condition or circumstances that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.

Treatment and Treatment Schedule

Subjects will enter this OLE study at the Rollover visit on Day 1, which will occur on the same day as the Week 24 visit (the last visit of the treatment period) of the preceding GLPG1690-CL-204 study. Subjects who roll over to this OLE study will participate in the posttreatment follow-up period of the OLE study instead of Follow-up in Study GLPG1690-CL-204.

At the Rollover visit, subjects begin the 104-week treatment period. The subsequent visits during the open-label treatment period will take place at Weeks 2, 4, 8, 16, 28, 40, 52, 64, 76, 88, and at Week 104 (End of Treatment [EoT]). Two follow-up visits will be planned 4 weeks and 12 weeks after the last administration of investigational medicinal product (IMP). In case of withdrawal, an Early Discontinuation (ED) visit will be scheduled. Additional unscheduled visits are allowed for any safety assessments if clinically indicated.

Investigational Medicinal Product, Dosage, and Mode of Administration

The IMP is GLPG1690.

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

The dose will be 600 mg GLPG1690 orally once daily (q.d.) (as 3 GLPG1690 film-coated tablets of 200 mg).

Statistical Analysis

Safety will be analyzed using the full analysis set (FAS), which will be defined as all subjects who had at least one intake of IMP in the OLE study.

Subjects will be analyzed according to the prior treatment group in the preceding GLPG1690-CL-204 study. All safety data collected on or after the first dose of IMP administration in the preceding GLPG1690-CL-204 study 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 in Study GLPG1690-CL-204, and overall. In addition, similar summaries of safety data collected only after the first intake of IMP during this OLE study will be provided.

Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead electrocardiograms (ECGs).

[redacted]

[redacted]

1. INTRODUCTION

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 3 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 (GI) tract, the musculoskeletal system, the retroperitoneal space, and the heart. Current treatment options for systemic sclerosis are limited and include topical skin treatments, nonsteroidal 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 unmet medical need.

Mode of Action

GLPG1690 is a novel, potent, and selective small-molecule inhibitor of autotaxin (ATX), targeting disease relevant signal transduction pathways, currently in development for the treatment of systemic sclerosis.

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, et al. 2000). Literature data have identified the ATX/LPC axis as the main source of LPA in blood (Tanaka, et al. 2006, Tsuda, et al. 2006).

LPA acts through 6 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, 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.

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

Rationale for the Study

GLPG1690-CL-204 is a Phase 2a placebo-controlled study to evaluate the efficacy, safety, and tolerability of orally administered GLPG1690 for 24 weeks in subjects with systemic sclerosis. GLPG1690-CL-206 is an open-label extension (OLE) study of GLPG1690-CL-204 to evaluate the long-term safety, tolerability and efficacy of orally administered GLPG1690.

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 9).

1.1. Background - Nonclinical Studies

1.1.1. 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.

1.1.2. Pharmacology

1.1.2.1. 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 and phospholipase C. Moreover, GLPG1690 showed no inhibition in a panel of kinases. In a Cerep diversity panel (98 targets including receptors and ion channels),

[redacted]

GLPG1690 dose-dependently inhibited the production of connective tissue growth factor, interleukin 6 (IL-6), and endothelin-1 upon transforming growth factor β-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 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.

1.1.2.2. 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.

1.1.3. 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 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 GI tract, glandular tissues, liver, and uveal tract. GLPG1690 and/or metabolites showed some affinity 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). Sex 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.

1.1.4. Toxicology

1.1.4.1. 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, embryofetal development studies in rats and rabbits, fertility studies in male and female rats, non-TgrasH2 mice preliminary studies, preliminary carcinogenicity studies, and in 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 1000 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 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 postimplantation 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.

1.2. Background - Clinical Studies

1.2.1. Clinical Safety

In clinical pharmacology studies, GLPG1690 has been administered to 85 healthy subjects as single doses (dose range: 20 to 1500 mg) and 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. 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 2 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, who remained on treatment in the study).

None of these serious TEAEs were considered related to IMP according to the investigator. 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.

1.2.2. Clinical Efficacy

During 12 weeks of treatment of subjects with IPF in Study GLPG1690-CL-202, forced vital capacity (FVC) values remained stable in the majority of subjects taking GLPG1690 600 mg q.d., and declined in subjects taking placebo.

1.2.3. 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 1000 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 h.

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 [$AUC_{0\text{-}24h}$], respectively). Exposure of GLPG1690, as measured by the area under the plasma concentration-time curve from time zero extrapolated to infinity ($AUC_{0\text{-}\infty}$), 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), 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.

