Galápagos

CLINICAL STUDY PROTOCOL

Project Number:	GLPG1690
Study Number:	GLPG1690-CL-202
Study Title:	Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter, Exploratory Phase IIa Study to Assess Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690 Administered for 12 Weeks in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Development Phase:	IIa
Status:	Final
Version:	3.0
Date:	16-Oct-2015
EudraCT:	2015-004157-41
IND:	Not applicable
Sponsor:	Galapagos NV Industriepark Mechelen Noord Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium
Medical Lead:	[redacted], MD MBA Tel: [redacted] Mobile: [redacted]
Clinical Study Lead:	[redacted], MSc Tel: [redacted] Mobile: [redacted]

CLINICAL STUDY PROTOCOL HISTORY

CSP / Amendment #	Date	Generic / Country / Site Specific
CSP v2.0	13-Oct-2015	Section 2.5 and 4.1: Details independent medical safety review are removed as these are described in section 7
		Section 5.6.2 and 5.7.4: clarified that bronchoscopy/HRCT is taken post dose if applicable
		Section 4.7.1 Timing of home- and site-based spirometry ~~versus study drug intake~~ As timing vs study drug intake is described in previous paragraph
		Reference list: one more author name added for several references
		Appendix 4: instructions in CYP3A4 removed as these are described in section 3.4.7
CSP v3.0	15-Oct-2015	History table was not included in CSP v2.0

EMERGENCY CONTACT INFORMATION

In case of a **Serious Adverse Event (SAE)**, the investigator must fax or e-mail the Galapagos Clinical Study SAE Form within 24 hours to the [redacted] Medical Affairs (MA) Department:

[redacted] MA SAE Fax #: [redacted]

or

e-mail: [redacted]

In case of **medical questions during the course of the study,** the investigator must contact:

- **Europe:**
  [redacted]
  UKRAINE
  +[redacted]

  [redacted]

In case of **urgent medical questions**, the investigator should call the 24/7 emergency #:

[redacted]

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

[redacted]	[redacted]
AE	adverse event
ANCOVA	analysis of covariance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
ATX	autotaxin
AUC	area under the curve
$AUC_{0\text{-}24h}$	area under the concentration-time curve from time 0 to 24 hours
$AUC_{0\text{-}\tau}$	area under the plasma drug concentration-time curve of a dosing interval
AUEC	area under the effect-time curve
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
b.i.d.	*bis in die*, twice daily
BLM	bleomycin
BW	body weight
C_τ	trough plasma concentration (just before the next dosing i.e. predose sample)
CCL18	chemokine motif ligand 18
Cl	clearance
C_{max}	maximum concentration
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTGF	connective tissue growth factor
CYP	cytochrome P450
D	day
DBP	diastolic blood pressure
DLCO	diffusing capacity for the lungs for carbon monoxide
ECG	electrocardiogram
ECM	extracellular matrix
eCRF	electronic case report form

EDC	electronic data capture
EDV	early discontinuation visit
E_{max}	maximum % reduction from baseline
ENPP	ectonucleotide pyrophosphatase/phosphodiesterase
EOS	end of study
ERS	European Respiratory Society
EU	European Union
FC	food consumption
FEF	forced expiratory flow
FEF_{25-75}	forced expiratory flow between 25 and 75% of exhaled volume
FEV_1	forced expiratory volume in 1 second
FIH	first in human
FRC	functional residual capacity
FRI	functional respiratory imaging
FSH	follicle-stimulating hormone
FU	follow-up
FVC	forced vital capacity
GCP	Good Clinical Practice
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
IC_{50}	inhibitory concentration 50%
ICAM-1	intercelullar adhesion molecule type 1
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IL8	interleukin 8
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
KL-6	Krebs von den Lungen 6
LC-MS/MS	liquid chromatography-mass spectrometry
LFT	liver function test
LPA	lysophosphatidic acid
LPC	lysophosphatidylcholine
MMP	matrix metalloproteinase
Muc1	mucin type 1

NOAEL	no observed adverse effect level
PD	pharmacodynamics
PDE	phosphodiesterase
PK	pharmacokinetics
PLA	phospholipase A
PLC	phospholipase C
QA	quality assurance
q.d.	*quaque die*, once daily
S100A12	S100 calcium-binding protein A12
SAE	serious adverse event
SAS	Statistical Analysis Software
SBP	systolic blood pressure
SE	standard error
SGRQ	St. George's Respiratory Questionnaire
[redacted] MA	[redacted] Medical Affairs
SLB	surgical lung biopsy
SP	safety pharmacology
SP-A	surfactant protein A
SP-D	surfactant protein D
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factor β
TLC	total lung capacity
t_{max}	time to maximum plasma concentration
$t_{1/2}$	terminal half life
ULN	upper limit of normal
US	United States
VCAM-1	vascular cell adhesion molecule type 1
V_{ss}	volume of distribution
WBC	white blood cell

Definition of Terms

QTc	corrected QT interval
QTcF	QT interval corrected for heart rate according to Fridericia's formula: $QTcF = QT \times (1000/RR)^{1/3}$

STUDY SPECIFIC PROCEDURES

1. STUDY FLOW CHART

EVENT			DOSING PERIOD						EDV	FU
Visit	**Visit 1 Screening**	**Visit 2 Baseline**		**Visit 3 [1] W1**	**Visit 4 [1] W2**	**Visit 5 [1] W4**	**Visit 6 [1] W8**	**Visit 7 [1] W12**		**Visit 8/ EOS W14**
Study days (D)	**D-28 to D-4**	**D-1**	**D1**	**D7 ±2 days**	**D14 ±2 days**	**D28 ±3 days**	**D56 ±3 days**	**D84 ±3 days**		**D98 ±3 days**
Informed consent	X									
Historical HRCT sent to central review [2]	X									
SLB sent to central review [2, 3]	X									
Demographics	X									
Medical history/Concurrent illnesses	X									
Inclusion/exclusion criteria	X									
Serology	X									
FSH test [4]	X									
DLCO	X									
Confirm all eligibility criteria		X								
Randomization		X								

[1] Subjects will be asked to come to the study center in the morning at approximately the same time on every visit.
[2] The HRCT and SLB need to be sent to central review at least 8 days prior to the baseline visit to allow for central reading and confirmation of diagnosis.
[3] If available
[4] Only at screening in case there is doubt on whether a female subject is postmenopausal.

EVENT			DOSING PERIOD						EDV	FU
Visit	**Visit 1 Screening**	**Visit 2 Baseline**		**Visit 3 [1] W1**	**Visit 4 [1] W2**	**Visit 5 [1] W4**	**Visit 6 [1] W8**	**Visit 7 [1] W12**		**Visit 8/ EOS W14**
Study days (D)	**D-28 to D-4**	**D-1**	**D1**	**D7 ±2 days**	**D14 ±2 days**	**D28 ±3 days**	**D56 ±3 days**	**D84 ±3 days**		**D98 ±3 days**
Dispense study drug		X		X	X	X	X			
Collect study drug				X	X	X	X	X	X	
Study drug intake [5]			*On a daily basis*							
Check study drug accountability and compliance				X	X	X	X	X	X	
Diary card dispensing		X		X	X	X	X			
Diary card collection				X	X	X	X	X	X	
Clinical laboratory tests [6]	X	X		X	X	X	X	X	X	X
Vital signs [7]	X	X		X	X	X	X	X	X	X
Physical examination [8]	X	X		X	X	X	X	X	X	X
12-Lead ECG [9]	X			X	X	X	X	X	X	X
PK blood samples[10]		X		X	X	X	X	X	X	X

[5] Subjects will begin to take treatment the morning following randomization (*i.e.*, on Day 1). Study drug intake at Visits 3, 4, 5, 6, and 7 will take place at the study center after all predose assessments have been performed.
[6] Clinical laboratory tests include hematology, serum/plasma chemistry, coagulation, and urinalysis.
[7] Vital signs include blood pressure, respiratory rate, heart rate, and oral temperature.
[8] Height and weight will be measured at screening only.
[9] A 12-lead ECG will be performed after the subject has been in supine position for at least 5 minutes.
[10] All PK samples will be taken predose. At Day 28, in addition to predose, samples will be taken 1.5 h, 4 h, and 6 h post dose

EVENT			DOSING PERIOD						EDV	FU
Visit	**Visit 1 Screening**	**Visit 2 Baseline**		**Visit 3 [1] W1**	**Visit 4 [1] W2**	**Visit 5 [1] W4**	**Visit 6 [1] W8**	**Visit 7 [1] W12**		**Visit 8/ EOS W14**
Study days (D)	**D-28 to D-4**	**D-1**	**D1**	**D7 ±2 days**	**D14 ±2 days**	**D28 ±3 days**	**D56 ±3 days**	**D84 ±3 days**		**D98 ±3 days**
PD blood samples [11] (LPA)		X				X		X	X	X
Biomarker blood samples [12]		X				X		X	X	X
BALF sample (bronchoscopy)		X						X	X [13]	
Spirometry [14]	X	X		X	X	X	X	X	X	X
Home-based spirometry		X	*On a daily basis*							
SGRQ		X				X		X	X	X
HRCT [15]		X						X	X	
(S)AE assessment	*Throughout the study*									
Concomitant medications	*Throughout the study*									

AE=adverse event; BALF=bronchoalveolar lavage fluid; D=day; DLCO= diffusing capacity for the lungs for carbon monoxide; ECG=electrocardiogram; EDV=early discontinuation visit; EOS=end of study; FU=follow-up; FRI=functional respiratory imaging; FSH=follicle stimulating hormone; HRCT=high-resolution computed tomography; LPA=lysophosphatidic acid; PD=pharmacodynamics; PK=pharmacokinetic; SAE=serious adverse event; SGRQ=St George's Respiratory Questionnaire; SLB=surgical lung biopsy; W=week

[11] All PD samples will be taken predose. At Day 28, in addition to predose, samples will be taken 1.5 h and 6 h post dose
[12] All blood samples will be collected predose.
[13] If feasible for the subject
[14] All spirometry evaluations should be performed prior to administration of bronchodilator.
[15] To measure FRI parameters. During the baseline visit an additional scan of the upper airway will be taken.

2. INTRODUCTION

2.1. IDIOPATHIC PULMONARY FIBROSIS

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, severely debilitating, and ultimately lethal lung disease predominantly affecting elderly male smokers or ex-smokers with a median age of 65-70 years (Cordier & Cottin, 2013). The disease is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis (*i.e.*, median survival of 2-5 years following diagnosis) (Kim, Collard, & King, 2006; Collard, et al., 2007; Meltzer & Noble PW, 2008; Ley, Collard, & King, 2011; Raghu, et al., 2011).

The estimated IPF prevalence ranges from 14.0 to 27.9 cases per 100,000 population in the United States (US) and from 1.3 to 23.4 cases per 100,000 population in Europe (data from 1990-2011). The estimated IPF incidence in these studies ranges from 6.8-8.8 cases per 100,000 population in the US and from 0.2-7.4 cases per 100,000 population in Europe (Thomeer, Costabe, Rizzato, Poletti, & Demedts, 2001; Raghu, Weycker, Edelsberg, Bradford, & Oster, 2006; Fernández, et al., 2010; Navaratnam, et al., 2011)

Over the past decade, extensive research has been conducted to address the unmet medical need for effective IPF treatment. Two treatments (pirfenidone and nintedanib) targeting the biologic processes that drive fibrosis are currently approved in the European Union (EU) and US. Pirfenidone (antifibrotic, antiinflamatory, and antioxidant treatment marketed as Esbriet®; indicated in adults for the treatment of mild to moderate IPF), was the first drug to be licensed specifically for IPF. Phase III studies had varying results but overall, it was demonstrated that the drug improved progression-free survival and slowed the decline in forced vital capacity (FVC). Moreover, pirfenidone may have a mortality benefit (Spagnolo, et al., 2010; Taniguchi, et al., 2010; Noble, et al., 2011; King, et al., 2014). The drug was approved in the EU in 2011 and in the US in 2014. Nintedanib (tyrosine kinase inhibitor marketed as Ofev®; indicated in adults for the treatment of IPF), was initially developed as an anticancer agent. In phase III studies, it significantly reduced the decline in FVC compared with placebo. A trend towards a reduced death rate was also observed; however, the studies were not powered to detect differences in mortality (Richeldi, et al., 2014). The drug was approved in the US in 2014 and in the EU in 2015. Both treatments appear to slow disease progression but are frequently associated with side effects potentially limiting the use in clinical practice (Esbriet. Summary of Product Characteristics.; Ofev. Summary of Product Characteristics.; Raghu, et al., 2015).

There thus remains a significant unmet medical need for the investigation and development of novel IPF treatments targeting disease-relevant pathways and several other candidate treatments with different mechanism of action are currently in phase II and III or in earlier phases of clinical development.

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

2.2. BACKGROUND AUTOTAXIN

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

ATX, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2) or lysophospholipase D, is a ~120 kDa protein that belongs to the ENPP family of enzymes. ATX is the only ENPP enzyme with lysophospholipase D 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 2 unsaturated bonds (Bandoh, Aoki, Taira, Tsujimoto, Arai, & Inoue, 2000). Literature data have identified the ATX/LPC axis as the main source of LPA in blood (Tsuda, et al., 2006; Tanaka, et al., 2006). In serum from heterozygous mice, for example, both ATX activity and LPA level were about half of those from wild-type mice, showing that ATX is responsible for the bulk of LPA production in serum.

Several publications suggest a role for ATX in the control of disease-affected lung function through effects on lung epithelial cells, fibroblasts, and smooth muscle cells (Magkrioti & Aidinis, 2013). In general, inflammatory conditions in the lung are often described as associated with increased ATX and LPA levels. Studies related to IPF indicated an increase in LPA levels in the BALF of patients (Tager, et al., 2008), an increase of ATX levels in human fibrotic lung (Oikonomou, et al., 2012) and an elevation of LPA 22:4 in exhaled breath condensate of patients (Montesi, et al., 2014). Further, LPA1 knock-out and inhibitor studies revealed a key role for LPA in fibrotic processes in lung and were complemented by studies using cell-specific knock-out mice lacking ATX in bronchial epithelial cells and macrophages. These mice were shown to be less sensitive to models of lung fibrosis (Oikonomou, et al., 2012). The role of LPA in lung remodeling relates to the effects of LPA on both lung fibroblasts (through LPA1) and epithelial cells (through LPA2). It has been demonstrated that LPA2 plays a key role in the activation of transforming growth factor β (TGFβ) in epithelial cells under fibrotic conditions (Xu, et al., 2009).

