Galápagos

CLINICAL STUDY PROTOCOL

Project Number:	GLPG1205
Study Number:	GLPG1205-CL-220
Study Title:	A Phase II randomized, double-blind, placebo-controlled, 26-week study to evaluate the efficacy, safety and tolerability of GLPG1205 in subjects with idiopathic pulmonary fibrosis
Development Phase:	II Status: Final
CSP Version:	3.00 **Date:** 30-Apr-2020
Amendment:	2
EudraCT:	2017-004302-18
CT.gov No.:	NCT03725852
IND No.:	Not applicable
Sponsor:	Galapagos NV Generaal De Wittelaan L11 A3 2800 Mechelen, Belgium
Study Physician:	[redacted], MD
General Protocol	

EMERGENCY CONTACT INFORMATION

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

[redacted] Fax #: [redacted]

or

E-mail: [redacted]

In case of **medical questions during the course of the study**, the investigator must contact the contract research organization (CRO) Medical Monitor or, if unavailable, his/her back up.

CRO Medical Monitor:

[redacted], [redacted], [redacted]

Back up:

[redacted], [redacted], [redacted]

Sponsor Back-up contact:

[redacted]

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CLINICAL STUDY PROTOCOL HISTORY

CSP / Amendment #	Date	General / Country Specific
CSP Version 1.00	30-Mar-2018	General
CSP Version 1.00 Amendment 1	12-Sep-2018	[redacted]
CSP Version 1.00 Amendment 1	12-Sep-2018	[redacted]
CSP Version 2.00 Amendment 1	24-Jan-2019	General
CSP Version 3.00 Amendment 2	30-Apr-2020	General

SUMMARY OF CHANGES

Amendment 2 Global (dated 30 Apr 2020)

The overall reason for this amendment:

The main reason for this amendment is to include the Urgent Safety Measures (USMs dated 02-April-2020) in the clinical study protocol. These USMs aim to mitigate the risk for patients diagnosed with idiopathic pulmonary fibrosis (IPF) participating in the GLPG1205-CL-220 (PINTA) study with regard to the Coronavirus 2019 disease (COVID-19) pandemic.

To this end, the visit window at the end of the treatment period (Visit 9, Week 26) is enlarged (from -28 days up to +56 days) including extension of study medication intake, i.e. up to a maximum of 56 days beyond 26 weeks of treatment.

The chronic preclinical good laboratory practice toxicology studies up to a duration of 39 weeks support this approach (see Section 2.1.4 of this clinical study protocol and the Investigator's Brochure). Furthermore, the 2 reviews of unblinded PINTA study data by the independent Data Monitoring Committee have not raised any safety concerns.

In addition, the window for the End of Study follow-up Visit 10 (± 4 days) is increased to -7 days up to +28 days.

If the originally planned Visit 9 or Visit 10 are postponed, then an alternative approach is to conduct unscheduled remote or home visits at that initial visit date, and thereafter at least every 14 days until the newly scheduled Visit 9 or Visit 10 can be performed on site within the enlarged visit window.

Alternative visit strategies applicable for Visits 3 to 8 and the early end of treatment Visit (EOT) are also included in this amendment, as well as the option of direct-to-patient shipment of the Investigational Medical Product (IMP) in case a subject is not able to visit the site for IMP resupply.

The measures intend to mitigate the impact of the current COVID-19 pandemic for the participating IPF subjects. The objective is to reduce the risk of infection for the participating subjects by increasing the flexibility of study visits and thereby avoiding exposure risk.

Due to COVID-19 measures, for individual subjects the overall study duration may be extended up to a maximum of 84 days (12 weeks) from the originally planned duration.

The changes made to the general clinical study protocol version 2.0, dated 24-Jan-2020, are described below, with a brief rationale / description of each change and the applicable sections.

Amendment 2 Global (dated 30 Apr 2020)
Increase of Visit 9 and Visit 10 windows due to the COVID-19 pandemic. **Applicable Sections:** 6.1 Timing of Assessments 6.1.1 Description of Visits 6.10 Schedule of Activities
Addition of an alternative approach for scheduling Visit 9, Visit 10, and early EOT Visit due to the COVID-19 pandemic. **Applicable Sections:** 6.1.1 Description of Visits 6.10 Schedule of Activities
Addition of instructions for Unscheduled Visits due to the COVID-19 pandemic. **Applicable Sections:** 6.1 Timing of Assessments 6.2 Unscheduled Visits
Addition of an alternative approach for scheduling Visit 3 to Visit 8 due to the COVID-19 pandemic. **Applicable Sections:** 6.1.1 Description of Visits
Enabling Direct-to-patient (DTP) shipment of the IMP due to the COVID-19 pandemic. **Applicable Sections:** 5.3 Packaging, Labeling, and Distribution

Amendment 1 Global (dated 24 Jan 2019)
The overall reason for this amendment: The main reasons for this amendment are: clarification of the protocol; incorporation of feedback from health authorities (including changes made in local amendments), ethics committees and investigators; updates to permitted and prohibited concomitant medications; clarification of safety monitoring; and enhancing the feasibility of the study.
The changes made to the general clinical study protocol version 1.0, dated 30-Mar-2018, are described below, with a brief rationale / description of each change and the applicable sections.
Incorporation of changes made in 2 local amendments, Amendment 1 [redacted] and Amendment 1 [redacted] as detailed in the summary of changes for each local amendment below. **Applicable Sections:** 2.3.2 Clinical Study Design Rationale 4.3.3 Exclusion Criteria 4.3.4.2 Prior and Concomitant Medications
The study physician has changed, and the CT.gov number has been added. **Applicable Section:** Title page Sponsor Signature page