1.2.4. Clinical Pharmacodynamics

After a single administration of GLPG1690, a significant dose dependent reduction of LPA C18:2 was observed in plasma. This effect started from 0.5 hours after IMP intake, reached a plateau at 1 to 6 hours postdose (depending on dose), and was sustained over time up to 24 hours after IMP intake. Multiple once or twice daily 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 predose 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 for the percentage reduction from baseline and maximum effect (expressed as a percentage reduction from baseline).

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.

2. CLINICAL STUDY OBJECTIVES

2.1. Primary Objective

- To evaluate the long-term safety and tolerability of GLPG1690 in subjects with systemic sclerosis.

2.2. Other Objectives

- [redacted]

3. INVESTIGATIONAL PLAN

3.1. Clinical Study Design

This is an open-label, multicenter, single-arm, 104-week extension study for subjects with systemic sclerosis who completed the 24-week double-blind treatment period of Study GLPG1690-CL-204. Up to 30 subjects may roll over from Study GLPG1690-CL-204 into this OLE study.

A schematic diagram of the clinical study design is provided inFigure 1Figure 1: Schematic Study Overview.

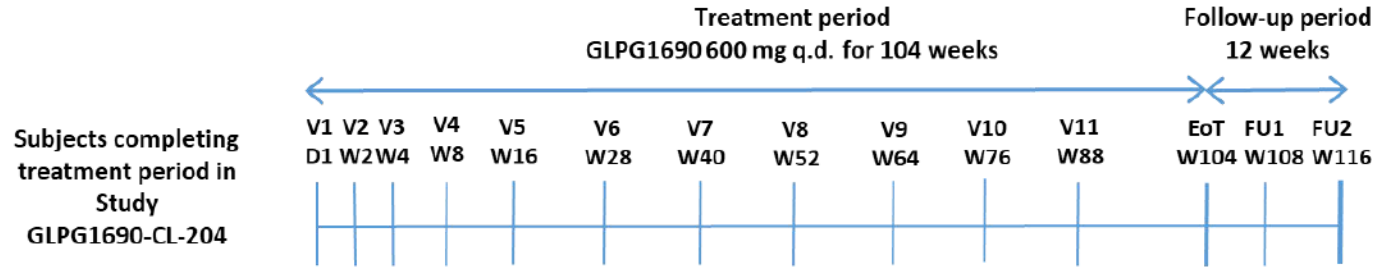

Figure 1: Schematic Study Overview

D=Day, EoT=end of study, FU=Follow-up, V=Visit, W=Week.

For the in- and exclusion criteria please refer to Section 3.6.1, "Inclusion Criteria" and Section 3.6.2, "Exclusion Criteria".

Subjects will enter this OLE study at the Rollover visit on Day 1, which will occur on the same day as the Week 24 visit (the last visit of the treatment period) of the preceding GLPG1690-CL-204 study. Subjects who roll over to this OLE study will participate in the posttreatment follow-up period of the OLE study instead of Follow-up in Study GLPG1690-CL-204.

After the Rollover visit, the subsequent visits during the open-label treatment period will take place at Weeks 2, 4, 8, 16, 28, 40, 52, 64, 76, 88, and at Week 104 (End of Treatment [EoT]). In case of withdrawal, an Early Discontinuation (ED) visit will be scheduled. After the 104-week open-label treatment period (or early discontinuation of treatment), 2 follow-up visits will be planned 4 weeks and 12 weeks after the last administration of IMP. Additional unscheduled visits are allowed for any safety assessments if clinically indicated.

Subjects will receive 600 mg GLPG1690, orally q.d., starting the day after the Rollover visit. For detailed information regarding dosage form, packaging and labeling of the IMP please refer to Section 4.2, "Dosage and Administration" and Section 4.3, "Packaging, Labeling and Distribution".

Each subject will be in the study for up to 116 weeks (104 weeks of treatment and 12 weeks of follow-up).

3.2. End of Study Definition

The end of the study is reached when the last follow-up visit, as planned according to the Schedule of Activities (Section 5.9), of the last subject is performed.

3.3. Clinical Study Rationale

GLPG1690 is a potential first-in-class disease-modifying drug for systemic sclerosis, and its safety and efficacy in this disease are currently being evaluated in a randomized, double-blind, placebo-controlled, 24-week Phase 2a study, GLPG1690-CL-204.

Due to the chronic, progressive nature of the disease, patients would be expected to receive long-term treatment. To acquire additional data on long-term safety, tolerability and efficacy of GLPG1690 in systemic sclerosis, GLPG1690-CL-206 extends GLPG1690-CL-204 as an open-label study for 104 weeks of treatment.