Available literature and preclinical pharmacology data generated by Galapagos, suggest that interventions targeting the ATX/LPA pathway could lead to a new class of therapy for IPF.

More information on the study drug is provided in the Investigator's Brochure and summarized in the sections below. (Investigator Brochure GLPG1690, Edition 2, October 2015)

2.3. BACKGROUND GLPG1690 – NON-CLINICAL DATA

2.3.1. Physical, Chemical, Pharmaceutical Properties, and Formulations

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-α]pyridin-3-yl)-(methyl)amino)-4-(4-fluorophenyl)-thiazole-5-carbonitrile.

The clinical formulation used in this study is an oral capsule containing GLPG1690 as the free base.

2.3.2. Pharmacology

2.3.2.1. Primary and Secondary Pharmacology

GLPG1690 is an ATX inhibitor (inhibitory concentration 50% [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 4 (PDE4) and PDE5 (enzymes with phosphodiesterase activity), and phospholipase A (PLA) or phospholipase C (PLC) (enzymes with phospholipase A or C activity, respectively). Moreover, GLPG1690 showed no inhibition in a panel of kinases. In a Cerep diversity panel (98 targets including receptors and ion channels), only 3 targets displayed more than 50% inhibition at 10 μM. LPA is the biomarker of choice for the ATX inhibitor program as it is quantifiable in plasma and other biological fluids by liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS).

GLPG1690 dose-dependently inhibited the production of connective tissue growth factor (CTGF) upon TGFβ-triggering in normal human dermal fibroblasts.

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 in a prophylactic bleomycin (BLM) 21-days mouse model of lung fibrosis, measured as the reduction in lung weight and Ashcroft score, was similar to that of the pirfenidone comparator. Significant prevention of collagen deposit in the lung was observed in the GLPG1690 group only. After GLPG1690 treatment, the increase of LPA levels in bronchoalveolar lavage fluid (BALF) after BLM exposure was reduced for several LPA species. In addition, the efficacy of GLPG1690 in the tobacco smoke challenge model in mice, measured as the capacity to reduce inflammatory cell recruitment to the lungs, was indicative of the anti-inflammatory capacity of GLPG1690. This is seen as relevant, as inflammation is one important component in the pathophysiology of IPF.

2.3.2.2. Safety Pharmacology

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

2.3.3. Nonclinical Pharmacokinetics and Product Metabolism

The absolute oral bioavailability was moderate in rodents (25-36%), 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 (V_{ss}) ranging from 0.35 L/kg in the mouse to 0.55 L/kg in the monkey.

Upon repeated once daily (*q.d.*) oral dosing of GLPG1690, no significant accumulation was observed in the rat and some accumulation (up to approximately 9-fold) was observed in the dog at the highest tested dose of 100 mg/kg/day. Gender differences in PK profiles were observed in rats but not in dogs.

The total plasma clearance (Cl) 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 only 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. In human, 8 metabolites resulting from hydrolysis, hydroxylation, addition of water, demethylation, or reduction were detected in plasma and/or urine. These metabolites were also observed in rat and dog plasma.

In vitro interaction studies of GLPG1690 with CYPs showed some degree of inhibition, with IC_{50} values $\geq$ 13-fold the free steady state maximum plasma concentration (C_{max}) expected in human after a 600 mg dose, as well as some induction at concentrations $\geq$ 60-fold the expected free steady state C_{max}. Towards key drug transporters, some inhibition by GLPG1690 was observed, with IC_{50} values $\geq$ 7-fold the free steady state C_{max} expected in human after a 600 mg dose. Therefore, it can be concluded that drug-drug interactions with GLPG1690 are unlikely.

2.3.4. Toxicology

2.3.4.1. General Toxicology

The dose-limiting effects in the repeated dose toxicity studies with GLPG1690 in the rat consisted of reduced food consumption (FC) and markedly decreased body weight (BW) gain at 1000 mg/kg/day for 4 weeks. In dogs, the dose-limiting effects corresponded to decreased white blood cells (WBCs) and FC, emesis and BW loss, associated with poor clinical conditions as reported at the dose of 150 mg/kg/day in the 13-week study.

In the 13-week study in rats, the no observed adverse effects level (NOAEL) was at the dose of 40 mg/kg/day in males and 400 mg/kg/day in females, corresponding to area under the concentration-time curve from time 0 to 24 hours (AUC_{0-24h}) values of 68.3 µg.h/mL and 1680 µg.h/mL, respectively (which is approximately 0.9- and 22-fold higher, respectively, than the anticipated free plasma AUC_{0-24h} [0.532 µg.h/mL] in human after a 600 mg dose). In the 13-week study in dogs, the NOAEL was considered to be the dose of 50 mg/kg/day, corresponding to a mean AUC_{0-24h} of 1010 µg.h/mL (which is approximately 21-fold higher than the anticipated free plasma AUC_{0-24h} [0.532 µg.h/mL] in human after a 600 mg dose). The clinical signs, the changes in hematological and clinical biochemistry, and the pathological findings observed at the NOAEL in the rat and dog were considered non-adverse because they were mild in intensity, had no functional or morphological adverse correlate, and were fully reversible after a 4-week treatment-free recovery period.

Reproductive embryo-fetal development studies were performed in rats and rabbits with GLPG1690. In rats, the maternal and developmental NOAELs for GLPG1690 were determined at 60 mg/kg/day and 10 mg/kg/day, respectively. These NOAELs correspond to a mean AUC_{0-24h} of 324 and 21.4 µg.h/mL on Day 17 post-coitum, respectively, which is

approximately 4- and 0.3-fold higher than the anticipated free plasma $AUC_{0\text{-}24h}$ (0.532 µg.h/mL) in human after a 600 mg dose. In rabbits, the maternal and developmental NOAELs were concluded to be 15 mg/kg/day and 5 mg/kg/day, respectively. These NOAELS correspond to a mean $AUC_{0\text{-}24h}$ of 50.8 µg.h/mL and 8.10 µg.h/mL on Day 16 post-coitum, respectively (which is approximately 0.4- and 0.06-fold higher than the anticipated free plasma in human after a 600 mg dose).

GLPG1690 did not show genotoxic effects *in vitro* or *in vivo*. No phototoxic effects with GLPG1690 have been observed *in vivo* in rats.

2.4. BACKGROUND GLPG1690– CLINICAL DATA

To date, GLPG1690 (or placebo) has been administered in fed state to 40 healthy male subjects in a Phase I first-in-human (FIH) study (Study GLPG1690-CL-101). GLPG1690 (or placebo) was administered as a single oral suspension at a dose ranging from 20 mg to 1500 mg or a 300 mg capsule (Part 1 of the study). GLPG1690 (or placebo) was administered as a twice daily (*b.i.d.*) dose of 150 mg or a *q.d.* dose of 600 mg or 1000 mg for 14 days (Part 2 of the study).

Administration of single (up to 1500 mg) and multiple ascending oral doses of GLPG1690 (up to 1000 mg *q.d.*) for 14 days in healthy male subjects can be considered safe and well tolerated. No deaths, other serious adverse events (SAEs), or treatment-emergent adverse events (TEAEs) leading to study drug discontinuation have been reported. All TEAEs were at most moderate in severity. No clinically relevant abnormalities related to laboratory parameters, electrocardiogram (ECG), vital signs, or physical examinations were reported.

Single (up to 1500 mg) and multiple ascending oral doses of GLPG1690 (up to 1000 mg *q.d.*) for 14 days were assessed in healthy male subjects under fed conditions. GLPG1690 was rapidly absorbed with a median time to maximum plasma concentration (t_{max}) of 0.5-2 h. The terminal half-life ($t_{1/2}$) after *q.d.* oral dosing for 14 days was 5.8 h. Steady-state exposure of GLPG1690 increased 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 h) and rapid. There was no impact on the urinary 6β-OH-cortisol/cortisol ratio after repeated dosing suggesting a lack of CYP3A4 induction by GLPG1690.

After a single administration of GLPG1690, a significant dose-dependent percentage reduction of LPA 18:2 was observed in plasma. This effect started from 0.5 h post dose, reached a plateau, and was sustained over time up to 24 h post dose. Multiple *q.d.* or *b.i.d.* ascending doses resulted in a similar effect on LPA 18:2. A strong reduction in LPA 18:2 levels was already observed at predose Day 14, pointing to a sustained effect over 14 days.

The effect on LPA 18:2 was also confirmed by area under the effect-time curve (AUEC) for the % reduction from baseline and maximum % reduction from baseline (E_{max}).

2.5. CLINICAL RISKS/BENEFITS

IPF is a chronic and progressive lethal lung disease for which two treatments (pirfenidone and nintedanib) are currently approved in the EU and US. These treatments appear to slow disease progression but are frequently associated with side effects potentially limiting the use in clinical practice. There thus remains a significant unmet medical need for the investigation and development of novel IPF treatments targeting disease-relevant pathways.

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

As with any new compound in early development, no benefit can be expected for the individual subjects and safety is paramount. The subjects therefore need to be closely monitored by repeated assessment of clinical and vital signs, ECG, and laboratory safety parameters.

GLPG1690 has been evaluated in a phase I FIH study whereby the administration of single (up to 1500 mg) and multiple ascending oral doses of GLPG1690 (up to 1000 mg *q.d.* for 14 days) in healthy male subjects was considered safe and well tolerated. All TEAEs, the most common ones being headache and diarrhea were at most moderate in severity and transient in nature. No clinically relevant abnormalities related to laboratory parameters, ECG, vital signs, or physical examination were reported.

As there is limited clinical experience with GLPG1690 so far, the study drug should not be administered to subjects with moderate to severe renal impairment, hepatic impairment (Child-Pugh B or Child-Pugh C), or pediatric subjects. The study drug may be administered to elderly subjects. Based on available pre-clinical data, the impact of aging on the elimination of GLPG1690 should not be significant. The hepatic clearance is predicted to be low suggesting GLPG1690 undergoes low metabolism in humans. In terms of renal elimination, < 2% of GLPG1690 is excreted unchanged in urine. Consequently, the fecal route is likely the main route of elimination with secretion of GLPG1690 and potential metabolites via the bile into the feces.

The risk of treatment with GLPG1690 in adult subjects is primarily related to fertility, pregnancy, and lactation. GLPG1690 induced reversible changes in sperm parameters as well as reversible microscopic findings in the seminiferous tubules in the 13-week oral toxicity studies in rats and dogs. Even though no animal fertility studies have been performed so far, a decreased male fertility cannot be excluded in patients while on treatment with GLPG1690. Moreover, GLPG1690 showed teratogenic effects in both rats and rabbits, with induction of major 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 no data are available on excretion in milk. In view of the limited knowledge of the possible effects of GLPG1690 on pregnancy and lactation at this stage of development, GLPG1690 should not be given to pregnant or lactating women. In addition, highly effective contraceptive measures should be taken in women of childbearing potential and in men who have expressed the will to father a child to prevent pregnancy and to avoid the risk of exposure of the embryo or fetus.

To enhance the safety and integrity of the study data, an independent medical safety review will be implemented. (See Section 7 for additional information).

Please refer to the Investigator's Brochure for additional information. (Investigator Brochure GLPG1690, Edition 2, October 2015)

2.6. RATIONALE FOR THE STUDY

Recent literature has suggested a role for ATX, an enzyme with lysophospholipase D activity responsible for the production of LPA, in disease-affected lung function. Interventions targeting the ATX/LPA pathway could lead to a new class of therapy for IPF.

GLPG1690 is the first ATX inhibitor in clinical development for the oral treatment of IPF. Preclinical studies suggested a high level of target engagement (21-day BLM mouse models): after GLPG1690 treatment, the increase of LPA levels in BALF after BLM exposure was reduced for several LPA species. Moreover, GLPG1690 provided similar or better results than pirfenidone - in the same model - in terms of the reduction in lung weight and Ashcroft score and prevention of collagen deposit in the lung. In addition, GLPG1690 dose-dependently inhibited the production of CTGF upon TGFβ-triggering in normal human dermal fibroblasts.

Results from a FIH study generated promising PD results (LPA reduction) and indicated the study drug was generally safe and well tolerated in a population of healthy subjects.

As a next step in the clinical development of GLPG1690, its safety, tolerability, PK, and PD properties will be evaluated in this Phase IIa study in subjects with IPF.

Rationale for the Study Design

This is a randomized, double-blind, parallel group, placebo-controlled, multicenter, exploratory Phase IIa study including subjects with IPF. The randomized double-blind study design was chosen as it is the most rigorous method to generate high quality scientific data. In addition, a placebo-controlled study contains internal evidence of assay sensitivity (*i.e.*, when a difference is demonstrated, it is interpretable without reference to external findings), measures absolute safety and efficacy (*i.e.*, it measures the total pharmacologically mediated effect of treatment), is very efficient (*i.e.*, can measure treatment effects with a smaller sample size compared with any other type of controlled study), and minimizes the effect of subject and investigator expectations (ICH E10, 2000).

The subject eligibility criteria are typical for patient studies in IPF. Since the disease typically affects elderly subjects, it was chosen to include subjects aged ≥ 40 years. Subjects could neither use the 2 drugs approved for the treatment of IPF (*i.e.*, pirfenidone and nintedanib) nor warfarin, imatinib, ambrisentan, azathioprine, cyclophosphamide, cyclosporine A, prednisone at steady dose > 15 mg/day, and any other experimental IPF therapy within 4 weeks prior to screening and during the study in order to avoid any confounding effects these drugs may have on the safety, tolerability, PK, PD, or exploratory endpoints evaluated in the current study.

The treatment duration of 12 weeks was chosen as currently, the preclinical safety of the drug has been evaluated up to a maximum of 13 weeks treatment duration.

Rationale for the Outcome Measures

Safety and tolerability will be assessed by the evaluation of adverse events (AEs), selected clinical laboratory parameters, vital signs, physical examinations, and ECG, all of which are standard safety evaluations in clinical development.