Amendment 1 Global (dated 24 Jan 2019)
The protocol has been edited for clarity and minor corrections have been made. **Applicable Section:** Throughout the protocol
The secondary objective/endpoints evaluating time to major clinical endpoints has been modified: – "All cause mortality" will be assessed in addition to only respiratory-related mortality to complement this endpoint. – "Need for placement on the lung transplant list" was removed because of differences in management of transplants and lists of candidates between countries preventing the analysis as an aligned endpoint. This event has also been removed from the events that will be adjudicated. **Applicable Sections:** Summary Section 3.2 Secondary objectives Section 4.1.2 Secondary endpoints Section 6.4.3 Clinical Endpoints Section 7.3.4.2 Secondary Efficacy Endpoints Analysis Section 8.2 Clinical Endpoint Adjudication
Eligibility criteria – Inclusion criterion 3: The time from first diagnosis of idiopathic pulmonary fibrosis (IPF) has been increased from 3 years to 5 years, to facilitate recruitment to the study considering the longer survival rates after introduction of nintedanib and pirfenidone as standard of care treatments for IPF, and to align with other Phase 3 studies in IPF. The diagnostic guideline used should be that applicable at the time of diagnosis of IPF. Accordingly, a patient diagnosed in 2015 is eligible using the 2011 American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) guidelines, but a new diagnosis should follow the 2018 guidelines. The references have been updated. The requirement for subjects receiving treatment with pirfenidone or nintedanib to be on a stable dose for at least 8 weeks before screening, and during screening has been introduced. A stable dose is defined as the highest tolerated dose. – The prednisone (or equivalent) dose allowed has been reduced to ≤10 mg/day (inclusion criterion 3 and exclusion criterion 18) to reduce background medications with drug-drug interaction (DDI) potential (cytochrome P450 3A4 [CYP3A4] inducer). – All forms of lung biopsy will be accepted, rather than only surgical lung biopsy (inclusion criterion 4). – The definition of disease progression within the last 9 months as assessed by forced vital capacity has been clarified (inclusion criterion 5). – The requirement for stability of co-medication for pre-existing conditions has been restricted to treatment for chronic diseases and conditions, and the stability of treatment relaxed to limit only to clinically relevant changes (inclusion criterion 6 and Section 4.3.4.2) to reflect the real life situation of the patient and to facilitate study participation of IPF subjects. – The requirements for completion of the 6-Minute Walk Test have been further clarified (inclusion criterion 9) by adding "without a condition putting the subject at risk of falling during the test (at investigator's discretion). The use of a cane is allowed, while the use of a stroller is not allowed at all, under any circumstances". – Exclusion criterion 2 has been modified to exclude only a current immunosuppressive condition.

Amendment 1 Global (dated 24 Jan 2019)

- The exclusion criterion 3 hepatitis test requirements have been modulated because GLPG1205 is not a strong immunosuppressor and the risk for hepatitis reactivation is considered to be low. The following changes have been made:
- Hepatitis B surface antigen and hepatitis B core antibody have been replaced with hepatitis B surface antigen only
- Hepatitis C virus (HCV) antibody testing is replaced with an assay for anti-HCV antibody that is, if positive, confirmed by HCV RNA positivity
- "History of hepatitis from any cause with the exception of hepatitis A" has been removed, and replaced with "Subjects with a resolved hepatitis A at least 3 months prior to first dosing of the investigational medicinal product (IMP) can be included."
- Addition of moderate to severe liver impairment to exclusion criterion 13 to increase the safety of the subjects and to be in line with Section 2.4.
- The threshold for creatinine clearance defining abnormal renal function in exclusion criterion 14 has been lowered from <60 mL/min to <30 mL/min, to reflect the advanced age of IPF population and considering the limited renal excretion of GLPG1205.
- Exclusion criterion 15 excludes subjects who underwent major surgery within 3 months prior to screening or who have major surgery planned during the study period. A note that being on a lung transplant list is allowed has been added because being on a list is not associated with a high chance of a lung transplant occurring and should not exclude the patient from treatment in the study.
- The minimum interval between participation in a drug, device or biologic investigational research study and this study has been set as within 12 weeks or 5 half-lives of the agent whichever is longer (exclusion criterion 17).
- Additional medications have been added to exclusion criterion 19 for subjects on medications with known drug-drug interactions (DDI) with GLPG1205
  - Medications which are known dual CYP3A4 and CYP2C19 inhibitors (non-exhaustive list provided in Appendix 8). Rationale: GLPG1205 primary metabolism pathways are CYP3A4 and CYP2C19. A strong inhibition of those pathways could lead to increased exposure to GLPG1205 and potential safety/tolerability issues.
  - Medications which are known to be CYP3A4 or CYP2C19 strong inducers (non-exhaustive list provided in Appendix 9). Rationale: GLPG1205 primary metabolism pathways are CYP3A4 and CYP2C19. A strong induction of these pathways could lead to decreased exposure to GLPG1205 and lack of efficacy.