In addition, this study will enable the subjects assigned to placebo in the preceding study to receive active treatment.

3.3.1. Dose Rationale

Subjects will receive GLPG1690 600 mg orally q.d., as in the active arm of the preceding GLPG1690-CL-204 study.

3.3.2. Clinical Study Design Rationale

During the initial 8 weeks of this study, visits are scheduled with the same frequency as in the GLPG1690-CL-204 study to enable close monitoring of the subjects, especially of subjects previously assigned to the placebo group and receiving GLPG1690 for the first time.

After completion of the 104-week treatment period, or premature treatment discontinuation, subjects will be asked to attend the 2 follow-up visits. The follow-up period in this OLE study is identical to that in the GLPG1690-CL-204 study. [redacted]

3.4. Endpoints

For this OLE study, safety and tolerability are the primary endpoints.

[redacted]

[redacted]

3.4.1. Primary Endpoint

– Incidence of TEAEs, serious adverse events (SAEs), AEs over time.

3.4.2. Other Endpoints

– [redacted]

3.5. Potential Risks and Benefits

There are currently no approved drugs for the treatment of systemic sclerosis. GLPG1690 is the first ATX inhibitor in clinical development for the oral treatment of IPF. Only data from the clinical development program of GLPG1690 are available. There is currently no data on the use of GLPG1690 for the prolonged duration planned in this study. GLPG1690 was generally safe and well tolerated in previous clinical studies. This section further describes potential risks and how these are mitigated.

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 3.6.3.1.

QT Interval Prolongation

The potential effect of GLPG1690 on QT interval prolongation is under investigation. Consequently, subjects meeting the stopping rules for QT/QTc-changes 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 3.6.3.2).

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 latest IB for GLPG1690 and relevant updates/addenda for additional information on the safety of the IMP.

3.6. Clinical Study Population

3.6.1. Inclusion Criteria

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

1. Male or female subjects who completed the 24-week treatment period of Study GLPG1690-CL-204 and who according to the investigator's judgment may benefit from long-term treatment with GLPG1690.
2. Able and willing to comply with the protocol requirements and to sign the informed consent form (ICF) as approved by the Independent Ethics Committee (IEC) / Institutional Review Board (IRB), prior to the eligibility evaluation.
3. Subject must be able and willing to comply with restrictions on concomitant medication as described in Section 3.6.3.2.
4. Female subjects of childbearing potential must have a negative urine pregnancy test.
5. Female subjects of childbearing potential or male subjects with female partners of childbearing potential are willing to comply with the contraceptive methods described in

Section 3.6.3.1 during the clinical study and for at least 90 days after the last dose of the IMP for male subjects and at least 30 days after the last dose of the IMP for female subjects.

3.6.2. Exclusion Criteria

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

1. Investigator or other study staff or relative thereof who is directly involved in the conduct of the study.
2. Any condition or circumstances that, in the opinion of the investigator, may make a subject unlikely or unable to complete the study or comply with study procedures and requirements.
3. Persistent abnormal laboratory values (including and not limited to hematology, liver and renal function values), according to the investigator's clinical judgment (considering systemic sclerosis disease- and medication-related changes).
4. Female subject intending to become pregnant or breastfeed.
5. A history of being admitted to an institution under an administrative or court order, if applicable by local legislation.

3.6.3. Prohibition and Restrictions

3.6.3.1. Precautions for Sexual Intercourse

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

3.6.3.1.1. Female Subjects

In line with the Heads of Medicines Agencies' Clinical Trial Facilitation Group 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 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 is considered a highly effective contraceptive measure only if it is the preferred and usual lifestyle of the subject. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study.

Periodic abstinence (e.g. calendar, symptothermal, postovulation 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. In months with no study visit, the monthly pregnancy test will be performed at home by the subject using home testing kits. The site will instruct 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 and record in the 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 must report this immediately, and under no circumstances later than 24 hours after being made aware.

The safety of GLPG1690 during breastfeeding is unknown. Nursing women are not allowed to take part in this clinical study.

3.6.3.1.2. 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.

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[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).

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

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

In a case where the female partner of a male subject has undergone documented surgical sterilization that was performed more than one 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).

Male subjects who wish to father a child should stop treatment with IMP and wait for at least 90 days before stopping the contraceptive measures detailed in this section.

No sperm donation is allowed from the first dose of IMP during the clinical study until at least 90 days after the last dose of IMP.