The PK assessments are included since the PK profile in IPF patients may differ from that of healthy subjects included in the FIH study. Information obtained on the PK of GLPG1690 will guide dose selection in future clinical studies.

The PD properties of GLPG1690 will be assessed through the analysis of plasma LPA, a PD biomarker of ATX inhibition. The effect of GLPG1690 on LPA in plasma has been confirmed

in the FIH study, where GLPG1690 reduced LPA levels in a dose-dependent way. The current PD analysis will confirm the effect in a population of IPF patients.

In addition, effects of GLPG1690 on different LPA species will be assessed pre- and post-treatment in the BALF, representative for target engagement in a matrix closer to the lung. Such data were already generated in the mouse BLM model: several LPA species increased in the BALF after BLM inhalation and were reduced again after GLPG1690 treatment. These data correlated with a positive effect of GLPG1690 on a series of fibrotic readouts (lung weight, Ashcroft score, collagen deposit in lung).

Pulmonary function will be assessed using standard spirometry; FVC is currently the most commonly used and accepted endpoint in clinical studies investigating IPF treatments (Saketkoo, et al., 2014). Spirometry, or more specifically FVC reflects the burden of the IPF progress, and is relatively easy to measure and reproducible (Nathan & Meyer, 2014). However, since conventional pulmonary function tests such as spirometry have their limitations (*e.g.*, they cannot detect early signs of disease due to the compensatory behavior of healthy lung areas; in IPF, many spirometry endpoints remain normal even though the disease progresses) and since a study duration of 12 weeks may be considered too short to detect any differences in FVC, pulmonary function will also be assessed through high-resolution computed tomography (HRCT) scans used for generating functional respiratory imaging (FRI). FRI provides regional information about lung structure and allows for earlier demonstration of disease progression and/or therapeutic effects (De Backer, et al., 2015; Vos, et al., 2015). Furthermore, central reading of these images should reduce assessment bias.

In addition, change in the levels of a selection of biomarkers in blood and BALF (through bronchoscopy) will be assessed. Even though there currently are no validated biomarkers that track IPF progression or response to IPF treatment, a number of protein biomarkers have been shown to be increased in IPF (*e.g.,* ATX, Krebs von den Lungen 6/mucin type 1 [KL-6/Muc1], surfactant protein A (SP-A), chemokine motif ligand 18 [CCL18], surfactant protein D (SP-D), matrix metalloproteinase (MMP) 1, MMP7, intercelullar adhesion molecule type 1 (ICAM1), vascular cell adhesion molecule type 1 (VCAM1), interleukin 8 (IL8), and S100 calcium-binding protein A12 (S100A12) (Greene, et al., 2002; Rosas, et al., 2008; Hara, et al., 2012; Kaminski, et al., 2012; Oikonomou, et al., 2012; Richards, et al., 2012; Jenkins & Goodwin, 2014; Nathan & Meyer, 2014) (Jenkins, et al., 2015). Change in a selection of biomarkers of disease activity will be evaluated in the current study. Results will help to refine our current understanding of the effect of GLPG1690 on IPF pathophysiology and will guide endpoint selection in future clinical studies.

Finally, since IPF is a chronic, severely debilitating, and ultimately lethal disease, any treatment should aim to improve subject's quality of life; therefore, patient-reported outcomes are important parameters in any study in IPF. The St. George's Respiratory Questionnaire (SGRQ), a quality of life measurement tool, was selected for the current study (Nathan & Meyer, 2014; Swirgis, Esser, Conoscenti, & Brown, 2014).

Information on the rationale for dose selection is provided in Section 2.7.

2.7. RATIONALE FOR THE CHOICE OF DOSE AND DOSING INTERVAL

A dose of 600 mg GLPG1690 administered *q.d.* has been selected to be evaluated for this phase IIa study.

Both preclinical and clinical study results were used to predict an efficacious dose. In the 21-day prophylactic BLM mouse model, GLPG1690's efficacy was reached (in terms of reduction of Ashcroft score) with AUC of 11 µg.h/mL, corresponding to 26 µg.h/mL in humans after correction for plasma protein binding. Moreover, a GLPG1690 plasma concentration of 1 µg/mL in healthy subjects allowed triggering maximum LPA 18:2 (PD) biomarker reduction (90%) which could be maintain over 24 hours with an AUC of 24 µg.h/mL. Both study results predict GLPG1690's efficacious dose to be around 220 mg.

A dose of 600 mg GLPG1690 *q.d.* is expected to be high enough to reach a plateau in the PD response in a population of subjects with IPF. In addition, 600 mg GLPG1690 is lower than the highest dose assessed in the FIH study in healthy subjects. In this study, administration of single (up to 1500 mg) and multiple ascending oral doses of GLPG1690 (up to 1000 mg *q.d.* for 14 days) in healthy male subjects was considered safe and well tolerated.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVES

- to evaluate the safety and tolerability of GLPG1690
- to characterize the PK and PD properties of GLPG1690

3.2. SECONDARY OBJECTIVES

- to evaluate the change from baseline in FVC
- to explore the change in biomarkers in blood and BALF
- to evaluate the change in FRI parameters
- to evaluate the change in quality of life measures

4. INVESTIGATIONAL PLAN

4.1. OVERALL STUDY DESIGN

This study is a randomized, double-blind, parallel group, placebo-controlled, multicenter, exploratory phase IIa study to evaluate the safety, tolerability, PK, and PD of GLPG1690 in subjects with IPF. In addition, several exploratory assessments will be performed. Male and female subjects of non-child-bearing potential with a confirmed diagnosis of IPF aged 40 years or older will be screened to determine eligibility as per the inclusion and exclusion criteria (see Section 4.2.2 and 4.2.3, respectively). The screening period will be up to 4 weeks.

Written informed consent must be obtained before any study-related procedures take place. During the screening period, following signing of the informed consent form (ICF), the subject's historical HRCT and surgical lung biopsy (SLB; if available) will be sent to central review for the confirmation of the IPF diagnosis through a:

- central review of the chest HRCT
- central review of the SLB (if available)

Note that both the chest HRCT and SLB need to be sent to central review at least 8 days prior to the baseline visit to allow for central reading and confirmation of IPF diagnosis. Additional details are provided in Appendix 2.

At baseline, after the subject's eligibility for the study has been confirmed, subjects will be randomized in a 3:1 ratio to GLPG1690 600 mg *q.d.* or matching placebo administered for 12 weeks.

The subjects will visit the clinical study center at screening (Day-28 to Day -4), Day -1 (baseline), Week 1 (Day 7), Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56), and Week 12 (Day 84) or the early discontinuation visit (EDV). In addition, a follow-up visit will be planned 2 weeks after the last administration of study drug (Week 98 [Day 98]). Each subject will be in the study for up to approximately 18 weeks (from screening to follow-up). The end of the study (EOS) will be defined as the last contact with the last subject in the study.

The assessments performed at each visit are detailed in the study flow chart (Section 1).

To enhance the safety and integrity of the study data, an independent medical safety review will be implemented. (See Section 7 for additional information).

4.2. STUDY POPULATION

4.2.1. Sample Size

Approximately 24 evaluable subjects with a centrally confirmed IPF diagnosis are planned to be randomized.

4.2.2. Inclusion Criteria

Subjects who meet all of the following criteria are eligible for the study:

1. Subjects who are able and willing to sign the ICF as approved by the independent ethics committee (IEC).
2. Male or female subjects of non-child-bearing potential aged ≥ 40 years on the day of signing the ICF.

   Note: Female subjects will be considered of non-childbearing potential if they are either sterilized, ovariectomized, hysterectomized, or postmenopausal (*i.e.*, at least 24 months of amenorrhea in the absence of other biological or physiological causes [in case of doubt, the subject's follicle stimulating hormone [FSH] levels will be determined and the subject will be considered postmenopausal if the FSH level is ≥ 35 mIU/mL).
3. Subjects with a chest HRCT performed within 12 months prior to screening visit.
4. Subjects with IPF diagnosed by a multidisciplinary team and confirmed by central review of the subject's HRCT pattern and SLB (if available) (see Appendix 2 for additional details).
5. Subjects meeting all of the following criteria:
   a. FVC ≥50% predicted of normal
   b. Diffusing capacity for the lungs for carbon monoxide (DLCO) ≥ 30% predicted of normal (corrected for hemoglobin) (see Appendix 3 for additional details).
6. Subjects with a forced expiratory volume in 1 second (FEV_1)/FVC (Tiffeneau-Pinelli index) ratio ≥ 0.70 (based on pre-bronchodilator spirometry).
7. Subjects who are on stable supportive care (*e.g.,* supplemental oxygen, pulmonary rehabilitation) for at least 3 weeks prior to screening and during screening period.
8. Subjects must be in a stable condition and acceptable for study participation based upon the results of a medical history, physical examination, vital signs, 12-lead ECG, and laboratory evaluation.
9. Subjects must have an estimated minimum life expectancy of 12 months in the opinion of the investigator.
10. Male subjects and their female partners must use a highly effective method of birth control. Additional details on these methods are provided in Section 4.2.4.
11. Subjects who are able to understand the importance of adherence to study treatment, study procedures and requirements, including the concomitant medication restrictions.

4.2.3. Exclusion Criteria

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

1. Subjects with a known hypersensitivity to any of the study drug ingredients or a history of a significant allergic reaction to any drug as determined by the investigator (*e.g.,* anaphylaxis requiring hospitalization).
2. Subjects with a history of or a current immunosuppressive condition (*e.g.,* human immunodeficiency virus [HIV] infection).
3. Subjects with a history of malignancy within the past 5 years (except for carcinoma in situ of the uterine cervix, basal cell carcinoma of the skin that has been treated with no evidence of recurrence, and prostate cancer medically managed through active surveillance or watchful waiting).

4. Subjects with clinically significant abnormalities detected on ECG regarding either rhythm or conduction (*e.g.,* QT interval corrected for heart rate using Fridericia's formula [QTcF] ≥450 ms, or a known long QT syndrome).

   Note: A first degree heart block will not be considered as a significant abnormality.
5. Subjects with acute IPF exacerbation within 6 weeks prior to screening and during the screening period.
6. Subject with a lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and during the screening period.
7. Subjects who have been smoking within 3 months prior to screening.
8. Interstitial lung disease (ILD) associated with known primary diseases (*e.g.,* sarcoidosis, amyloidosis, etc.), exposures (*e.g.*, radiation, silica, asbestos, coal dust, etc.), and drugs (*e.g.,* amiodarone, etc.).
9. Subjects with a history of lung volume reduction surgery or lung transplant.
10. Subjects with an unstable cardiac or pulmonary disease (other than IPF) within 6 months prior to screening or during the screening period, including but not limited to:
    a. unstable angina pectoris, myocardial infarction
    b. congestive heart failure requiring hospitalization
11. Subjects with any clinical condition or circumstance that in the opinion of the investigator may make a subject unsuitable for inclusion or unable to complete the study or comply with study procedures and requirements.
12. Subjects with a contra-indication for bronchoscopy and bronchoalveolar lavage in the opinion of the investigator.
13. Subjects with an abnormal liver function defined as aspartate aminotransferase (AST), alanine aminotransferase (ALT), or bilirubin >3 x upper limit of the normal range (ULN).
14. Subjects with an abnormal renal function defined as creatinine clearance < 50 mL/min using the Cockroft-Gault equation.
15. Subjects participating in a drug/device or biologic investigational research study (concurrently with the current study or within 8 weeks prior to screening).
16. Subjects using of any of the following therapies within 4 weeks before screening:
    a. Pirfenidone
    b. Nintedanib
    c. Warfarin
    d. Imatinib
    e. Ambrisentan
    f. Azathioprine
    g. Cyclophosphamide
    h. Cyclosporine A
    i. Prednisone at steady dose > 15 mg/day (for details, see Section 4.2.4)
    j. Any experimental IPF therapy
17. Subjects with active alcohol or substance abuse in the opinion of the investigator.

4.2.4. Prohibition and Restrictions

Smoking is forbidden at all times (from 3 months before screening to the end of the study).

The following therapies are not allowed during the course of the study (and within 4 weeks prior to screening): pirfenidone, nintedanib, warfarin, imatinib, ambrisentan, azathioprine, cyclophosphamide, cyclosporine A, prednisone at steady dose > 15 mg/day (*i.e.*, the use of prednisone is precluded unless subjects have been on a stable dose ≤ 15 mg daily and it is anticipated that they will continue on this stable dose for the duration of the study), and any experimental IPF therapy.

Male subjects and their female partners must use 2 generally accepted adequate contraceptive methods, 1 of which is a barrier method (*e.g.,* condom in combination with hormonal contraception stabilized for at least 1 month) from screening until 3 months after the study. In addition, sperm donation is not allowed until 3 months after the last study visit. In a case where the female partner of a male subject has undergone documented surgical sterilization that was performed more than 1 year before screening, the subject is not required to use an additional form of contraception.

4.2.5. Removal of Subjects from Therapy or Assessments

A subject may be discontinued from the 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.

Subjects may withdraw from the study at any time, for any reason, without jeopardizing their clinical care.