Applicable Section:

Section 4.3.2 Inclusion Criteria

Section 4.3.3 Exclusion Criteria

Section 4.3.4.2 Prior and Concomitant Medications

Section 6.5.2 Clinical Laboratory Evaluations

Appendix 1 High-resolution Computed Tomography/Biopsy Central Review Criteria

Appendix 8 Non-exhaustive List of Medications Known to be Dual Inhibitors of CYP3A4 and CYP2C19 Enzymes

Appendix 9 Non-exhaustive List of Medications Known to be Strong Inducers of CYP3A4 or CYP2C19

Amendment 1 Global (dated 24 Jan 2019)

The prohibition of medications known to prolong QT interval has been removed because there is no evidence for QT prolongation potential when taking GLPG1205 in the existing

- nonclinical (hERG assay, monkey telemetry) and
- clinical data (new GLPG1205 concentration/QTcF analysis of single-read electrocardiogram (ECG) data from the first in human single ascending dose (SAD)/multiple ascending dose (MAD) study in healthy subjects showing no significant relationship between deltaQTcF and GLPG1205 concentrations for the range of exposures investigated and also that all 90% for delta/deltaQTcF estimated at C_{max} of each cohort were below 10 ms).

Instead, chronic use or initiation of medication known to prolong the QT interval needs to be evaluated on a case-by-case basis.

- A list of medications that should be used with caution has been added in Appendix 10 as guidance (non-exhaustive list).
- Exclusion criterion 6 excluding subjects using medications known to prolong QT interval has been removed.
- Exclusion criterion 5 defining QTc findings for exclusion of subjects from the study has been clarified.
- The rule for discontinuation of subjects based on QTc interval has been adjusted to an increase from baseline (Visit 2) in QTcF of >60 ms or QTcF ≥501 ms (in line with CTCAE Version 5.0 Grade 3) on at least 2 separate ECGs at the same visit.
- Vital signs and ECG normal ranges have been adjusted to better reflect the IPF patient population.

Applicable Sections:

Section 2.4 Potential risks and benefits

Section 4.3.3 Exclusion criteria

Section 4.3.4.2 Prior and concomitant medications

Section 4.3.5 Removal of subjects from therapy or assessments

Section 6.5.4 12-lead electrocardiogram

Appendix 4 Normal ranges

Appendix 8 Medications known to prolong QT interval

The categories of liver function test findings that should lead to discontinuation of treatment with IMP have been revised in line with guidance on drug-induced liver injury (US Food and Drug Administration. Guidance for Industry. Drug-Induced Liver Injury: Premarketing Clinical Evaluation. 2009).

Applicable Section:

Section 4.3.5 Removal of subjects from therapy or assessments

Amendment 1 Global (dated 24 Jan 2019)
The instruction to withdraw subjects from the study if IMP is interrupted for more than 10 days has been removed and replaced with "investigator may also decide to stop the treatment in case of interruption of IMP for cumulatively >30 days" to give the investigator more freedom to operate and to keep the IPF patient in the study. Subjects who are discontinued from IMP will be requested to complete the end of treatment (EOT) and end of study (EOS) visits per protocol, discontinuation should remain in the judgement of the investigator. **Applicable Section:** Section 4.3.5 Removal of subjects from therapy or assessments Section 5.2 Dosage and administration
For screening, the conditions in which assessments may be repeated have been added, and rescreening of a patient is allowed once. **Applicable Section:** Section 6.1 Timing of assessments
The timing of the quality of life St. George's Respiratory Questionnaire (SGRQ) questionnaire has been changed: it is recommended that it is performed before any other visit-related procedures to minimize the procedure-dependent bias on the quality of life assessment. **Applicable Section:** Section 6.1 Timing of assessments
[redacted]
The list of clinical laboratory tests has been revised to reflect the standard panel of investigations typically used in the IPF patient population. Creatine kinase (CK) has been added to the chemistry panel of safety laboratory assessments to ensure adequate monitoring of subjects who may be receiving statins during the clinical trial. Rationale: GLPG1205 is currently in clinical development in IPF and it is estimated that in the IPF population, approximately 30% of the subjects will be on statin background therapy for managing dyslipidemia. Despite generally displaying a safe profile, there has been occurrences of raised levels of plasma concentration of some statins (simvastatin, atorvastatin, cerivastatin, lovastatin, rosuvastatin, pravastatin, and fluvastatin) when used in conjunction with other drugs, which led to the serious rare occurrence of rhabdomyolysis. Statins have different pathways involved in their disposition (either via metabolic enzymes and/or via transporters). Since it cannot be ruled out that GLPG1205 could interfere with some of those pathways (leading to cumulative net effect difficult to predict from in vitro studies), and no in vivo clinical drug-drug interaction studies have been conducted yet, there is a need to further monitor subjects who may be on statin background therapy by including monitoring of CK in the clinical safety lab panel. **Applicable Section:** Section 4.3.4.2 Prior and concomitant medications Section 6.5.2 Clinical laboratory evaluations