3.6.3.2. Prior and Concomitant Medications

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 GLPG1690-CL-206. It is required that these medications 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 during the treatment period:

- warfarin, antifibrotic agents (including colchicine, minocycline, tyrosine kinase inhibitors [nilotinib, imatinib, dasatinib, nintedanib], pirfenidone), or Type 1 oral collagen
- 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 and the following biologics: tocilizumab or other drugs targeting IL-6/IL-6 receptor, abatacept, anti-tumor necrosis factor drugs, rituximab, belimumab, or other monoclonal antibodies
- bosentan

If during the study, the subject's condition necessitates the use of one of the above-mentioned 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 non-exhaustive 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 liver function tests (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 should be avoided during the study to ensure proper exposure to GLPG1690 (see Appendix 2). GLPG1690 exposure increased by 3 to 4 fold when coadministered with strong CYP3A4 inhibitors and dual strong 3A4 and potent P-gp inhibitors compared to GLPG1690 administered alone. 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 new co-medication, in particular 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 that are metabolized/transported by the above-mentioned 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.

3.6.3.3. 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.

3.6.3.4. Other Prohibitions and Restrictions

Not applicable.

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

A subject may be withdrawn from the clinical study at any time without the subject's consent if the investigator or sponsor determines that it is not in the best interest of the subject to continue participation. In such case, the reason for withdrawal will be documented in the source documents, and the subject will complete the ED visit and, or follow-up visit(s) 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 may be unblinded to the treatment received during GLPG1690-CL-204 if appropriate. Repeat counseling on birth defect risk must be offered.
- Arrhythmia or conduction abnormality, including but not limited to prolonged QT interval corrected for the heart rate using Fridericia's formula (QTcF), where the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher (QTc >500 ms on at least 2 separate ECGs).
- An increase for QTcF with >60 ms change from the GLPG1690-CL-204 baseline or QTcF >500 ms at any ECG recording needs to be confirmed by an ECG recording as soon as possible after the original abnormal recording at the same visit. If the abnormal recording is discovered after the visit, the recording should be confirmed as soon as possible. In case of an abnormal ECG on both of these 2 recordings is confirmed, 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 temporarily discontinued for this subject.

- Increase in LFTs:
  - Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) elevations >8x upper limit of normal (ULN).
  - AST and/or ALT elevations >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.

For a subject having:

- AST or ALT ≥8xULN
- AST or ALT ≥3xULN 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 ≥1.5xULN or INR >1.5)

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

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

– All these 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 IMP, 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 the 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 site (lost-to-follow-up) should be contacted by the site so that their health status can be assessed and documented in the source documents. The site should make every effort to understand whether the subject is alive, including checking the medical records and contacting general practitioner or relatives, if necessary. All attempts must be documented in the source documents. 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.

3.7. Measures to Minimize Bias

3.7.1. Randomization

This is an open-label study with one dose level of IMP; no randomization will be performed.

At the Rollover visit (visit 1), subjects confirmed to be eligible for this OLE study will be enrolled. Subjects will retain the subject identification number assigned in GLPG1690-CL-204.

3.7.2. Blinding and Unblinding

This is an open-label clinical study and treatment in this extension study will not be blinded.

Before the unblinding of the GLPG1690-CL-204 study, the blind of treatment received in Study GLPG1690-CL-204 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 whenever possible and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he or she feels rapid emergency unblinding is necessary, but is required to inform the sponsor in a timely fashion after unblinding has occurred.

The blind of treatment received in Study GLPG1690-CL-204 can be broken by the investigator via interactive web response system.

4. INVESTIGATIONAL MEDICINAL PRODUCTS

4.1. Identity of the Investigational Medicinal Product(s)

The IMP (GLPG1690) 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).

A full list of excipients used in the film-coated tablet formulation is available in the latest version of the IB for GLPG1690 and relevant updates/addenda.

4.2. Dosage and Administration

The dose will be 600 mg GLPG1690 q.d. (as 3 GLPG1690 film-coated tablets of 200 mg).

The IMP is to be taken around the same time every day with food (e.g. breakfast, small meal, or a snack) or after food intake, 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.

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.

4.3. Packaging, Labeling and Distribution

The film-coated tablet for oral use will be packaged in blisters. 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. 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.

The distribution 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.

4.4. Storage

Sites are to store IMP supplies in a secure area below 30°C, protected from light, until dispensed. Sites will be required to monitor the storage temperature by using at least a min-max temperature-recording device and to keep a minimum to maximum temperature log, which must be completed each working day in order to establish a record of compliance with these storage conditions. The investigator will instruct subjects on how the IMP should be stored at home.