Subjects **may be withdrawn from the study** for any of the following reasons:

- noncompliance with the study drug
- noncompliance with the study procedures
- lost to follow-up
- SAEs or severe AEs can be considered a reason for discontinuation of treatment, preferably after consultation with the medical monitor
- investigator request
- sponsor request

A subject **may be withdrawn from the study after discussion between the investigator and the medical monitor** for any of the following reasons:

- use of concurrent therapy that was not permitted
- prolonged interruption of study drug (*i.e.*, interruption > 7 days)
- life-threatening AE or an SAE that places the subject at immediate risk
- increase in liver function tests (LFTs) to 3 x ULN (if the baseline LFTs are normal) or an increase that exceeds an absolute value of 5 x ULN (regardless of whether baseline LFTs are normal)

A subject **must be withdrawn from the study** for any of the following reasons:

- serious infections (those requiring parenteral antimicrobial therapy and/or hospitalization)

- arrhythmia or conduction abnormality (including but not limited to prolonged QTcF, where the severity is categorized as Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or higher)
- clinical laboratory test results, which are determined by the investigator in consultation with the medical monitor to be clinically significant and require discontinuation of study drug; changes in LFTs are defined as follows (confirmed upon repeat testing):
  - elevated ALT or AST of > 8 x ULN
  - elevated ALT or AST of > 5 x ULN for > 2 weeks
  - total bilirubin > 2 x ULN and/or clinical jaundice, in association with elevation of ALT or AST > 3 x ULN
  - no convincing alternative etiology (*e.g.*, viral hepatitis, alcohol ingestion, trauma) for the elevated transaminase is identified, regardless of whether ALT or AST levels had improved
- unblinding of a subject's study treatment assignment to the subject, the site staff, or the blinded sponsor staff while on study drug
- close of the study by the sponsor or regulatory authorities
- wish of the subject to withdraw (At any time and for any reason, a subject's participation in the study may terminate at his/her request without prejudice to his/her future medical care.)
- worsening of the subject's disease condition, which in the investigator's opinion needs an alternative treatment approach

In case clinically significant laboratory test results are a potential reason for discontinuation from the study drug and withdrawal from the study, retesting should be prompted (within 3 to 5 days) after the investigator has consulted with the medical monitor. A decision regarding subject discontinuation should be made only after the results from the retest are available.

Subjects who stop study drug for any reason will not be replaced. Subjects withdrawing from the study will be encouraged to complete the same final evaluations as subjects completing the study according to the protocol, particularly safety evaluations in the subject's interest so that data can be recorded in the same way as for subjects who completed the study. The reason(s) for withdrawal will be documented in the electronic case report form (eCRF). Note that randomized subjects who drop out before the first administration of the study drug will be replaced.

Reasonable efforts (3 attempts) will be made to get confirmation on the reasons for dropout for subjects who are lost to follow-up. These attempts must be documented in the subject's file.

The sponsor has the right to terminate the study at any time in case of safety concerns or if special circumstances concerning the study drug 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 study termination.

4.3. INVESTIGATIONS MEDICINAL PRODUCTS

4.3.1. Identity of the Investigations Medicinal Products

The study drug GLPG1690 will be supplied to the study center, by and under the responsibility of the sponsor, who will also provide the investigator with appropriate certificates of analytical conformity and EU QP release documents.

The study drug GLPG1690 will be presented as oral capsules (size 00), containing 200 mg G451990 (G451990 is the compound code for GLPG1690). The placebo will be provided as a matching capsule.

A full list of excipients used in the oral capsule formulation is available in the Investigator's Brochure. (Investigator Brochure GLPG1690, Edition 2, October 2015) At the investigational site, the study drug supplies must be handled and stored safely and properly, and kept in a secured location to which only the investigator and authorized staff have access.

4.3.2. Dosage and Administration

A dose of 600 mg *q.d.* or placebo *q.d.*, administered in the morning, will be evaluated. Subjects will receive 600 mg GLPG1690 (3 capsules of 200 mg) or placebo *q.d.* for 12 weeks.

Study drug dosing will take place at the time points indicated in the study flow chart (Section 1). When dosing takes place at the clinical study center, a volume of 240 mL water will be provided to each subject to be consumed immediately and completely at the time of dosing. Subjects will be instructed to swallow the study drug whole, and not chew the drug 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. If the study drug is not taken within 12 hours after the planned time, the missed dose should be skipped.

Dose changes during the study are not allowed. Instead, the subject should either temporarily stop all intake or permanently stop study drug. Every effort should be made to contact the medical monitor before stopping study drug (temporarily or permanently).

4.3.3. Randomization

A total of approximately 24 subjects will be randomized in a 3:1 allocation ratio to active treatment with GLPG1690 or placebo.

Allocation of each subject to a given treatment will be described in a randomization list prepared by the CRO. This randomization list will be created using permuted blocks. Upon qualification for the study, subjects will be randomized using a computerized interactive voice/web response system ([redacted]) to placebo or GLPG1690.

For each subject at each visit, the study center will contact the [redacted] system for the appropriate treatment number to be dispensed. Each medication kit will contain the relevant study drug for the period until the next visit.

Subjects and study personnel will be blinded to the treatment assignment. Additional details on blinding and unblinding are provided in Section 4.3.8.

4.3.4. Packaging, Labeling, and Distribution

The study drug packaging, labeling, QP release, and distribution will be performed by [redacted] (Belgium). Study drug manufacturing will be performed by [redacted] (Belgium).

The oral capsules will be packaged in high density polyethylene bottles with a high density polyethylene closure and grouped in a carton box for shipment.

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

The study drug is to be dispensed according to the protocol. The distribution will only occur after all required documentation is obtained including study approval by the Competent Authorities and the IEC.

Each medication kit will be identified with a unique kit number and will contain sufficient capsules for the subject until the next scheduled study visit. The medication kits will be labeled according to local requirements.

4.3.5. Storage

Sites are to store all drug supplies in a secured location to which only the investigator and authorized staff have access.

Study drug must be stored at room temperature (15-25°C). Sites will be required to monitor the storage temperature by using a min-max temperature-recording device and to keep a temperature log, completed each working day, to establish a record of compliance with storage conditions. The investigator will instruct subjects on how to store the study drug after it has been dispensed.

In accordance with the International Conference on Harmonization (ICH) Good Clinical Practice (GCP), the investigator will be responsible for the monitoring, receipt, storage, dispensing, and accounting of all study drug supplies according to accepted medical and pharmaceutical practice. All details of study drug supplies receipt, storage, administration and return will be recorded and the records must be retained in the investigator's site file. Accurate site records of drug inventory and dispensing must be maintained. All records must be made available to Galapagos, the contract research organization (CRO), and appropriate regulatory agencies upon request. At the end of the study, this record will be checked against all used and unused medication by the monitor.

4.3.6. Treatment Compliance and Drug Accountability

For each dose taken, the date, time and number of capsules taken should be recorded on the subject's diary card (see Section 5.3 for additional information).

The investigator or designated study personnel will maintain a log of all study drug dispensed and returned. Drug supplies for each subject will be inventoried and accounted for throughout the study. All clinical supplies will be stored in locked facilities.

Subjects will return any unused study drug and empty bottles at each study visit and/or early discontinuation visit (if applicable). Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure proper subject dosing.

All unused medication and empty bottles will be returned to the drug supplier/CRO depot as applicable at the closure of the study site or will be destroyed at the site, upon sponsor decision.

4.3.7. Prior and Concomitant Therapy

Should any treatment other than the study drug be used during the course of the study, the name of the drug, the dosage, the route, and the dates (and time) of administration must be recorded in the eCRF system. Prior and concomitant medications (taken up to 8 weeks prior to Day 1) will be recorded from the study inclusion date (ICF signed) until the last visit.

Concomitant therapies taken for the long-term treatment of preexisting conditions can continue during the study provided they are in accordance with the inclusion and exclusion criteria (see Section 4.2.2 and Section 4.2.3, respectively). It is required that these medications be stabilized prior to study entry and continued without variation of dose or regimen during the study.

In a case additional concomitant medication needs to be administered or dose adjustments for preexisting conditions need to be performed during the study, the risk/benefit to the subject should be carefully assessed and consideration given to the timing of any necessary introduction of new medications. It is recommended that the medical monitor is contacted to check if the subject could be included in the study or if some of the concomitant drugs should be stopped and/or replaced.

If the subject shows a worsening of his/her IPF disease condition (acute IPF exacerbation), all treatment options are allowed at the investigator's discretion. The decision to continue treatment with study drug should be taken on a case-by-case basis, preferably after discussion with the study's medical monitor.

Drug-drug Interactions

The only CYP enzyme involved in GLPG1690 metabolism is CYP3A4. Therefore, caution should be exercised when coadministering GLPG1690 with drugs/nutraceutics known as CYP3A4 inducer in order to ascertain GLPG1690 exposure. A (non-exhaustive) list of CYP3A4 inducers is provided in Appendix 4.

In vitro interaction studies of GLPG1690 with CYPs showed some degree of inhibition, with IC_{50} values $\geq$ 13-fold the free steady state C_{max} expected in human after a 600 mg dose, as well as some induction at concentrations $\geq$ 60-fold the expected free steady state C_{max}. Towards key drug transporters, some inhibition by GLPG1690 was observed, with IC_{50} values $\geq$ 7-fold the free steady state C_{max} expected in human after a 600 mg dose. Therefore, it can be concluded that drug-drug interactions with GLPG1690 are unlikely. However, in case of coadministration of drugs with narrow therapeutic index, like warfarin, theophylline, or digoxin, precautions and specific monitoring should be considered.

It is recommended that the medical monitor is contacted to check whether the subject could be included in the study or if some of the concomitant drugs/nutraceutics should be stopped and/or replaced prior to dosing with GLPG1690.

4.3.8. Blinding and Unblinding

This is a randomized, double-blind study.

The subject, investigator, study coordinator, sponsor, and the entire study processing team will remain blinded to treatment assignment. The blind can be broken only if the investigator deems it necessary for the safe treatment of a subject, and whenever possible the medical monitor and sponsor should be consulted before breaking the blind.

If the blind is broken for any reason during the course of the study, the moment on which the subject's data were unblinded and all other relevant information will be documented by the investigative site, the CRO, and other sponsor designees, as appropriate. The reason for breaking the blind will be indicated and justified in the source documentation and in the eCRF. The blind can be broken by the investigator via the [redacted] system.

All subjects who are unblinded while on the study will be withdrawn at the moment of unblinding, with the reason for unblinding given as the reason for discontinuation from the study. If an AE leads to unblinding, the AE should be given as the reason for unblinding and the AE should also be recorded in the eCRF. All subjects who are unblinded should, where possible, complete the EDV. AEs will be recorded from the signature of the ICF until the final follow-up visit. In case an AE is ongoing at that time, it will be followed up until resolution or until stabilization by the investigator as much as possible.

5. STUDY ASSESSMENTS

5.1. TIMING OF ASSESSMENTS

The study assessments as described below will be performed at the time points specified in the study flow chart, provided in Section 1. Visits are to be scheduled within a window of ±2 (Visits 3 and 4) or 3 days (Visits 5, 6, 7, and the follow-up visit) and in such a way that the total study duration from baseline to last dosing does not exceed 13 weeks.

The sequence of study assessments, if planned at one study visit, will be as follows (if applicable):

1. physical examination, oral body temperature, ECG, systolic and diastolic blood pressure (SBP and DBP), supine heart rate, respiratory rate
2. SGRQ
3. assessment of (S)AE(s) and concomitant medication
4. blood sampling for PK
5. blood sampling for safety laboratory analysis
6. blood sampling for PD
7. blood sampling for biomarkers

8. spirometry [16]
9. DLCO [16]
10. HRCT-scan [16]
11. bronchoscopy (biomarkers and PD in BALF)

5.2. INITIAL SUBJECT AND DISEASE CHARACTERISTICS

Written informed consent must be obtained before any study-related procedures take place. During the screening period, following signing of the ICF, the subject's historical HRCT and SLB (if available) will be sent to the central reader for the confirmation of the IPF diagnosis through a:

- central review of chest HRCT
- central review of SLB (if available)

Note that both the chest HRCT and SLB need to be sent to central review at least 8 days prior to the baseline visit to allow for central reading and confirmation of IPF diagnosis. Additional details are provided in Appendix 2.

In addition, information on demographics and medical history/concomitant diseases (including the multidisciplinary diagnosis of IPF at the site, the duration of disease, disease progression prior to screening, the medications used to treat the disease, drinking, and smoking habits) will be collected. A physical examination will take place and vital signs, ECG, clinical laboratory assessments (including serology, FSH [if applicable]), spirometry, and DLCO will be conducted to determine the subject's eligibility for study participation.

Note that if screening spirometry measurements fail to meet acceptability and repeatability criteria as specified by the American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines (Miller, Hankinson, & Brusasco, 2005), repeat spirometry evaluation may be performed once. If repeat values are within the acceptability criteria and completed within the screening window, the subject is eligible for the study.

At baseline, after the subject's eligibility for the study has been confirmed, the subject will be randomized into the study to receive treatment with GLPG1690 600 mg *q.d.* or placebo. Study drug will be dispensed and all subjects will be handed a diary card (additional information is provided in Section 5.3). All baseline assessments are specified in the study flow chart, provided in Section 1.

5.3. SUBJECT DIARY CARD

Subjects will be given a diary card at Day -1 (baseline) to record the following:

- From Day 1 through Day 84 (or the EDV), subjects will be asked to record the date (and time) of study drug intake and the number of capsules taken for each administration.
- From Day 1 to Day 84 (or the EDV), subjects will be asked to indicate whether a home-based spirometry test was done and if no such test was done, the reason(s) why should be provided.

[16] Subjects taking inhaled bronchodilators can do this after spirometry assessments (and DLCO) and prior to the performance of the HRCT.

– From Day 1 to Day 84 (or the EDV), subjects will be asked to record changes in concomitant medication regimen, including new medicines not captured in medication history, use of bronchodilators, any other concomitant medication used as well as any emerging AE.

Subjects will be instructed to bring the diary card and used/unused study drug to each visit. All diary card data will be entered in the eCRF by the designated site personnel.

5.4. SAFETY ASSESSMENTS

The safety and tolerability assessment will be based on the collection of AEs (including IPF exacerbations), physical examinations, vital signs measurements, 12-lead ECG, and safety laboratory assessments (standard hematology, serum/plasma chemistry, coagulation tests, and urinalysis).

5.4.1. Adverse Events

AEs will be reported and documented as described in Section 8.

5.4.1.1. Acute IPF Exacerbation

All acute IPF exacerbations will be reported and documented as (S)AEs (see Section 8). An acute IPF exacerbation is defined as an acute and clinically significant deterioration of unidentifiable cause in patients with underlying IPF. Diagnostic criteria are defined as follows (Collard, et al., 2007):

1. The subject has a previous or concurrent diagnosis of IPF.

2. The subject shows unexplained worsening or development of dyspnea within 30 days.

3. The HRCT shows new bilateral ground-glass abnormality and/or consolidation superimposed on a background reticular or honeycomb pattern consistent with usual interstitial pneumonia pattern.