Amendment 1 Global (dated 24 Jan 2019)
The definition of the Full Analysis Set has been revised to remove the requirement to have postbaseline efficacy data (and the Safety Analysis Set was removed because it duplicated the revised definition of the Full Analysis Set). **Applicable Section:** Section 7.2.3 Full analysis set
The information provided to comply with the EU General Data Protection Regulation, has been summarized to describe the subject's data protection as embodied in the new regulation. **Applicable Section:** Section 10.3 Confidentiality
The definition of an acute IPF exacerbation has been updated to be in line with the most recent criteria. **Applicable Section:** Appendix 2
The contraindications for the 6-Minute Walk Test have been corrected; Oxygen saturation measured by pulse oximetry should be <88% (not <83%) after 10 minutes of rest of breathing room air or at baseline oxygen flow rate. **Applicable Section:** Appendix 3 Contraindication for the 6-minute Walk Test
The normal ranges and thresholds for abnormalities for vital signs and electrocardiogram parameters have been adapted to better reflect the IPF patient population. The HR lower bound has been changed from <40 bpm to ≤50 bpm (vital signs and ECG assessments); the PR lower bound has been changed from 110 to 120 ms; and the systolic blood pressure upper bound has been changed from 140 to 150 mmHg. **Applicable Section:** Appendix 4 Normal ranges

Amendment 1 [redacted] (dated 12-Sep-2018)
The overall reason for this amendment: In response to a specific request [redacted], a new version of the clinical study protocol (CSP) has been created, specific for [redacted]
The change made to the general clinical study protocol version 1.0, dated 30-Mar-2018, is described below, reflecting a brief rationale of each change and the applicable sections. The corrections herewith were highlighted in ***bold italic*** in the applicable sections.
Clarification of the recommendations related to the use of nintedanib or pirfenidone, which should be administrated according to the local SmPCs, as done in normal clinical practice. **Applicable Section:** 4.3.4.2 Prior and Concomitant Medications

Amendment 1 [redacted] (dated 12-Sep-2018)
The overall reason for this amendment: In response to a specific request [redacted], a new version of the clinical study protocol (CSP) has been created, specific for [redacted]
The changes made to the general clinical study protocol version 1.0, dated 30-Mar-2018, are listed below, reflecting a brief rationale of each change and the applicable sections. The corrections herewith were highlighted in ***bold italic*** in the applicable sections.
The use of ambrisentan was part of the exclusion criteria. This criterion was updated to exclude all other endothelin inhibitors (e.g. bosentan and macitentan). In addition, the occasional use of sildenafil was deleted as requested by the authorities. Other minor changes were done in this section. **Applicable Sections:** 2.3.2 Clinical Study Design Rationale 4.3.3 Exclusion Criteria

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

6MWT	6-Minute Walk Test
AE	adverse event
ALAT	Latin American Thoracic Association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the plasma drug concentration-time curve
AUEC	area under the effect-time curve
BCRP	breast cancer resistance protein
BLM	bleomycin
C_{avg}	average plasma concentration
CK	creatine kinase
C_{max}	maximum observed plasma concentration
COVID-19	Corona virus disease 2019
CRF	case report form
CRO	contract research organization
CSP	clinical study protocol
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DBP	diastolic blood pressure
DLCO	diffusing capacity for the lungs for carbon monoxide
DNA	deoxyribonucleic acid
DTP	direct-to-patient
ECG	electrocardiogram
EMA	European Medicines Agency
E_{max}	maximum effect (expressed as a % reduction from baseline)
EOT	end of treatment
ERS	European Respiratory Society
EU	European Union
FDA	Food and Drug Administration
FEF_{25-75}	forced expiratory flow between 25% and 75% of exhaled volume
FEV_1	forced expiratory volume in one second

FFA	free fatty acid
FFA1, FFA2, FFA3, FFA4	free fatty acid sensing receptors
[redacted]	[redacted]
[redacted]	[redacted]
FSH	follicle stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GPCR	G protein-coupled receptor
HBs Ag	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration (concentration resulting in 50% inhibition)
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMP	investigational medicinal product
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IWRS	interactive web response system
JRS	Japanese Respiratory Society
LB	lung biopsy
LFT	liver function test(s)
MAD	multiple ascending dose
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MRP2	multidrug resistance-associated protein 2
NOAEL	no observed adverse effect level

OCT	organic cation transporter
[redacted]	[redacted]
P-gP	P-glycoprotein
PK	pharmacokinetic(s)
q.d.	*quaque die*, once daily
QTc	corrected QT interval
QTcF	QT interval corrected for the heart rate using Fridericia's formula
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SGRQ	St. George's Respiratory Questionnaire
SUSAR	suspected unexpected serious adverse reaction
TBL	total bilirubin
TEAE	treatment emergent adverse event
[redacted]	[redacted]
ULN	upper limit of normal
US	United States

Definition of Terms

QTcF	QTcF = QT x $(1000/RR)^{1/3}$ with RR= direct ECG measurement of the distance between R waves in msec

1. SUMMARY

Rationale:

Idiopathic pulmonary fibrosis (IPF) is a chronic and progressive lethal lung disease for which two oral treatments (pirfenidone and nintedanib) are approved in the European Union (EU), United States (US) and other regions around the world.

These treatments appear to slow disease progression however, the residual decline in lung function (as measured by forced vital capacity [FVC]) remains substantial. In addition, both compounds are frequently associated with side effects potentially limiting the use in clinical practice.

There thus remains a significant unmet medical need for the development of additional therapies targeting different disease pathways that could potentially prove to be more effective by further preventing the decline in FVC with an acceptable safety profile.

Recent published data suggest the relevance of GPR84 in fibrotic pathways. In humans, first signs of clinical efficacy have been shown in a clinical study in subjects with IPF investigating a compound targeting GPR84 as well as GPR40. It thus can be anticipated that compounds targeting GPR84 could lead to a new class of therapy for IPF.