4.5. Treatment Compliance and Drug Accountability

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

For each dose taken at home, the date and number of tablets taken should be recorded on the subject diary card (Section 5.4). Any interruption or change in treatment (together with the reason for change) should be documented on the subject diary card. Subjects will return any unused IMP and empty IMP packages at each visit. At each clinical study center visit, clinical study center staff will review treatment compliance by assessing the number of returned IMP. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure the proper subject dose. Subjects with poor compliance will be retrained by the clinical study site. Upon sponsor approval, all unused IMP and empty IMP packages should be returned to the drug supplier/drug depot or will be destroyed at the site. In case of destruction by the site or the supplier/drug depot, an acceptable destruction process should be in place and a destruction certificate should be provided to the sponsor.

5. 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 5.9).

5.1. Timing of Assessments

The study assessments will be undertaken at time points as specified in the Schedule of Activities in Section 5.9. A window of ±2 days is allowed for Visits 2 and 3, a window of ±4 days is allowed for Visit 4, and a window of ±7 days is allowed for Visits 5, 6, 7, 8, 9, 10, 11, the EoT Week 104 visit (or ED visit), and for the 2 follow-up visits.

The ICF needs to be signed before any study procedure for this extension study is carried out.

[redacted] Subsequently, the 12-lead ECG is recommended to be performed before any invasive study procedures such as blood draws, which should be done at the end of the visit, as much as possible.

5.2. 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.

5.3. Subject and Disease Characteristics

Subjects who complete the GLPG1690-CL-204 24-week treatment will be evaluated for eligibility to enter this study at the Rollover visit (Visit 1) (which is on the same day as the Week 24 visit of GLPG1690-CL-204). For subjects enrolled into this study, the GLPG1690-CL-204 Follow-up visits will not be performed. After giving written informed consent, the inclusion and exclusion criteria will be checked to assess eligibility for the study. IMP will be dispensed and diary cards will be issued to subjects enrolled in the study.

Demographics, baseline characteristics, medical history and prior and concomitant medication data will be derived from the baseline data of Study GLPG1690-CL-204.

5.4. Subject Diary Card

Subjects will be given diary cards from visit 1 until follow-up visit 2 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 3.6.3.1.1).
- 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.

5.5. Efficacy Assessments

[redacted]

[redacted]

5.5.3. [redacted]

[redacted]

5.5.3.1. [redacted]

[redacted]

5.5.3.2. [redacted]

[redacted]

5.5.4. [redacted]

[redacted]

5.6. 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.

5.6.1. 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 or at the ED visit.

Detailed definitions, ratings and reporting requirements for AEs and SAEs are found in Section 8.

5.6.2. 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, activated partial thromboplastin time, and prothrombin 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, high density lipoprotein, low 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.
- **Pregnancy test for females:**
  urine dipstick on a monthly basis until the FU1 follow-up visit (only for WOCBP). Unscheduled FSH lab testing may be performed if a female subject reports an amenorrhea ≥12 months during the study.

The clinical laboratory evaluations will be performed at visits specified in the Schedule of Activities in Section 5.9 (see also Section 5.1, "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.

5.6.3. Physical Examination

Physical examinations will be performed as appropriate for any symptoms reported by the subject. They 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 5.9. The person conducting the physical examination will document this in the subject's medical records. Clinically significant abnormal findings should be recorded as AEs.

5.6.4. Vital Signs

Vital signs (systolic and diastolic blood pressure, 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 5.9. Clinically significant abnormal values should be recorded as AEs.

5.6.5. 12-lead Electrocardiogram

At the time points specified in the Schedule of Activities (see Section 5.9 and also Section 5.1, "Timing of Assessments"), triplicate 12-lead ECGs will be recorded and results will be sent for central reading. ECG recordings will be performed before blood sampling and after subjects rested for 5 minutes in supine position. The triplicate ECGs will be performed 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. The ECG will be reviewed by the investigator for clinically significant abnormalities before the end of the visit. 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.

5.7. Other Assessments

5.7.1. [redacted]

[redacted]

5.8. Sample Management

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

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

5.9. Schedule of Activities

For detailed instructions on the clinical study procedures, please see referred sections and Section 5.1, "Timing of Assessments".