4. There is no evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage [17].

5. Alternative causes, including the following, are excluded:

- left heart failure
- pulmonary embolism
- identifiable cause of acute lung injury [18]

[17] Evaluation of samples should include studies for routine bacterial organisms, opportunistic pathogens and common viral pathogens.
[18] Causes of acute lung injury include sepsis, aspiration, trauma, reperfusion pulmonary edema, pulmonary contusion, fat embolization, inhalational injury, cardiopulmonary bypass, drug toxicity, acute pancreatitis, transfusion of blood products, and stem cell transplantation.

5.4.2. Clinical Laboratory Evaluations

Blood samples of approximately 16 mL (or approximately 21 mL at screening only) will be collected predose by venipuncture (or indwelling catheter for pharmacokinetic sampling days) in the arm at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1. In addition, urine samples for the clinical laboratory assessments will be collected. Subjects do not need to be fasted at the time of sampling.

Blood and urine samples will be collected for the following clinical laboratory tests:

- hematology: hematocrit, hemoglobin, red blood cell count, WBC total count, WBC differential count (absolute and relative), and platelets
- serum/plasma chemistry: glucose, urea, creatinine, uric acid, sodium, potassium, calcium, chloride, phosphorus, AST, ALT, gamma glutamyl transferase, total bilirubin, alkaline phosphatase, albumin, total proteins, triglycerides, cholesterol, and brain natriuretic peptide
- coagulation parameters: international normalized ratio and partial thromboplastin time
- urinalysis: pH, glucose, proteins (quantitative); ketones, and microscopic examination of the sediment (cylinders, erythrocytes, leucocytes)
- serology: hepatitis B surface antigen, hepatitis B virus antibody, HIV-1 and HIV-2 antibody (only at screening)
- FSH (only at screening in case there is doubt on whether a female subject is postmenopausal)

The laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator to follow-up and resolve any safety concerns.

Note that in case clinically significant laboratory test results are a potential reason for discontinuation from the study drug and withdrawal from the study, retesting should be prompt (within 3 to 5 days) after the investigator has consulted with the medical monitor. A decision regarding subject discontinuation should be made only after the results from the retest are available (see Section 4.2.5 for additional information).

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

5.4.3. Vital Signs

Vital signs will be measured predose at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1. Vital signs must be taken after 5 min in the supine position, prior to the bronchoscopy.

Vital signs will include supine heart rate, respiratory rate, SBP, DBP, and oral body temperature.

Normal ranges are provided in Appendix 4.

5.4.4. Physical Examination

The physician (or a trained assistant or nurse practitioner, as applicable by local regulations) will perform a full physical examination (including ear, nose, throat, neck, chest, abdomen, and extremities) predose at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1.

Height and weight will be measured at screening only (with shoes off).

5.4.5. Electrocardiogram

A 12-lead ECG will be performed predose at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1. The ECG must be taken after 5 min in the supine position, prior to any blood sampling. Each ECG will be interpreted by the investigator for clinical significance.

Normal ranges are provided in Appendix 4.

5.5. PHARMACOKINETIC ASSESSMENTS

PK assessments will include analysis of GLPG1690. Plasma concentrations of GLPG1690 will be measured using a validated LC-MS/MS method, and will be performed by the bioanalytical laboratory in charge of these analyses ([redacted]).

Other measurements (*e.g.*, metabolism studies, stability studies) may be performed if deemed appropriate.

5.5.1. Biological Samples

Blood samples of 1 mL will be collected by venipuncture (or indwelling catheter for pharmacokinetic sampling day) in the arm at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1.

All details on sample handling and shipment instructions will be provided in a separate laboratory manual.

5.5.2. Pharmacokinetic Parameters

PK parameters will be derived with Phoenix WinNonlin (Version 6.2 or higher).

The following PK parameters, where appropriate, will be determined using non-compartmental analysis for GLPG1690 from individual concentration-time profiles in plasma:

- C_{max} maximum observed plasma concentration
- t_{max} the time of occurrence of C_{max}
- $AUC_{0-\tau}$ area under the plasma drug concentration-time curve of a dosing interval

– C_τ trough plasma concentration (just before the next dosing i.e. predose sample)

Additional PK parameters may be calculated if appropriate.

5.6. PHARMACODYNAMIC ASSESSMENTS

5.6.1. Biological Samples (Blood)

Blood samples of 2 mL will be collected by venipuncture (or indwelling catheter for pharmacokinetic sampling days) in the arm at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1.

All details on sample handling and shipment instructions will be provided in a separate laboratory manual.

5.6.2. Biological Samples (BALF)

Bronchoscopies for the collection of BALF samples will be conducted (post dose if applicable) at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1.

All details on sample collection through bronchoscopy will be provided in a separate, study-specific bronchoscopy/BALF manual. All details on sample handling and shipment instructions will be provided in a separate laboratory manual.

5.6.3. Pharmacodynamic Parameters

LPA species (C18:2) will be determined in plasma. Other LPA species might be analyzed if deemed appropriate.

All detectable LPA species will be determines in the supernatant of the BALF.

5.7. EXPLORATORY EFFICACY ASSESSMENTS

5.7.1. Pulmonary Function by Spirometry

Pulmonary function will be assessed through spirometry both performed at the study center (at screening, baseline, and thereafter post dose at the time points indicated in the study flow chart [provided in Section 1] and according to sequence of study assessments as described in Section 5.1) and at home (at baseline and thereafter post dose; on a daily basis in the morning). Specific instructions on how to perform the spirometry at home are provided in a separate spirometry user manual.

The site-based spirometry must meet the criteria for acceptability and repeatability as defined in the ATS/ERS guidelines (Miller, Hankinson, & Brusasco, 2005)

Pulmonary function will be measured in standardized manner, results will be transmitted electronically and confirmed by a central reader.

Timing of home- and site-based spirometry

The spirometry test is to be performed in the morning, preferably at approximately the same time (± 1 h) every day/visit.

Timing of home- and site-based spirometry versus bronchodilator use

All spirometry evaluations should be performed pre-bronchodilator. Pre-bronchodilator spirometry is defined as spirometry testing performed for a subject who has:

- withheld their short-acting β-agonist (*e.g.,* albuterol) or anticholinergic (*e.g.,* ipratropium bromide) for >6 h prior to the spirometry assessment AND
- withheld their long-acting bronchodilator (*e.g.*, salmeterol, formoterol) for ≥ 12 h and other longer-acting agents (*e.g.*, indacaterol, tiotropium) for ≥ 24 h prior to the spirometry assessment

In case the subject is on bronchodilators, he/she can use the bronchodilator after the spirometry but prior to HRCT for FRI parameters.

Spirometry parameters and calculation of predicted values

The following parameters will be measured as part of the spirometry assessment:

- FEV_1 (L) and percent predicted FEV_1
- FVC (L) and percent predicted FVC
- FEV_1/FVC ratio
- Forced expiratory flow (FEF) between 25 and 75% of exhaled volume (FEF_{25-75})

The '2012 Global Lung Function Initiative Equations' will be used to estimate the predicted values (Quanjer, et al., 2012).

5.7.2. Biomarker Analysis

5.7.2.1. Biological Samples (Blood)

Blood samples of 14 mL will be collected predose by venipuncture (or indwelling catheter for pharmacokinetic sampling days) in the arm at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1.

All details on sample handling and shipment instructions will be provided in a separate laboratory manual.

5.7.2.2. Biological Samples (BALF)

See Section 5.6.2 for details on bronchoscopies.

5.7.2.3. Biomarkers to be Analyzed

The following exploratory biomarkers will be evaluated in blood samples:

- KL-6/Muc1
- surfactant protein A and D
- CCL18
- ATX
- MMP1, MMP7
- markers of extracellular matrix (ECM) turnover (neoepitope assay)

The following additional biomarkers may be analyzed in blood samples if deemed appropriate after results of the above exploratory markers have become available:

- oxydative stress: ICAM-1 and VCAM-1
- neutrophil recruitment, activation: IL8, S100A12
- other biomarkers might be analyzed if deemed appropriate (*e.g.*, serique protein, serique miRNA)

ATX will be determined in the supernatant of the BALF. Bronchoalveolar lavage (BAL) cell count will be performed. BAL cell pellets will be stored for possible future analyses (transcriptomics, proteomics).

5.7.3. Quality of Life

The SGRQ will be completed predose at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1.

The SGRQ is a 50-item questionnaire split into 3 domains: symptoms (assessing the frequency and severity of respiratory symptoms), activity (assessing the effects of breathlessness on mobility and physical activity), and impact (assessing the psychosocial impact of the disease). Scores are weighted such that every domain score and the total score range from 0 to 100, with higher scores indicating a poorer health-related quality of life.

Subjects must be able to read and complete the SGRQ by themselves. They should not receive any help from anyone (such as family and friends) or study staff in interpreting or responding to the questions. The study staff will review the questionnaires after completion to ensure that all questions are completed. In case of missing information, the subject will be asked to complete the missing items.

5.7.4. Functional Respiratory Imaging

HRCT will be performed (post dose if applicable) at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1. HRCT scans will be used to generate FRI measurements allowing for an evaluation of regional IPF disease manifestation and disease progression. In case the subject is on bronchodilators, he/she can use the bronchodilator after the spirometry but prior to HRCT for FRI parameters.

At each computed tomography (CT) assessment an inspiratory and an expiratory scan will be taken. During the baseline visit an additional scan of the upper airway will be taken. The inspiratory and an expiratory scan will expose the subject to a total radiation dose of approximately 4-5 mSv per visit, including the initial CT localizer radiograph (topogram scout). The upper airway scan will expose a subject to approximately 1 mSv. A radiation dose of approximately 2-2.5 mSv is equivalent to approximately 1 year of background radiation (based on the assumption of an average "effective dose" from natural background radiation isof 3.1 mSv per year in the US and 2.4 mSv per year in Europe. (USNRC, 2014; WNA, 2015)

All CT images will be imported into [redacted] for analysis. This software package converts the HRCT images into patient specific, 3-dimensional computer models of the lung lobes, the airway lumen and wall, and the vascular tree. The airway and vascular tree are evaluated at functional residual capacity (FRC) and total lung capacity (TLC) level and can be segmented down to bronchi/vessels with a diameter of around 1-2 mm. Beyond this point the HRCT resolution is insufficient to distinguish alveolar and intraluminal air, or blood vessel tissue and surrounding lung tissues. A typical airway model includes 5-10 generations, depending mainly on the disease state of the individual patient. Afterwards the airway lumen models will be processed further to obtain a model that is suitable for flow calculations.

The following FRI parameters based on low-dose inspiratory-expiratory multi-slice CT images and computational fluid dynamics flow simulations will be evaluated.

- lobar volumes at FRC and TLC
- airway volumes at FRC and TLC
- airway resistance
- internal lobar airflow distribution
- low attenuation or emphysema score at TLC
- blood vessel density or fibrosis score at TLC
- airway wall thickness at TLC
- air trapping at FRC
- mass of deposited particles per defined airway section

5.8. TOTAL BLOOD VOLUME

The estimated total volume of blood that will be collected for each subject throughout the study is maximum 215 mL.

If deemed necessary by the investigator (see Section 5.4.2), additional samples may be obtained to ensure the safety of the subject. Due to this possibility, the blood volumes described above are a best estimation.

After the study is completed, any left-over blood samples may be stored under the control of the sponsor. These samples may be used by the sponsor/partner, or by other companies

belonging to the sponsor for future research on the mode of action of GLPG1690 and/or future research in IPF.

6. STATISTICAL METHODS

All statistical calculations will be performed by the CRO using the SAS (Version 9.1.3 or higher) software for statistical computations and SAS for graphical purposes.

The statistical analysis and visualization of the FRI parameters will be implemented in R version 3.0.2 or higher (The R Foundation for Statistical Computing, Vienna, Austria) by [redacted]

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

All data collected in this study will be documented using summary tables, figures and subject data listings.

6.1. DETERMINATION OF SAMPLE SIZE

Strict statistical criteria were not used to determine the sample size for this study. The number of subjects included in this study should give reasonable precision around the estimates derived for the safety, PK, and PD evaluation.

6.2. POPULATION FOR ANALYSES

6.2.1. All Screened Subjects

All subjects who signed an ICF.

6.2.2. All Randomized Subjects

All subjects randomized into the study.

6.2.3. Safety Analysis Set

All randomized subjects who received at least 1 dose of study drug.

6.2.4. Pharmacokinetics Analysis Set

All randomized subjects who received at least 1 dose of study drug and for whom evaluable PK data were available. Subjects with a protocol deviation that may impact the PK results will be excluded from this population.

6.2.5. Pharmacodynamics Analysis Set

All randomized subjects who have at least one dose of study drug and have at least one post-baseline assessment with PD data.

6.2.6. Intent to Treat Analysis Set

All randomized subjects who have at least one dose of study drug and have at least one post-baseline assessment with exploratory endpoint data.

6.3. STATISTICAL ANALYSES

6.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, standard error (SE), median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data. Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 5% level. Data will be pooled across centers and countries.

No formal interim analysis is planned for this study.

6.3.2. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, will be presented descriptively.

Use of study drug and concomitant medications will also be presented descriptively.

6.3.3. Analyses of Safety Data

A descriptive analysis of the TEAEs, laboratory assessments, 12-lead ECG, and vital signs will be performed. Changes from baseline and shifts according to normal ranges will be presented as well.

Physical examination results will be listed only.

AEs will be fully described and coded according to the Medical Dictionary for Regulatory Activities Dictionary.

6.3.4. Pharmacokinetic Analyses

Descriptive statistics will be calculated for the plasma concentrations and PK parameters. Mean (± SE) concentration-time profile will be generated.

Individual subject GLPG1690 concentrations and PK parameters will be listed.

6.3.5. Pharmacodynamic Analyses

In blood, LPA C18:2 species peak area ratio will be used to calculate the percentage reduction versus baseline. Baseline will be the average of the predosing duplicates (predose sample from Day -1).

The percentage reduction from baseline will be calculated as follows:

% reduction = 100-(100 x visit/baseline).

Individual and mean percentage reduction from baseline over time plots will be generated.

The AUEC as well as E_{max} on Day 28 will be determined from individual effect time profiles.