GLPG1205 is a novel, selective, and potent GPR84 antagonist, which has shown a good safety and tolerability profile at the targeted dose of 100 mg once daily (quaque die [q.d.]) in clinical studies.

Consequently, it seems appropriate to investigate the efficacy, safety, tolerability and pharmacokinetics (PK) of GLPG1205 compared to placebo in subject with IPF on top of local standard of care (defined as receiving nintedanib, pirfenidone, or neither nintedanib nor pirfenidone).

Objectives:

Primary Objective

- To evaluate the efficacy of GLPG1205 treatment in subjects with IPF on pulmonary function as evaluated by FVC compared to placebo over 26 weeks.

Secondary Objectives

- To evaluate the safety and tolerability of GLPG1205 treatment compared to placebo over 26 weeks.
- To evaluate the impact of GLPG1205 treatment compared to placebo on time to any major events (whichever occurs first) defined as:
  - Mortality (all cause and respiratory-related)
  - Hospitalization (all-cause and respiratory-related)
- To evaluate the changes from baseline in functional exercise capacity measured by the 6-Minute Walk Test (6MWT), in IPF subjects treated with GLPG1205 compared to placebo at Week 26.
- To evaluate the changes in quality of life measures in IPF subjects treated with GLPG1205 compared to placebo over 26 weeks.
- To evaluate the PK of GLPG1205, nintedanib and pirfenidone in IPF subjects.

Other Objectives

[redacted]

Endpoints:

Primary Endpoint

– Change from baseline in FVC (mL) over 26 weeks compared to placebo.

Secondary Endpoints

– Safety and tolerability changes over time (baseline to 26 weeks).
– Time to any major events (whichever occurs first) defined as:
  • Death (all-cause and respiratory-related)
  • First hospitalization (all-cause and respiratory-related)
– Change from baseline in functional exercise capacity, assessed by the 6MWT at Week 26.
– Change from baseline until 26 weeks in quality of life measures, assessed by the St. George's Respiratory Questionnaire (SGRQ) total score and domains and proportion of SGRQ responders.
– Plasma concentrations of GLPG1205, nintedanib and pirfenidone.

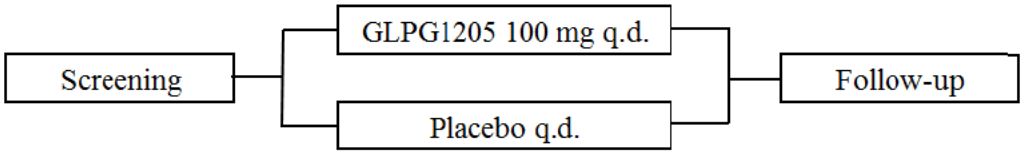
Other Endpoints

[redacted]

Design:

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

Approximately 60 eligible subjects with a centrally confirmed IPF diagnosis are planned to be randomized in a 2:1 ratio to GLPG1205 100 mg (q.d.) taken as 2 capsules, or matching placebo q.d. administered for 26 weeks on top of local standard of care. Standard of care is defined as receiving nintedanib, pirfenidone or neither nintedanib nor pirfenidone. Randomization will be stratified for background standard of care.



The subjects will be in the study for a duration of approximately 34 weeks: up to 4 weeks of screening, 26 weeks of treatment, and 4 weeks of follow-up.

2. INTRODUCTION

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 [1]. 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) [2, 3, 4, 5, 6].

The estimated IPF prevalence ranges from 14.0 to 27.9 cases per 100,000 population in the US and from 1.3 to 23.4 cases per 100,000 population in Europe (data from 1990-2011). The estimated IPF incidence 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 [7, 8, 9, 10]. The incidence and prevalence of IPF increases dramatically with age; and in patients >65 years, the estimated prevalence of IPF is as high as 400 cases per 100,000 people [11].

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 biological processes that drive fibrosis, are currently approved in the European Union, the United States, and other regions around the world.

- Pirfenidone (antifibrotic, anti-inflammatory 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 demonstrated that the drug improved progression-free survival and slowed the decline in FVC. Moreover, pirfenidone may have a mortality benefit [12, 13, 14, 15]. 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 in subjects with IPF. A trend towards a reduced death rate was also observed; however, the studies were not powered to detect differences in mortality [16]. 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 (e.g. gastrointestinal related side effects) potentially limiting the use in clinical practice [17, 18, 19].

There thus remains a significant unmet medical need for the investigation and development of novel IPF treatments targeting disease-relevant pathways. Several other candidate treatments with different mechanism of action are currently in Phase II and III or in earlier phases of clinical development. Considering the progressive and irreversible nature of this disease, it is highly desirable to evaluate efficacy of new potential treatments when added on top of the local standard of care.

Over the last decade, a growing number of G protein-coupled receptors (GPCRs) have been identified for which the ligands are energy substrates or metabolic intermediates. Free fatty acids (FFAs) have been reported to activate different GPCRs, including FFA1, FFA2, FFA3, FFA4, and GPR84. These FFA-sensing receptors are proposed to play important roles in the pathophysiology of a variety of diseases, including neuro-inflammatory diseases and metabolic disorders. GPR84 has been described as a pro-inflammatory receptor. The ligand-induced activation of GPR84 mediates both activation and migration of neutrophils and

macrophages, which play crucial roles in the maintenance of homeostasis in several clinical pathologies such as neuro-inflammation, metabolic disorders, chronic pain and fibrotic diseases like pulmonary fibrosis.