EVENT	TREATMENT PERIOD												FOLLOW-UP	
Study Visit	**Roll-over Visit 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**EoT / ED**	**FU1**	**FU2**
Study Week (W) or Day (D) ± days (d)	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W16 ±7d**	**W28 ±7d**	**W40 ±7d**	**W52 ±7d**	**W64 ±7d**	**W76 ±7d**	**W88 ±7d**	**W104 ±7d**	**W108 ±7d**	**W116 ±7d**
Informed consent	✓													
Inclusion/exclusion criteria	✓													
Pregnancy test	(✓)[1]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Symptom-directed physical examination	(✓)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Vital signs	(✓)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
12-Lead ECG	(✓)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Clinical laboratory tests	(✓)[1]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
[redacted]														

EVENT	**TREATMENT PERIOD**												**FOLLOW-UP**	
Study Visit	**Roll-over Visit 1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**EoT / ED**	**FU1**	**FU2**
Study Week (W) or Day (D) ± days (d)	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W16 ±7d**	**W28 ±7d**	**W40 ±7d**	**W52 ±7d**	**W64 ±7d**	**W76 ±7d**	**W88 ±7d**	**W104 ±7d**	**W108 ±7d**	**W116 ±7d**
[redacted]														
Dispense subject diary	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Collect subject diary		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Dispense IMP	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Review IMP compliance		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Dose IMP	q.d. from the day after the Rollover visit to the end of the treatment period													
AE assessment	Throughout the study													
Concomitant medications	Throughout the study													

W=Week(s), D=Day(s), EoT=End of Treatment, ED=Early Discontinuation, FU=follow-up, [redacted]

[1] Rollover visit data in parentheses are those collected as part of the activities at the last visit (Week 24) of the preceding core Study GLPG1690-CL-204, which is on the same day as the Day 1 Rollover visit of this study.

6. STATISTICAL METHODS

All statistical methods will be detailed in a statistical analysis plan that will be prepared prior to database lock. 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 statistical analysis plan.

6.1. Determination of Sample Size

Thirty subjects (20 on 600 mg oral q.d. GLPG1690 and 10 on placebo) are planned to be randomized in the preceding GLPG1690-CL-204 study. All subjects who completed the 24-week double-blind treatment in this preceding study, signed the ICF of the OLE study, and are eligible for the OLE will be included. Thus, up to 30 subjects may roll over and be enrolled in this OLE study. No formal sample size calculation was performed.

6.2. Population for Analyses

6.2.1. All Enrolled Subjects

All subjects who were found eligible to participate in the clinical study.

6.2.2. Full Analysis Set

The OLE full analysis set (FAS) is defined as all subjects who had at least one intake of IMP in the OLE study.

6.3. Statistical Analyses

6.3.1. 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. Data will be pooled across centers and countries.

Tables will be presented by randomization group of the preceding GLPG1690-CL-204 study.

Baseline will be defined as the last measurement before the first dose of IMP in the preceding GLPG1690-CL-204 study, [redacted] for [redacted] safety.

6.3.2. Interim Analysis

Interim analyses may be performed during this clinical study, after unblinding of the GLPG1690-CL-204 study, to allow sponsor planning of future clinical studies. There is no plan to terminate the study earlier based on these interim analyses.

6.3.3. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, and concomitant therapies will be analyzed descriptively. Baseline will be defined as the last measurement before the first dose of IMP in the preceding GLPG1690-CL-204 study.

6.3.4. Analyses of Efficacy Parameters

All efficacy parameters will be analyzed descriptively in the full analysis set (Section 6.2.2) unless otherwise specified.

Results will be presented for all time points in the preceding GLPG1690-CL-204 and GLPG1690-CL-206 studies and by treatment group of the preceding GLPG1690-CL-204 study.

[redacted]

6.3.4.1. [redacted]

[redacted]

6.3.5. Analyses of Safety Data

All safety analyses will be performed using the FAS (Section 6.2.2). Subjects will be analyzed according to the prior treatment group in the preceding GLPG1690-CL-204 study. All safety data collected on or after the first dose of IMP administration in the preceding GLPG1690-CL-204 study 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 in Study GLP1690-CL-204, and overall. In addition, similar summaries of safety data collected only after the first intake of IMP during this OLE study will be provided.

Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs.

6.3.5.1. Extent of Exposure

A subject's extent of exposure to the IMP will be generated from the IMP administration page of the CRF. Exposure data will be summarized by treatment group of the preceding GLPG1690-CL-204 study. Duration of exposure to the IMP will be expressed as the number of weeks between the first (in CL-204) and last dose of IMP, inclusive, regardless of temporary interruptions in IMP administration and summarized by treatment group, defined in CL-204. A similar summary for the duration of exposure from the first dose of IMP in the OLE up to the last dose will also be provided.

6.3.5.2. Adverse Events

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

Any AE (or any worsening of an AE) with an onset date on or after the IMP start date in the preceding GLPG1690-CL-204 study and no later than 30 days after last dose of IMP in GLPG1690-CL-206

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 the IMP and severity. In addition, TEAEs leading to premature discontinuation of the IMP will be summarized and listed. Also, all SAEs, including the non-treatment-emergent SAEs, will be listed.