PD marker percent reduction, AUECs and E_{max} will be compared between the treatment groups using an analysis of covariance (ANCOVA) model with the following covariates: disease severity (baseline FVC, baseline DLCO), age, gender, treatment group, country, and baseline value.

Within-group comparisons of PD marker level obtained on Day 28 at 1.5 h and 6 h post-dosing, and on Day 84, versus baseline will be investigated using a paired t-test

PD data will also be summarized descriptively per treatment and per time point.

The analysis will be performed for the LPA C18:2 species. Other LPA species might be analyzed if deemed appropriate.

In BALF, data for all LPA species detectable will be used for the analysis. LPA species peak area ratio will be used to calculate the percentage reduction versus baseline. Baseline will be the average of the predosing duplicates (predose sample from Day -1).

6.3.6. Exploratory Efficacy Assessments

Exploratory endpoint data at each post-dosing visit will be analyzed descriptively. Comparison between GLPG1690 and the placebo group will be done exploratively.

Analysis methods:

- Continuous parameters will be analyzed using descriptive statistics of actual values, changes from baseline, and percent changes from baseline. GLPG1690 and placebo will be compared using an ANCOVA model on the changes from baseline, with the following covariates: disease severity (baseline FVC, baseline DLCO), age, gender, treatment group, country, and baseline value. Within-group comparisons of each visit versus baseline will be investigated using a paired t-test. For FRI parameters these analyses will be performed using a mixed effects ANCOVA model with subject as a random factor and the factors listed above as fixed factors.
- Missing data will be imputed, also for subjects who prematurely discontinue the study. The primary imputation method will be last-observation-carried-forward. An observed-case analysis will also be performed.
- Additional exploratory analyses and graphical presentations may be performed when deemed useful to better understand the data.

6.3.7. Pharmacokinetic/ Pharmacodynamic and Pharmacokinetic/ Exploratory Efficacy Correlations

Individual and/or mean ± SE, safety, PD, exploratory efficacy endpoint, and/or GLPG1690 plasma concentrations may be plotted against one another.

PK/PD, PK/exploratory efficacy endpoint and safety correlation will be explored between GLPG1690 concentrations or PK parameters and selected exploratory PD or safety endpoints, but only if the latter are significantly altered by the treatment.

Exploratory safety/PK/PD/exploratory efficacy endpoint analyses may be added when deemed useful to better understand the collected data.

7. INDEPENDENT MEDICAL SAFETY REVIEW

In order to enhance the safety and integrity of the study, an independent medical safety review will be implemented. The review will be conducted by an independent pulmonologist experienced in the field of IPF. The independent expert will regularly review unblinded safety data to monitor the risk/benefit and assess any potential safety issues arising during the conduct of the study. This process will be described in a separate 'Independent Medical safety Review Charter'.

GENERAL PROCEDURES

8. ADVERSE EVENTS

8.1. DEFINITIONS

Adverse Event

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal (investigational or non-investigational) product, whether or not related to that medicinal (investigational or non-investigational) product.

Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose meets any of the following conditions:

- results in death
- is life-threatening (*i.e.*, the subject is at risk of death at the time of the event); it does not refer to an event that hypothetically might cause death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is a medically significant event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definitions above

Unlisted (Unexpected) Adverse Event/Reference Safety Information

An adverse event is considered unlisted if the nature or intensity is not consistent with the applicable product reference safety information. For a study drug, the expectedness of an adverse event will be determined by whether or not it is listed in the Investigator's Brochure.

Associated With the Use of the Drug

An AE is considered associated with the use of the drug if the causality is possible, probable, or certain by the definitions listed in Section 8.3.

8.2. INTENSITY OF ADVERSE EVENT

Each AE must be rated on a 3-point scale of increasing intensity:

- **Mild:**

  Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required

- **Moderate:**

  Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention/therapy required

- **Severe:**

  Marked limitation in activity; some assistance usually required; medical intervention/therapy required, hospitalization possible

If there is a change in intensity of an AE, it must be recorded as a separate event.

8.3. CAUSALITY ASSESSMENT

The following decision choice will be used by the investigator to describe the causality assessment between the reported event and the investigational medicinal product.

- **Unrelated:**

  No relationship between the AE and the administration of study drug; related to other etiologies such as concomitant medications or subject's clinical state

- **Unlikely:**

  Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible); disease or other drugs provide plausible explanations

- **Possible:**

  Event or laboratory test abnormality, with reasonable time relationship to drug intake which could also be explained by disease or other drugs; information on drug withdrawal may be lacking or unclear

- **Probable:**

  Event or laboratory test abnormality, with reasonable time relationship to drug intake; event unlikely to be attributed to disease or other drugs; response to withdrawal is clinically reasonable and rechallenge not required

- **Certain:**

  Event or laboratory test abnormality, with plausible time relationship to drug intake which cannot be explained by 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 necessary

8.4. ACTION TAKEN REGARDING INVESTIGATIONAL PRODUCT (IF APPLICABLE)

The action taken must be described by choosing among:

- **Dose not changed:**

  In case no action is taken regarding the study drug.

- **Drug permanently withdrawn:**

  In case a subject is permanently withdrawn from the study.

- **Drug temporarily withdrawn:**

  In case the study drug is temporarily withdrawn.

- **Not applicable:**

  Other situations (*e.g.*, in case an AE started after the last study drug administration)

8.5. OUTCOME

Each AE must be rated by choosing among:

- recovered/resolved
- recovered/resolved with sequelae
- not recovered/not resolved
- fatal
- recovering/resolving
- unknown

8.6. RECORDING ADVERSE EVENTS

AEs will be recorded from the signature of ICF until the final follow-up visit. In case an AE is ongoing at that time, it will be followed up until resolution or until stabilization by the investigator as much as possible.

It is the responsibility of the investigator to collect all AEs (both serious and non-serious) derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questioning (such as "How do you feel?").

Any adverse or unusual event occurring during or after the clinical study (until the follow-up visit), whether observed by the investigator or investigational staff, or spontaneously reported by the subjects, will be recorded in the e-source system.

8.7. MANAGING SERIOUS ADVERSE EVENTS

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. 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. The subject will be followed until the SAE resolves or until the subject is medically stabilized.

8.8. REPORTING SERIOUS ADVERSE EVENTS / PREGNANCIES

8.8.1. Serious Adverse Events

All SAEs, whether or not deemed drug-related, must be recorded on the eCRF and SAE form and reported by the investigator to [redacted] Medical Affairs ([redacted] MA) within 24 h by facsimile. Other means of transmission can be decided where facsimile is not possible. The SAE should include 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 for all subjects that experience an SAE. It is critical that the information provided on the [redacted] SAE form matches the information recorded on the eCRF for the same event. In addition, the same information is to be recorded in the source documents.

Copies of additional laboratory tests, consultation reports, post mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and applicable. Follow-up reports relative to the subject's subsequent course must be submitted to [redacted] MA until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

8.8.2. Pregnancy

All initial reports of pregnancies in partners of male subjects included in the study must be reported to [redacted] MA by the investigator within 24 h of knowledge of the event, using a pregnancy form.

The investigator will contact the subject at the expected time of delivery for follow-up. Abnormal pregnancy outcomes are considered SAEs and must be reported using the SAE form.

8.9. REPORTING SERIOUS ADVERSE EVENTS TO COMPETENT AUTHORITIES/ETHICS COMMITTEES

[redacted] MA assumes responsibility for appropriate reporting of AEs to the regulatory authorities. [redacted] MA will also report to the investigator(s) all SAEs that are unlisted (unexpected) and associated with the use of the drug. The investigator(s) (or [redacted] MA where required) must report these events to the appropriate IEC that approved the protocol unless otherwise required and documented by the IEC.

AEs reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

After termination of the clinical study (last subject last contact in the study), any unexpected safety issue that changes the risks benefit analysis and is likely to have an impact on the subjects who have participated in it, will be reported by the sponsor/[redacted] MA as soon as possible to the Competent Authority(ies) concerned together with proposed actions.

9. STUDY CLOSURE CONSIDERATIONS

The sponsor reserves the right to close the investigational site or terminate the study at any time for any reason. In case of an early termination of the study or temporary halt by the sponsor, the IEC and regulatory authority should be notified within 15 calendar days, including a detailed written explanation of the reasons for the termination/halt.

The end of study declaration will be submitted to the regulatory authorities and IEC after the complete study has ended in all participating centers, in all countries. This notification will also be submitted within 90 days of the end of the study.

Reasons for the closure of an investigational site or termination of a study by the sponsor may include but are not limited to:

- successful completion of the study at the center
- the overall required number of subjects for the study has been recruited
- failure of the investigator to comply with the protocol, ICH-GCP guidelines or local requirements
- safety concerns
- sufficient data suggesting lack of efficacy
- inadequate recruitment of subjects by the investigator

10. STUDY MATERIALS

10.1. INVESTIGATIONAL MEDICAL PRODUCTS

The investigator acknowledges that the study drugs are investigational and as such must be handled strictly in accordance with the clinical study protocol and the container label. Supplies must be retained in a limited access area and under the appropriate environmental conditions as specified on delivery. Upon receipt of the study drugs, the investigator or delegate will verify whether the correct amount of study drugs are delivered and whether those are intact.

Supplies should be dispensed under the supervision of the investigator or sub-investigator, or by a hospital pharmacist. Local regulations should be adhered to. It is the investigator's or delegate's responsibility to ensure that subjects return their study drugs (including empty packages, *e.g.,* empty blisters). Returned study drugs must not be dispensed again, even not to the same subject. Each time study drugs is dispensed to or returned by the subject, this must be documented on the Drug Accountability Form. Whenever a subject brings his/her medication to the site for pill count this is not seen as a return of supplies. Unused medication and medication returned by the subject must be available for verification by the monitor.

All used and unused investigational medication will be returned to the sponsor or will be passed over for destruction on-site (conform local regulations) or by an authorized destruction unit after authorization by the sponsor. This will be documented on the Drug Return Form and a destruction certificate, if applicable.

10.2. STUDY DOCUMENTS

The following documents must be provided to the sponsor or representatives before shipment of study drugs to the study center:

- a signed and dated protocol and amendment(s), if any
- a copy of the signed and dated written IEC approval specifying the documents being approved: the protocol, amendments, informed consent form, any other written information provided to the subject and subject recruitment materials

  This approval must clearly identify the study by protocol title and study number.
- regulatory authority approval or notification, if required

- documentation on which the assessment of the investigator's qualifications was based (*e.g.,* curriculum vitae)

The following documents must be provided to the sponsor or representatives prior to enrollment of the first subject:

- the names of the current members or composition of the IEC and their position in the health-care institution or their credentials

  In case the (sub) investigator is a member of the IEC, documentation must be obtained to state that this person did not participate in the voting for the study.
- completed Investigator Financial Disclosure Forms from the investigator and all sub-investigators
- signed and dated study agreement, if applicable
- signed and dated financial agreement
- documentation on which the assessment of the (sub-)investigators' qualifications was based (*e.g.,* curriculum vitae)
- current laboratory normal ranges for all tests required by the protocol that will be performed
- laboratory documentation demonstrating competence and test reliability (*e.g.* accreditation/license), if applicable

10.3. PARTICIPATION CARDS

If the subjects are not under 24-h supervision of the investigator or his/her staff (out-subjects), they must be provided with a Subject Participation Card indicating the name of the investigational product, the study number, the investigator's name and a 24-h emergency contact number. The subject should be advised to keep the participation card in his/her wallet at all times.

10.4. SOURCE DATA

The nature and location of all source documents will be discussed during the Site Initiation Visit and will be documented in the site initiation visit report to ensure that all sources of original data required to complete the eCRF are known and are accessible for verification by the monitor. If electronic records are maintained, the method of verification must be discussed and agreed upon between the investigational staff and the monitor.

The required source data are discussed during the Site Initiation Visit, should include sequential notes containing at least the following information for each subject:

- subject identification (name, date of birth, gender)
- documentation that subject meets eligibility criteria, *i.e.*, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria)
- participation in study (including study number)
- study discussed and date of informed consent
- dates of all visits

- documentation that protocol specific procedures were performed
- results of efficacy parameters, as required by the protocol
- start and end date (including dose regimen) of study drug (preferably drug dispensing and return should be documented as well)
- record of all AEs and other safety parameters (start and end date, and preferably including causality and intensity)
- concomitant medication (including start and end date, and dose

  If relevant, dose changes should be motivated).
- date of study completion and reason for early discontinuation, if applicable

Source data may be directly captured from devices transferred from 3rd partners (*e.g.,* laboratory data) or entered manually into the eCRF system.

It is recommended that the author of an entry in the source documents is identifiable. Following ICH GCP Guidelines, direct access to source documents must be granted for the purpose of verifying that the data recorded on the eCRF are consistent with the original source data.

10.5. ELECTRONIC DATA CAPTURE

Electronic Data Capture (EDC) will be used for this study, meaning that all CRF data will be entered in eCRFs at the investigational site. All data related to the study must be recorded in the EDC system in English.

The eCRFs should always reflect the latest observations on the subjects participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or after the subject's visit. To avoid inter-observer variability, every effort should be made to ensure that all efficacy evaluations are completed by the same individual who made the initial baseline determinations. The investigator must verify that all data entries in the CRFs are accurate and correct. If certain information is not done, not available or not applicable or unknown, the investigator should indicate this in the eCRF. The investigator will be required to electronically sign off on the clinical data.

During monitoring visits, the monitor will review the eCRFs, evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance.

If additional corrections are needed, the responsible monitor or data manger will raise a query in the EDC application. The appropriate investigational staff will answer queries sent to the investigator. This will be audit trailed by the EDC system meaning that the name of investigational staff, time and date stamp are captured.

11. ARCHIVING

The investigator shall maintain the study specific documents as specified in "Essential Documents for the Conduct of a Clinical Trial (ICH E6, section 8) 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 investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor.

It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

Under no circumstance shall the investigator re-locate or dispose of any 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 study, the investigator must permit access to such reports. The subject is granting access to his/her source data by signing the informed consent.

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

12. CONFIDENTIALITY

All information concerning the product and the sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential by the sponsor 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 study and will not use it for other purposes.