Moreover, nonclinical effects with GLPG1205, a GPR84 antagonist, in disease-relevant models suggest an important role for the receptor in the pathogenesis of pulmonary fibrosis.

GPR84 has been described to play an important role in fibrotic processes, which is demonstrated with GPR84 knock-out mice that displayed significantly reduced kidney fibrosis compared to wild type mice in a chronic kidney model induced with adenine-supplemented diet [20]. In addition, PBI-4050 a compound in clinical development targeting GPR84 as well as GPR40, has shown benefit in patients with IPF with and without addition of nintedanib [21].

GLPG1205 is a novel, potent and selective inhibitor of GPR84, and the first of its class in clinical development for the oral treatment of pulmonary fibrosis. In the following, a summary of the nonclinical and clinical development of GLPG1205 is presented. For full details, the reader is referred to the most current version of the investigator brochure (IB) and any relevant addenda.

2.1. BACKGROUND - NONCLINICAL STUDIES

2.2. BACKGROUND - CLINICAL STUDIES

2.2.1. Clinical Pharmacokinetics

At the time of study initiation, GLPG1205 or placebo had been administered to 98 healthy subjects in total in 4 Phase I clinical studies for which results have been reported. Additionally, 63 subjects with moderate to severe ulcerative colitis had been exposed to GLPG1205 100 mg q.d. or placebo for 12 weeks in one Phase II clinical study.

In healthy male subjects, GLPG1205 was rapidly absorbed with a median time to maximum plasma concentration of 2 to 4 hours. After q.d. oral dosing for 14 days, steady state in GLPG1205 plasma concentrations was reached by Day 10, with an overall accumulation ratio of 5.4 which is consistent with the long half-life of approximately 100 h. Steady-state exposure of GLPG1205 increased in proportion between 50 to 100 mg GLPG1205 q.d. Excretion of unchanged GLPG1205 in human urine was low (<0.5% in 24 h) and rapid.

Steady-state concentrations were reached by Day 2 instead of Day 10, if a 250-mg loading dose on Day 1 was followed by a 50-mg q.d. maintenance dose up to Day 14.

After 14-day q.d. administration of 50 mg as oral dose in 3 age groups of subjects (18 to 50 years, 65 to 74 years and 75 years or older); regardless of the age, steady state was attained within 9 dosing days and despite a trend for higher exposure in the age group 65 to 74 years, there was no statistical difference in PK parameters between the 3 age groups. Based on these data it could not be concluded that age has an impact on GLPG1205 bioavailability.

The between-subject variability in GLPG1205 PK after multiple doses was low for C_{max} and AUCs as shown by maximum coefficients of variation of around 30%.

After dosing with 100 mg GLPG1205 q.d. for 13 days, co-administration with a cocktail of sensitive substrates for CYP2C9 (warfarin), CYP2C19 (omeprazole) and CYP1A2 (caffeine) on the last dosing day indicated that GLPG1205 does not interact with these CYP enzymes in human.

The oral bioavailability of GLPG1205 given as 100 mg capsules was similar to that of 90 mg as aqueous nanosuspension used in the first-in-human study (in-between-studies comparison), and was not affected by food.

The PK of GLPG1205 in subjects with ulcerative colitis were similar to those observed in healthy subjects at the same dose levels.

2.2.2. Clinical Pharmacodynamics

Both single- and multiple-dose administrations of GLPG1205 to healthy subjects result in an extensive and sustained reduction of ligand binding to the GPR84 receptor in whole blood,

suggesting that the compound could be able to prevent and/or decrease at least one step in neutrophil migration and/or activation induced by activation of the GPR84 receptor. The inhibitory effect can be maintained over 24 hours with q.d. dosing. Ligand binding inhibition (area under the effect-time curve [AUEC] and maximum effect [E_{max}]) was correlated with the exposure to GLPG1205 (C_{max} and average plasma concentration [C_{avg}]) in plasma.

2.2.3. Clinical Efficacy

So far, only patients with moderate to severe ulcerative colitis were exposed to GLPG1205 for 12 weeks. The analyses revealed no clear evidence of efficacy.

2.2.4. Clinical Safety

Administration of single (up to 800 mg) and multiple (up to 100 mg q.d. for 14 days) oral doses of GLPG1205 in healthy male subjects can be considered well tolerated. No deaths, serious adverse events (SAEs) or treatment-emergent adverse events (TEAEs) leading to study drug discontinuation were reported. The most frequently reported treatment-related TEAEs were headache and gastrointestinal disorders like nausea and all TEAEs were rated at most moderate in intensity. None of the treatment-emergent abnormalities in laboratory, electrocardiogram (ECG) and vital signs parameters or physical examination abnormalities were considered clinically significant by the investigator.

Multiple dosing with GLPG1205 200 mg q.d. (first-in-human study - multiple ascending dose [MAD] part) did not show an acceptable safety profile with three subjects discontinuing the study drug due to headache after dosing with GLPG1205. Two subjects in the GLPG1205 200 mg q.d. group showed abnormally high laboratory values for hematocrit, hemoglobin and in red blood cell count, which were considered clinically significant by the investigator. This resulted in 100 mg q.d. being considered as the maximum tolerated dose after multiple dosing, which may be used in future clinical studies with GLPG1205.

Administration of a single GLPG1205 100 mg dose in fasted or fed state and co-administration of multiple doses of GLPG1205 100 mg with a single dose of a cocktail of CYP2C9, CYP2C19 and CYP1A2 substrates was considered well tolerated. Age or administration of a GLPG1205 loading dose (250 mg) did not affect the safety profile of GLPG1205.