In addition, summaries and/or listings will be provided for the suspected symptoms/AEs of [redacted] with an onset date on or after the IMP start date until the end of follow-up (including information from follow-up visit 2).

6.3.5.3. Clinical Laboratory Evaluations

Laboratory assessments will be analyzed descriptively. Changes from baseline (Day 1 predose) in the GLPG1690-CL-204 study and shifts according to normal ranges will be presented as well. Analyses will be done per prior treatment group in GLPG1690-CL-204. Similar analyses of safety data collected only during this OLE study will be provided.

6.3.5.4. Physical Examinations

Only abnormal postbaseline physical examination results will be listed.

6.3.5.5. Vital Signs

Vital signs will be analyzed descriptively. Changes from baseline (Day 1 predose) in GLPG1690-CL-204 and shifts according to normal ranges will be presented as well. Analyses will be done per prior treatment group as defined in GLPG1690-CL-204. Similar analyses of safety data collected only during this OLE study will be provided.

6.3.5.6. 12-Lead Electrocardiogram

A descriptive analysis will be done for the 12-lead ECG. Changes from baseline (Day 1 predose) in GLPG1690-CL-204 and shifts according to normal ranges will be presented as well. Analyses will be done per prior treatment group in GLPG1690-CL-204. Similar analyses of safety data collected only during this OLE study will be provided.

6.3.6. Analysis of Other Assessments

Exploratory efficacy and safety analyses may be added when deemed useful to better understand the collected data. Individual and/or mean ± standard error efficacy and safety may be plotted against one another.

6.3.7. Additional Statistical Considerations

Not applicable.

7. DATA MONITORING

An independent medical safety review will be implemented for GLPG1690-CL-204 as well as for this GLPG1690-CL-206 clinical study. The review will be conducted by an independent 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'.

8. SAFETY REPORTING

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

8.1.1. 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 posttreatment 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.

8.1.2. 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).

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

An AE is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For an 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.

8.1.4. Adverse Events of Special Interest

Not applicable.

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

Laboratory abnormalities without clinical significance based on the investigator's judgment are not considered AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology, and urinalysis) or other abnormal (clinical study-specific) assessments (e.g. ECG, radiography, vital signs) that require medical or surgical intervention, are associated with signs and/or symptoms, and/or lead to IMP interruption, modification or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 8.1.1 and 8.1.2, respectively. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis is to be reported (e.g. anemia instead of decreased hemoglobin).

The following liver enzyme elevations should be reported as SAEs:

- AST or ALT ≥8xULN
- AST or ALT ≥3xULN 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 ≥1.5xULN or INR >1.5)

8.1.6. 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 IMP
  - Abuse of IMP is defined as the persistent or sporadic, intentional excessive use of the IMP, which is accompanied by harmful physical or psychological effects.
  - Misuse of IMP is defined as a situation where the IMP is intentionally and inappropriately used not in accordance with the product information.
- Drug interaction or food interaction with IMP
  - A drug interaction with IMP is defined as a situation in which there is evidence or a suspicion that the IMP interacts with another drug when both are administered together.
  - A food interaction with IMP is defined as a situation in which there is evidence or a suspicion that the IMP interacts with a food when taken together.
- Medication error with IMP
  - A medication error with IMP is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the subject.
- Occupational exposure to IMP
  - Occupational exposure to IMP is defined as an exposure to the IMP as a result of one's professional or nonprofessional occupation.
- Overdose with IMP

An overdose of IMP is defined as the administration of a quantity of the IMP given per administration or cumulatively, which is the intake of more than 3 tablets/day.

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

8.2. 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.

8.2.1. 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.

8.2.2. 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 1 Grading of AE Severity

Grade	Adjective	Description
Grade 1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate	Local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening	Urgent intervention indicated
Grade 5	Death	Death-related AE
* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc. ** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.		

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

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

8.2.3. Outcome

Each AE must be rated by choosing among:

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

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

8.3.1. 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). 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-up on the subject until AE resolution or reasonable stabilization and to document in the subject's source documentation. No related updates or additional data on the AE should be reported in the CRF.

If a subject is documented as lost-to-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 8.3.2).

8.3.2. 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 posttreatment 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' posttreatment 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.

8.3.3. 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.

8.3.4. 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 8.3.1.

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 8.3.2.

8.4. 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 the reference safety information section in the IB or relevant local label as applicable.

All concerned investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any 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.

9. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

9.1. Sponsor's Responsibilities

9.1.1. 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.

9.1.2. 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 may include, but are not limited to:

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

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

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

9.1.3. Indemnification

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

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

9.1.4. Insurance

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

9.1.5. 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 9.4.1). 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.