In order to permit easy identification of the individual subject during and after the 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 will remain at the center and no copy will be made. Subject data like HRCT, blood samples, or BALF will be anonymized using Subject Identification Code List to prevent site from patient confidentiality breach when shared with third party for analysis.

13. REPORTING AND PUBLICATION

13.1. REPORTING

The results of the study will be reported in a single clinical study report. A summary of the final report will be provided to the investigators, to the applicable regulatory authorities and IECs if required by the applicable regulatory requirements within one year after end of study.

One participating investigator will be appointed for review and sign off the final clinical study report. The selection of this investigator will be determined by the recruitment performance and specific expertise related to the nature and the primary objectives of the study.

13.2. PUBLICATION

All information concerning the product and the sponsor's operations (such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information supplied to the investigator by the sponsor and not previously published) is considered confidential by the sponsor 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 study and will not use it for other purposes without the written approval of the sponsor.

It is understood by the investigator that the sponsor will use the information developed in this clinical study in connection with the development of the compound and therefore, may disclose it as required to other clinical investigators and to regulatory agencies. In order to allow for the use of the information derived from this clinical study, the investigator understands that he has an obligation to provide and disclose test results and all data developed during this study to the sponsor.

The investigator may not submit for publication or presentation, the results of this study without the prior written approval of the sponsor. The investigator should understand that it is not the sponsor's intention to prevent publication of such data as is generated in the study. However, the sponsor reserves the right to control the route and rate of such publication.

The sponsor will not unreasonably withhold consent to publish the data generated in this study. However, it is the policy of the sponsor not to allow the investigators to publish their results or findings prior to the sponsor's publication of the overall study results. The investigator agrees that before he/she publishes any results of this study, he/she shall provide the sponsor with at least 60 days for full review of the pre-publication manuscript prior to submission of the manuscript to the publisher. In accordance with generally recognized principles of scientific collaboration, co-authorship with any company personnel will be discussed and mutually agreed upon before submission of a manuscript to a publisher.

14. ETHICS

14.1. IEC

This study can only be undertaken after full approval of the clinical study protocol, informed consent, any other written information given to subjects, and subject recruitment materials has been obtained from the IEC. This approval document must be dated and clearly identify the

study and the related study documents being approved, including the subject compensation programs.

During the course of study the following documents will be sent to the IEC for review:

- changes to the Investigator's Brochure
- reports of AEs that are serious, unlisted and associated with the investigational drug

Substantial amendments and applicable informed consent form revisions must promptly be submitted to the IEC for review and approval prior to implementation of the change(s), except when necessary to eliminate an immediate hazard to the study subjects.

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

14.2. REGULATORY APPROVAL / NOTIFICATION

This clinical study protocol, title, and a list of investigational sites, IEC approvals, as well as other relevant documentation will be submitted to the local Regulatory Authorities for review and approval prior to study start. Upon completion, the Regulatory Authorities will be notified the study has ended. The study will only be undertaken in compliance with the local regulatory requirements.

14.3. ICH GCP

This study will be conducted in accordance with the current ICH-GCP Guideline E6. GCP is an international ethical and scientific quality standard for designing, conducting, recording and reporting studies that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of 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.

14.4. INFORMED CONSENT

The investigator or designated personnel must explain the study and the implications of participation (*e.g.,* objectives, methods, anticipated benefits and possible risks) to potential subjects or their legally acceptable representatives prior to any study-related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the study at any time. They will be informed that choosing not to participate or to withdraw from the study will not have an impact on the care the subject will receive for the treatment of his/her disease. In case the subject is unable to read and write, an impartial witness must confirm the informed consent.

The subject will be given sufficient time to read the ICF and to ask additional questions. After this explanation and before entry in the study, consent should be appropriately recorded by means of the subject's personally dated signature or by the signature of an independent witness who certifies the subject's consent in writing. After having obtained the consent, a copy of the signed and dated informed consent must be given to the subject.

If new information becomes available that may be relevant to the subject's willingness to participate in the study, the subject will be informed in a timely manner by means of an updated informed consent form. This amended informed consent form will be signed and dated by the subject and the investigator to document the willingness of the subject to continue with the study.

This signed and dated amended version will be filed together with the initial signed and dated informed consent form.

15. FINANCING AND INSURANCE

15.1. FINANCIAL DISCLOSURE

The disclosed financial interest of the investigator must be collected before screening of the first subject, following study completion at the investigator site and one year following overall study completion. The investigator 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 study. For any investigator(s) leaving the site prior to study completion, an Investigator Financial Disclosure Form should be obtained at the end of their contribution to the study.

15.2. INDEMNIFICATION

The sponsor will indemnify the investigator and hold harmless the investigator and his or her medical staff from any claim for damages, demand or cost arising from the activities to be carried out in compliance with the clinical study protocol.

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

15.3. INSURANCE

The sponsor ensures that suitable clinical study insurance coverage is in place prior to the start of clinical study. For subjects treated according to the clinical study protocol, injury possibly arising from participating in this study is covered by the liability insurance of the sponsor, unless malpractice from the investigator.

16. DATA QUALITY CONTROL / ASSURANCE

16.1. MONITORING

This clinical study will be monitored by sponsor representatives according to the current Standard Operating Procedure for the monitoring of clinical studies.

The monitor will perform on-site monitoring visits as frequently as necessary which will be documented on the monitoring log. Shortly before the study starts, the monitor will meet with the investigator and study staff involved to review the study-specific procedures on study conduct and recording the data in the eCRF. The first monitoring visit will take place as soon

as possible after first enrollment at the site and the investigator shall permit the monitor to verify the progress of the study on a continues basis. The investigator shall make the eCRFs available, provide missing or corrected data and sign the eCRFs. Key data transcribed onto the eCRFs, such as the subject's sex, date of birth, assessment dates, test results etc., will be reviewed against the available source documents. Personal information will be treated as strictly confidential and will not be made publicly available. Any inconsistency between source data and data recorded in the eCRF will be corrected.

The sponsor will ensure that appropriate QC steps are included into the different clinical study processes to guarantee adequate protection of the subjects and to guarantee the quality of the data.

16.2. AUDIT AND INSPECTION

To ensure compliance with relevant regulations, an independent Quality Assurance (QA) representative, regulatory authorities and/or IEC(s) may review this study. This implies that auditors/inspectors will have the right to inspect the study center(s) at any time during and/or after completion of the study and will have access to the data generated during the study, source documents, and subject's files. By participating in this study, investigators agree to this requirement.

REFERENCES

Bandoh, K., Aoki, J., Taira, A., Tsujimoto, M., Arai, H., & Inoue, K. (2000). Lysophosphatidic acid (LPA) receptors of the EDG family are differentially activated by LPA species. Structure-activity relationship of cloned LPA receptors. *FEBS Lett, 478(1-2)*, 59-65.

Collard, H., Moore, B., Flaherty, K., Brown, K., Kaner, R., King, T., et al. (2007). Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med 176*, 636-643.

Cordier, J., & Cottin, V. (2013). Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis. *Eur Respir J 183*, 916-923.

De Backer, J., Vos, W., Van Holsbeke, C., Ferreira, F., Nuyttens, L., Trehu, B., et al. (2015). Assessment of IPF disease pathology using functional respiratory imaging. *American Thoracic Society (ATS) International Conference.* . Denver, Colorado,USA.

Esbriet. Summary of Product Characteristics. (sd).

Fernández, P., Daniels, C., Schroeder, D., St Stauver, J., Hartman, T., Bartolmai, B., et al. (2010). Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study. *Chest*, 137(1):129.37.

Greene, K., King, T., Kuroki, Y., Bucher-Bartelson, B., Hunninghake, G., Newman, L., et al. (2002). Serum surfactant proteins-A and -D as biomarkers in idiopathic pulmonary fibrosis. *Eur Respir J (19(3)*, 439-46.

Hara, A., Sakamoto, N., Ishimatsu, Y., Tomoyuki, K., Nakashima, H., Hara, S., et al. (2012). S100A9 in BALF is a candidate biomarker of idiopathic pulmonary fibrosis. *Respir Med 106*, 571-580.

ICH E10. (2000). International Conference on Harmonisation of Technical Requirement for Registration of Pharmaceuticals for Human Use. Choice of control group and related issues in clinical trials E10.

Investigator Brochure GLPG1690, Edition 2. (October 2015).

Jenkins, G., & Goodwin, A. (2014). Novel approaches to pulmonary fibrosis. *Clin Med 14(6)*, s45-s49.

Jenkins, R., Simpson, J., Saini, G., Bentley, J., Russel, A., Braybrooke, R., et al. (2015). Longitudinal change in collagen degration biomarkers in idiopathic pulmonary fibrosis: an analysis from the prospective, multicentre PROFILE study. *Lancet Respir Med*, 1-11.

Kaminski, N., Richards, T., Baribaud, F., Flavin, S., Brodmerkel, C., Horowita, D., et al. (2012). Peripheral blood proteins predict mortality in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med 185(1)*, 67-76.

Kim, D., Collard, H., & King, T. J. (2006). Classifications and natural history of the idiopathic interstitial pneumonias. *Am Thorac Soc 3*, 285-292.

King, T., Bradford , W., Castro-Bernardini, S., Fagan, E., Glaspole, I., Glassberg, M., et al. (2014). A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Eng J Med*, 370:2083-92.

Ley, B., Collard, H., & King, T. (2011). Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med 183*, 431-440 .

Macintyre, N., Crapo, R., Johnson, D., van der Grinten, C., Brusasco, V., Burgos, F., et al. (2005). Standradisation of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J 26(4)*, 720-35.

Magkrioti, C., & Aidinis, V. (2013). Autotaxin and lysophosphatidic acid signalling in lung pathophysiology. *World J Respirol, 3(3)*, 77-103.

Meltzer, E., & Noble PW. (2008). Idiopathic pulmonary fibrosis. *Orphanet J Rare Dis 3*, 8.

Miller, M., Hankinson, J., & Brusasco, V. e. (2005). Standardisation of spirometry. *Eur Respir J, 26*, 319-338.

Montesi, S., Mathai, S., Brenner, L., Gorshkova, I., Berdyshev, E., Tager, A., et al. (2014). Docosatetraenoyl LPA is elevated in exhaled breath condensate in IPF. *BMD Pulm Med*, 14(5):1-7.

Nathan, S., & Meyer, K. (2014). IPF clinical trial design and endpoints. *Curr Opin Pulm Med 20(5)*, 463-471.

Navaratnam, V., Fleming, K., West, J., Smith, C., Jenkins, R., Fogarty, A., et al. (2011). The rising incidence of idiopathic pulmonary fibrosis in the UK. *Thorax*, 66(6):462-7.

Noble, P., Albera, C., Bradford, W., Costabel, U., Glassberg, M., Kardatzke, D., et al. (2011). Pirfenidone in patients with idiopathic pulmonary fibrosis. *Lancet*, 377:1760-9.

Ofev. Summary of Product Characteristics. (sd).

Oikonomou, N., Mouratis, M., Tzouvelekis, A., Kaffe, E., Valavanis, C., Vilaras, G., et al. (2012). Pulmonary autotaxin expression contributes to the pathogenesis of pulmonary fibrosis. *Am J Respir Cell Mol Biol*, 47(5):566-74.

Quanjer, P., Stanojevic, S., Cole, T., Baur, X., Hall, G., Culver, B., et al. (2012). Multi-ethnic reference values for spirometry for the 3-95 year age range: the global lung function2012 equations: Report of the Global Lung Function Initiative (GLI), ERS Task Force to established imrpoved Lung Function Reference Values. *Eur Respir J 40 (6)*, 1324-43.

Raghu, G., Collard, H., Egan, J., Martinez, F., Behr, J., Brown, K., et al. (2011). An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med 183*, 788-824.

Raghu, G., Rochwerg, B., Zhang, Y., Cuello Garcia, C., Azuma, A., Behr, J., et al. (2015). An official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*, 192: e3-e19.

Raghu, G., Weycker, D., Edelsberg, J., Bradford, W., & Oster, G. (2006). Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med 174*, 810-816.

Richards, T., Kaminski, N., Baribaud, F., Flavin, S., Brodmerkel, C., Horowitz, D., et al. (2012). Peripheral blood proteins predict mortality in idiopathic pulponary fibrosis. *Am J Respir Crit Care Med 185(1)*, 67-76.

Richeldi, L., du Bois, R., Raghu, G., Azuma, A., Brown, K., Costabel, U., et al. (2014). Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med*, 370:2071-82.

Rosas, I., Richards, T., Konishi, K., Zhang, Y., Gibson, K., Lokshin, A., et al. (2008). MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. *PLoS Med 5(4)*, e93.

Saketkoo, L., Mittoo, S., Huscher, D., Khanna, D., Dellaripa, P., Distler, O., et al. (2014). Connective tissue disease related interstitial lung diseases and idiopathic pulmonary fibrosis: provisional core sets of domains and instruments for use in clinical trials. *Thorax 69*, 429-436.

Spagnolo, P., Del Giovane, C., Luppi, F., Cerri, S., Balduzzi , S., Walters, E., et al. (2010). Non-steroid agents for idiopathic pulmonary fibrosis (review). *Cochrance Database Syst Rev*, Sept 8: CD003134.

Swirgis, J., Esser, D., Conoscenti, C., & Brown, K. (2014). The psychometric properties of the St George's respiratory questionnaire (SGRQ) in patients with idiopathic pulmonary fibrosis: a literature review. *Heath Qual Life Outcomes 12(124)*, 1-14.

Tager, A., LaCamera, P., Shea, B., Campanella, G., Selman, M., Zhao, Z., et al. (2008). The lysophophatidic acid receptor LPA1 links pulmonary fibrosis to lung injury by mediating fibroblast recruitment and vascular leak. *Nat Med, 14(1)*, 45-54.

Tanaka, M., Okudaira, S., Kishi, Y., Ohkawa, R., Iseki, S., Ota, M., et al. (2006). Autotaxin stabilizes blood vessels and is required for embryonic vasculature by producing lysophosphatidic acid. *J Biol Chem, 281(35)*, 25822-30.

Taniguchi, H., Ebina, M., Kondoh, Y., Ogura , T., Azuma, A., Suga, M., et al. (2010). Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J*, 35:821-9.