In a Phase II study in subjects with ulcerative colitis, 63 subjects were dosed with 100 mg GLPG1205 q.d. or placebo for up to 12 weeks. No deaths were observed. Three subjects in the GLPG1205 group presented with treatment-related SAEs: worsening of ulcerative colitis (2 subjects) and macular rash (1), which led to study discontinuation. In addition, 5 subjects reported SAEs which were not considered treatment-related by the investigator, including worsening of colitis ulcerative (1 subject), anemia (1), worsening of colitis ulcerative and anemia (1), head injury (1) and tendon rupture (1).

2.3. CLINICAL STUDY RATIONALE

IPF is a chronic and progressive lethal lung disease for which two oral treatments (pirfenidone and nintedanib) are approved in the EU and US. These treatments appear to slow disease progression however, the residual decline of FVC over one year remains substantial, with a further decline of FVC over 52 weeks of 125 mL and 114 mL in INPULSIS I and II (nintedanib) [16], respectively, and around 200 mL in the ASCEND study (pirfenidone) [15].

In addition, both compounds are frequently associated with side effects potentially limiting the use in clinical practice.

There thus remains a significant unmet medical need for the development of additional therapies targeting different disease pathways that could potentially prove to be more effective by further preventing the decline in FVC with an acceptable safety profile [22].

Recent published data suggest the relevance of GPR84 in fibrotic pathways underlined by GPR84 knock out mice used in models of kidney fibrosis [20]. In addition, PBI-4050 a compound in clinical development targeting both GPR84 and GPR40, has demonstrated first clinical benefit after 12 weeks of treatment in patients with IPF with and without addition of nintedanib [21]. It thus can be anticipated that compounds targeting GPR84 could lead to a new class of therapy for IPF.

GLPG1205 is a novel, selective, and potent GPR84 antagonist that has a good safety and tolerability profile at the targeted dose of 100 mg q.d.in clinical studies.

Consequently, it seems appropriate to investigate the efficacy, safety, tolerability and PK of GLPG1205 in subjects with IPF.

2.3.1. Dosing Rationale

A dose of 100 mg GLPG1205 administered q.d. has been selected to be evaluated for this Phase II study. It is the highest oral dose of GLPG1205 administered in healthy male subjects that can be considered safe and well tolerated for repeated administration. GLPG1205 caused an extensive and sustained reduction in ligand binding to the GPR84 receptor in whole blood, suggesting that the compound could be able to prevent and/or decrease at least one step in neutrophil and macrophage migration and/or activation induced by activation of the GPR84 receptor. The inhibitory effect can be maintained over 24h with q.d. dosing. Ligand binding inhibition (AUEC and E_{max}) was correlated with the exposure to GLPG1205 (C_{max} and C_{avg}) in plasma and at a dose of 100 mg q.d. at least 80% of binding inhibition is expected.

GLPG1205 100 mg q.d. was also used in a prior proof of concept study in which GLPG1205 or placebo was administered over 12 weeks in 63 subjects with ulcerative colitis. Overall, the intensities of the treatment-related AEs for the placebo and GLPG1205 treatment groups were moderate. There were no clinically meaningful trends in changes from baseline for any vital signs, ECG, or physical examination variables. There were no clinically relevant abnormalities reported on laboratory assessments. GLPG1205 given at repeated doses of 100 mg was, in general, safe and well-tolerated.

In light of significant unmet medical need for the investigation and development of novel IPF treatments, GLPG1205 100 mg q.d. is considered an adequate dose for the proposed proof of concept study in subjects with IPF.

2.3.2. Clinical Study Design Rationale

This is a randomized, double-blind, parallel group, placebo-controlled, multicenter, exploratory Phase II 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 (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use [ICH] E10, 2000). The 2:1 randomization to GLPG1205 100 mg avoids unnecessary exposure of subjects to placebo.

The subject eligibility criteria are typical for patient studies in IPF. The disease typically affects elderly subjects, so it was chosen to include subjects aged ≥40 years. Considering the progressive and irreversible nature of this disease, it is highly desirable to evaluate efficacy of new potential treatments when added on top of the local standard of care. Standard of care is defined as receiving nintedanib, pirfenidone, or neither nintedanib nor pirfenidone. Thus, this study will include all IPF subjects, independently of their (prior) use of standard of care. Subjects eligible for this study will be randomized to either GLPG1205 or placebo. Subjects who are either on nintedanib or pirfenidone may vary dosing during the study conduct if needed (e.g. due to dose limiting side effects) according to the discretion of the investigator. For subjects initially neither on nintedanib nor on pirfenidone, the addition of nintedanib or pirfenidone during the course of the study is allowed.

Subjects are not allowed to use non-evidenced based medication being used to treat IPF (i.e. warfarin; imatinib; endothelin inhibitors such as ambrisentan, bosentan, and macitenan; azathioprine; cyclophosphamide; cyclosporine A; methotrexate; sildenafil ; prednisone at steady dose >10 mg/day or equivalent glucocorticoid dose) within 4 weeks before screening and during screening, or planned during the study. Subjects are also not allowed to use any other experimental oral IPF therapy within 12 weeks or 5-half-lives of the agent, whichever is longer, prior to screening, or to have participated in an investigational drug antibody / biologic study within 6 months prior to screening. This is necessary in order to avoid any confounding effects these drugs may have on the safety, tolerability, PK, [redacted] endpoints evaluated in the current study.