9.1.6. 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. The sponsor shall have the right to review it and to make any comments. In accordance with generally accepted scientific collaboration principles, co-authorship with any staff member sponsor involved in the clinical study, will be discussed and mutually agreed upon before submission of any manuscript to a publisher.

9.2. Investigator's Responsibilities

9.2.1. 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.

9.2.2. 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.

9.2.3. 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.

9.2.4. 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.

9.3. Confidentiality

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

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

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

9.4. Ethical Considerations

9.4.1. Independent Ethics Committee / Institutional Review Board

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 IMP (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.

9.4.2. Informed Consent

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

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the clinical study, the subject's consent should be appropriately recorded by means of the subject's personally dated signature and by the investigator's dated signature. In case the subject is unable to read and/or write, oral consent in the presence of at least 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 study 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 will sign a specific ICF to participate in the data collection. Data about the health of the baby will be collected if the parents agree with the data collection and sign a specific ICF.

9.5. Data Quality Control/Assurance

9.5.1. 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).

9.5.2. 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.

10. REFERENCES

Allanore, Y, O Distler, A Jagerschmidt, S Illiano, L Ledein, E Boitiere, I Agueusop, C P Denton, and D Khanna. 2018. "Lysophosphatidic Acid Receptor 1 Antagonist SAR100842 for Patients With Diffuse Cutaneous Systemic Sclerosis: A Double-Blind, Randomized, Eight-Week Placebo-Controlled Study Followed by a Sixteen-Week Open-Label Extension Study." *Arthritis Rheumatol.* 70(10): 1634-1643.

Bandoh, K, J Aoki, M Taira, M Tsujimoto, H Arai, and K Inoue. 2000. "Lysophosphatidic acid (LPA) receptors of the EDG family are differentially activated by LPA species. Structure-activity relationship of cloned LPA receptors." *FEBS Letters* 478: 59-65.

Tanaka, M, S Okudaira, Y Kishi, R Ohkawa, and S Iseki. 2006. "Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid." *Journal of Biological Chemistry* 281: 25822-30.

Tsuda, S, S Okudaira, K Moriya-Ito, M Tanaka, and J Aoki. 2006. "Cyclic phosphatidic acid is produced by autotaxin in blood." *Journal of Biological Chemistry* 281: 26081-8.

Woosley RL, Heise CW, Romero KA. 2018. "QTDrugs Lists." *CredibleMeds.* July 24. www.CredibleMeds.org.

11. APPENDICES

Appendix 1: Known CYP2C8 Substrates

Excluded medication:

Amiodarone
Buprenorphine
Amiodaquine; Chloroquine
Repaglinide
Rosiglitazone, pioglitazone
Verapamil
Zopiclone

This non-exhaustive 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, if steady dose of prednisone or equivalent > 10 mg/day
Modafinil
Oxcarbazepine
Phenobarbital
Phenytoin
Pioglitazone
Rifabutin
Rifampin
St. John's wort

This non-exhaustive list is intended as a guidance for the investigator.

Appendix 3: Known Strong CYP3A4 Inhibitors

Excluded medication:

Clarithromycin
Itraconazole
Ketoconazole
Nefazodone
Telithromycin

This non-exhaustive 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 3.6.3.2)
Cyclosporine
Itraconazole - Ketoconazole
Tamoxifen
Verapamil

This non-exhaustive list is intended as a guidance for the investigator.

Appendix 5: Medication Known to Prolong QT Interval

Medications known to prolong QT interval are to be used with caution during the study. The following, based on the CredibleMeds list of medication known to prolong QT interval/cause Torsade de Pointes (Woosley RL 2018), is a non-exhaustive list of these medications:

Disopyramide
Dofetilide
Flecainide
Hydroxychloroquine
Ibutilide
Quinidine
Sotalol

This list is intended as a guidance for the investigator.

SIGNATURE PAGE – SPONSOR

Study Title:	A multicenter, open-label extension study to evaluate the long-term safety, tolerability and efficacy of orally administered GLPG1690 in subjects with systemic sclerosis.		
CSP Version:	2.00	Date:	08 January 2020

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

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.

[redacted], MD

Medical Leader	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title:	A multicenter, open-label extension study to evaluate the long-term safety, tolerability and efficacy of orally administered GLPG1690 in subjects with systemic sclerosis.		
CSP Version:	2.00	Date:	08 January 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-206-protocol 11156

Approval	[redacted]al Director Phase I Translational Medicine 10-Jan-2020 07:14:14 GMT+0000

Signature Page for glpg1690-cl-206-protocol 11156