Thomeer, M., Costabe, U., Rizzato, G., Poletti, V., & Demedts, M. (2001). Comparison of registries of interstitial lung diseases in three European countries. *Eur Respir J Suppl*, 32:114s-118s.

Tsuda, S., Okudaira, S., Moriya-Ito, K., Tanaka, M., Aoki, J., Arai, H., et al. (2006). Cyclic phosphatidic acid is produced by autotaxin in blood. *J Biol chem, 281(36)*, 26081-8.

USNRC. (2014, Dec 12). *United States Nuclear Refulatory Commission. Fact sheet on biological effects of radiation.* Opgeroepen op Jun 05, 2015, van http://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html

Vos, W., Van Holsbeke, C., Ferreira, F., Nuyttens, L., O'Riordan, T., De Backer, J., et al. (2015). Comparison of IPF disease pathology to healthy subjects using functional respiratory imaging. *Poster presented at the American Thoracic Society (ATS) International Conference.* . Denver, Colorado,USA.

WNA. (2015, May 22). *World Nuclear Association*. Opgeroepen op Jun 05, 2015, van Nuclear radiation and health effects: http://www.world-nuclear.org/info/safety-and-security/radiation-and-health/nuclear-radiation-and-health-effects/

Xu, M., Porte, J., Knox, A., Weinreb, P., Maher, T., Violette, S., et al. (2009). Lysophosphatidic acid induces αvβ6 integrin-mediated TGF-β activation via the LPA2 receptor and the small G protein Gαq. *Am J Pathol, 174(4)*, 1264-79.

APPENDICES

Appendix 1 Study Contact Information

Role	Contact Information
SPONSOR	GALAPAGOS NV Generaal De Wittelaan, L11 A3 2800 Mechelen, Belgium
Clinical Project Manager	[redacted], MSc – Galapagos NV Tel: [redacted] Mobile: [redacted] Email: [redacted]
Medical Monitor	[redacted], MD MBA - Galapagos NV Tel: [redacted] Mobile: [redacted] Email: [redacted]
Pharmacokineticist	[redacted], PhD - Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville, France Tel: [redacted] Fax: [redacted] Email: [redacted]
Pharmacodynamic Expert	[redacted] PhD - Galapagos SASU 102 Avenue Gaston Roussel 93230 Romainville, France Tel: [redacted] Email: [redacted]
Lead Biostatistics	[redacted] MSc – Galapagos NV Tel: [redacted] Email: [redacted]

Head Clinical Operations	[redacted], PhD - Galapagos NV Tel: [redacted] Mobile: [redacted] Email: [redacted]
Development Project Leader	[redacted], PhD - Galapagos NV Tel: [redacted] Mobile: [redacted] Email: [redacted]
(Home) Spirometry and central diagnosis (HRCT & Pathology)	[redacted] Belgium Tel: [redacted] E-mail: [redacted]
Functional Respiratory Imaging	[redacted] – Project Manager Belgium Tel: [redacted] Mobile: [redacted] E-mail: [redacted]
Central Laboratory: safety lab	[redacted] Belgium Tel: [redacted] E-mail: [redacted]
Bioanalytical Laboratory (Biomarkers)	[redacted]

	[redacted] Denmark Tel: [redacted] E-mail: [redacted]
Bioanalytical Laboratory (Blood GLPG1690 PK sample analysis)	[redacted] Tel [redacted] Fax [redacted]
Bioanalytical Laboratory (Blood and BALF PD (LPA) sample analysis)	[redacted] Croatia Tel: [redacted] Fax: [redacted] E-mail: [redacted]
Packaging and Labeling	[redacted] Belgium
Pharmacovigilance	[redacted] Belgium Tel: [redacted] Email: [redacted]
Contract Research Organization	[redacted] France Tel: [redacted] Email: [redacted]

Appendix 2 HRCT/Biopsy Central Review Criteria

All chest HRCTs and histopathology slides of surgical lung biopsies (if available) will be centrally reviewed by an independent radiologist and an independent histopathologist in order to confirm the diagnosis of IPF.

Confirmed IPF Diagnosis Based on HRCT only (No Lung Biopsy Available)

In the absence of a surgical lung biopsy, HRCT must qualify as "consistent with IPF". This will be defined as meeting either criteria A, B and C, or criteria A and C, or criteria B and C provided below.

A) Definite honeycomb lung destruction with basal and peripheral predominance.

B) Presence of reticular abnormality AND traction bronchiectasis consistent with fibrosis with basal and peripheral predominance.

C) Atypical features are ABSENT, specifically: nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern.

Appearances of a fibrosing lung disease with no definite HRCT features of a specific etiology will be considered "possible IPF". Convincing HRCT appearances of a diffuse lung disease other than IPF will be considered "definitely not IPF". Subjects with "possible IPF" (unless clear IPF diagnosis based on the SLB data) and "definitely not IPF" will not be allowed for inclusion in the study.

Confirmed IPF Diagnosis Based on Both HRCT and Lung Biopsy

In the presence of a surgical lung biopsy, the histology will be reviewed, based on the most recent ATS/ERS/JRS/ALAT Guideline. In such case, there will be a multi-disciplinary team approach to confirm or exclude the diagnosis of IPF. An HRCT "possible IPF" coupled with a surgical biopsy of "definite IPF" or "probable IPF", upon multidisciplinary team discussion, could qualify for inclusion as "consistent with IPF".

The decision-schedule used to decide whether a subject is eligible for study entry is provided below.

	SLB: Definite IPF	**SLB: Probable IPF**	**SLB: Possible IPF**	**SLB: Non Classifiable IPF**
HRCT: Consistent with IPF	Eligible	Eligible	Eligible	Eligible
HRCT: Possible IPF	Eligible	Eligible	Not Eligible	Not Eligible
HRCT: Definitely not IPF	Not Eligible	Not Eligible	Not Eligible	Not Eligible

HRCT=high-resolution computed tomography; IPF=idiopathic pulmonary fibrosis; SLB=surgical lung biopsy

An overview of the histopathological criteria for definite-probable-possible-non classifiable IPF is provided below.

SLB: Definite IPF (all 4 criteria met)	**SLB: Probable IPF**	**SLB: Possible IPF (all 3 criteria met)**	**SLB: Non Classifiable IPF (any of the 6 criteria)**
– Evidence of marked fibrosis/ architectural distortion, ± honeycombing in a predominantly subpleural/ paraseptal distribution – Presence of patchy involvement of lung parenchyma by fibrosis – Presence of fibroblast foci – Absence of features against a diagnosis of IPF suggesting an alternate diagnosis (see fourth column)	– Evidence of marked fibrosis / architectural distortion, ± honeycombing – Absence of either patchy involvement or fibroblastic foci, but not both – Absence of features against a diagnosis of IPF suggesting an alternate diagnosis (see fourth column) OR – Honeycomb changes only	– Patchy or diffuse involvement of lung parenchyma by fibrosis, with or without interstitial inflammation – Absence of other criteria for IPF (see IPF PATTERN column) – Absence of features against a diagnosis of IPF suggesting an alternate diagnosis (see fourth column)	– Hyaline membranes – Organizing pneumonia – Granulomas – Marked interstitial inflammatory cell infiltrate away from honeycombing – Predominant airway centered changes – Other features suggestive of an alternate diagnosis

IPF=idiopathic pulmonary fibrosis; SLB=surgical lung biopsy

Appendix 3 DLCO

At visit 1, DLCO must meet the following criteria (Macintyre, et al., 2005):

- 30% predicted of normal ≤ DLCO corrected for hemoglobin

For predicted normal values, different sites may use different prediction formulas, based on the method used to measure DLCO. In any case, the method used must be in compliance with the ATS/ERS guideline on DLCO measurements (Macintyre, et al., 2005), and the prediction formula appropriate for that method.

Raw data (gas mixture, equation used for prediction of normal) must be captured.

DLCO corrected for hemoglobin:

- Males: DLCO corrected for hemoglobin = DLCO measured x (10.22+Hb) /1.7Hb
- Females: DLCO corrected for hemoglobin = DLCO measured x (9.38+Hb)/ 1.7Hb

Hemoglobin is expressed in g/dL.

Appendix 4 CYP3A4 Inducers

The following drugs/nutraceutics are known CYP3A4 inducers (non-exhaustive list):

- Carbamazepine
- Phenytoin
- Oxcarbazepine
- Phenobarbital
- Butalbital
- St. John's wort
- Rifampicin
- Rifabutin
- Pioglitazone
- Troglitazone
- Glucocorticoids

Appendix 5 Normal Ranges

NORMAL RANGES FOR VITAL SIGNS

SBP (mmHg)	DBP (mmHg)	Heart rate (bpm)	Oral temperature (°C)
90 ≤ SBP ≤ 150	45 ≤ DBP ≤ 90	40 ≤ HR ≤ 100	35.5 ≤ t° ≤ 37.5

NORMAL RANGES FOR ECG PARAMETERS

PR (ms)	QRS (ms)	QTcF (ms)	Heart rate (bpm)
120 ≤ PR ≤ 220	QRS ≤ 120	QTc ≤ 450	40 ≤ HR ≤ 100

These normal ranges are applicable in supine position (after 5 min).

SIGNATURE PAGE – SPONSOR

Title Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter, Exploratory Phase IIa Study to Assess Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690 Administered for 12 Weeks in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

This Clinical Study Protocol has been reviewed and approved by the sponsor to ensure compliance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Medical Lead	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Title Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter, Exploratory Phase IIa Study to Assess Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690 Administered for 12 Weeks in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

I, the undersigned, have read this protocol and will conduct the study as described in compliance with the Clinical Study Protocol, in accordance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Investigator Name	Signature	Date

Galápagos

CLINICAL STUDY PROTOCOL AMENDMENT

Project Number:	GLPG1690
Study Number:	GLPG1690-CL-202
Amendment Type:	CSPA-GEN-I
Study Title:	Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter, Exploratory Phase IIa Study to Assess Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690 Administered for 12 Weeks in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Development Phase:	IIa
Status:	Final
Version:	1.0
Date:	19-Dec-2016
EudraCT:	2015-004157-41
IND:	Enter the IND number
Sponsor:	Galapagos NV Industriepark Mechelen Noord Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium
Medical Lead:	[redacted], MD, MSc Tel: [redacted] Mobile: [redacted]
Clinical Study Lead:	[redacted], MSc Tel: [redacted] Mobile: [redacted]

TABLE OF CONTENTS

1. RATIONALE

The description for storage and use of left over BALF samples was missing while the purpose of these samples is fully explained in the PIS/ICF. The protocol is updated to align both documents, to correct typo's and to record the change of Medical Monitor and Medical Lead responsibility. These updates are considered **non-substantial**.

2. SUMMARY OF CHANGES FROM PREVIOUS VERSION

Section	Summary of Changes
Cover page	Update Medical Lead
Emergency Contact information	Update Medical Monitor
4.1	Correct typo in section 4.1: Week 98 [Day 98] should be Week 14 [Day 98].
5.4.5	Correct typo for reference to Appendix 4, should be Appendix 5
5.8	Text corrected to align with the approved PIS/ICF

3. CHANGES IN TITLE PAGE

Medical Lead: [redacted] ~~MD MBA~~
~~Tel:~~ [redacted]
~~Mobile:~~ [redacted]

Medical Lead: [redacted], MD, MSc
Tel: [redacted]
Mobile: [redacted]

EMERGENCY CONTACT INFORMATION

In case of **medical questions during the course of the study**, the investigator must contact:

Europe:

[redacted] ~~MD~~
[redacted]
~~UKRAINE~~
[redacted]

[redacted]

~~In case of urgent medical questions, the investigator should call the 24/7 emergency #:~~

[redacted]

[redacted], MD
[redacted]
[redacted]
[redacted] Ukraine

[redacted]

In case of **urgent medical questions**, the investigator should call the 24/7 emergency #:

[redacted]

4. CHANGES IN CLINICAL STUDY SPECIFIC PROCEDURES

Change in section 4.1. Overall Study Design

…

The subjects will visit the clinical study center at screening (Day-28 to Day -4), Day -1 (baseline), Week 1 (Day 7), Week 2 (Day 14), Week 4 (Day 28), Week 8 (Day 56), and Week 12 (Day 84) or the early discontinuation visit (EDV). In addition, a follow-up visit will be planned 2 weeks after the last administration of study drug (~~Week 98~~ **Week 14** [Day 98]). Each subject will be in the study for up to approximately 18 weeks (from screening to follow-up). The end of the study (EOS) will be defined as the last contact with the last subject in the study.

Change in section 5.4.5 Electrocardiogram

A 12-lead ECG will be performed predose at the time points indicated in the study flow chart (provided in Section 1) and according to sequence of study assessments as described in Section 5.1. The ECG must be taken after 5 min in the supine position, prior to any blood sampling. Each ECG will be interpreted by the investigator for clinical significance.

Normal ranges are provided in ~~Appendix 4~~ **Appendix 5**

Change in section 5.8. Total Blood Volume

…

After the study is completed, any left-over blood samples **and bronchoalveolar lavage samples** may be stored under the control of the sponsor. These samples may be used by the sponsor/partner, or by other companies belonging to the sponsor for future research on the mode of action of GLPG1690 and/or future research in IPF.

SIGNATURE PAGE – SPONSOR

Title Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter, Exploratory Phase IIa Study to Assess Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690 Administered for 12 Weeks in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

This Clinical Study Protocol Amendment has been reviewed and approved by the sponsor to ensure compliance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

[redacted]

Medical Lead	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Title Randomized, Double-Blind, Parallel Group, Placebo-Controlled, Multicenter, Exploratory Phase IIa Study to Assess Safety, Tolerability, Pharmacokinetic and Pharmacodynamic Properties of GLPG1690 Administered for 12 Weeks in Subjects with Idiopathic Pulmonary Fibrosis (IPF)

I, the undersigned, have read this Clinical Study Protocol Amendment and will conduct the study as described in compliance with the Clinical Study Protocol Amendment, in accordance with International Conference on Harmonization (ICH) guidelines for Good Clinical Practices (GCP) and applicable regulatory requirements.

Investigator Name	Signature	Date