According to the analysis of the course of disease in placebo treated IPF subjects in clinical studies over 12 months by Nathan et al. [23] approximately 9.5% IPF subjects may experience a ≥10% decline in % predicted FVC after 6 months compared with baseline. Nintedanib and pirfenidone have been shown to have a beneficial effect on the rate of decline in lung function. It is anticipated that a potential efficacious effect of GLPG1205 in IPF can be substantiated after this period of time and distinguished from individual courses of the disease in both populations – patients receiving nintedanib, pirfenidone, or neither nintedanib nor pirfenidone.

Pirfenidone is primarily metabolized in humans via CYP1A2 with minor contributions from other CYP isoenzymes. A clinical study assessing the effect of GLPG1205 on a CYP1A2 probe substrate (caffeine) demonstrated that there was no impact of GLPG1205 on the CYP1A2 probe substrate (no inhibition nor induction).

Pirfenidone is a weak P-glycoprotein (P-gp) inhibitor and is a weak CYP2C9, 2C19 or 1A2, 2D6, and 3A4 inhibitor. GLPG1205 is not an efflux substrate (P-gp, BCRP, multidrug resistance-associated protein 2 [MRP2]) and has multiple CYPs involved in its metabolism (3A4, 2C19). Consequently, the coadministration of GLPG1205 with pirfenidone should not lead to drug interactions however plasma levels of both GLPG1205 and pirfenidone will be measured and tolerability will be closely monitored.

Nintedanib is a P-gp substrate and the fraction absorbed is metabolized via hydrolytic cleavage by esterases then glucuronidation and to a lower extend by CYP3A4. From in vitro data, GLPG1205 is likely to be a weak P-gp inhibitor and the likelihood that GLPG1205 may increase exposure to nintedanib can be considered low. In addition, the US product information for Ofev (nintedanib) states that coadministration with the strong P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on C_{max} in a dedicated drug-drug interaction study. A contra-indication is not warranted but patients should be monitored closely for tolerability.

Nintedanib demonstrated in in vitro studies little or no inhibition of CYP enzymes 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 4A11, and of UGT1A1 or UGT2B7 activities and is a weak inhibitor of P-gp. GLPG1205 is not an efflux substrate (P-gp, BCRP, MRP2) and has multiple CYPs involved in its metabolism (3A4, 2C19).

Consequently, co-administration of GLPG1205 with nintedanib should not lead clinically significant to drug interactions. However, plasma concentration of both GLPG1205 and nintedanib will be measured and tolerability will be closely monitored.

2.4. POTENTIAL RISKS AND BENEFITS

As IPF is characterized by progressive worsening of dyspnea and lung function and is associated with a poor prognosis. A significant unmet medical need for the investigation and development of novel IPF treatments with different mechanism of action remains for this targeted patient population.

Nonclinical data with GLPG1205 have demonstrated efficacy in the 21-day BLM mouse model similar to nintedanib. One other compound (PBI-4050) known to target both GPR84 and GPR40 has shown signals of beneficial efficacy in patients with IPF in an open-label study. GLPG1205 is anticipated to be the first inhibitor of only GPR84 in clinical development to be investigated for the oral treatment of IPF.

As there is limited clinical experience with GLPG1205 so far, the investigational medicinal product (IMP) should not be administered to subjects with moderate to severe renal impairment or hepatic impairment (Child-Pugh B or Child-Pugh C). Based on the bioavailability and safety results of a Phase I study in elderly healthy male subjects of 65 years and older, the IMP was well tolerated and can be administered to elderly subjects.

Throughout the study, safety of the individual patient is paramount. The subjects therefore need to be closely monitored by repeated assessment of clinical and vital signs, ECG, and laboratory safety parameters.

The allowed disease-related concomitant drugs were selected to minimize the risk of drug-drug interactions. However, precautions and specific monitoring as per standard medical practice is recommended.

The most frequently reported treatment-related TEAEs so far observed in patients or healthy volunteers in clinical studies with GLPG1205 were headache and nausea and all TEAEs were rated at most moderate in intensity. Potential side effects will be closely monitored and followed-up. In case of intolerance to GLPG1205 the dose may be decreased to 50 mg q.d.

Subjects with long QT syndrome or QTcF >450 ms for males and > 460 ms for females during screening will be excluded. The chronic use or initiation of medication known to prolong the QT interval needs to be evaluated on a case-by-case basis. Monitoring via 12-lead-ECG recording with central reading will be implemented for the duration of the study. A non-exhaustive list of medications known to prolong QT interval, intended as guidance for the investigator, is provided in Appendix 10.

Due to the known dose limiting side effects of nintedanib and pirfenidone, their dose levels can be adapted, during the study treatment and follow-up periods at the discretion of the investigators if deemed necessary, following the recommendation of the respective labels.

In view of the limited knowledge of the possible effects of GLPG1205 on pregnancy and lactation at this stage of development, GLPG1205 should not be given to pregnant or lactating women. Therefore only female subjects of non-child-bearing potential or males aged ≥40 years will be enrolled in the study.

To enhance the safety of the subjects and integrity of the study data, an independent medical safety review will be implemented. (See Section 8.1 for additional information).

Please refer to the most current version of the IB of GLPG1205 for additional information and any relevant addenda.

3. STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

- To evaluate the efficacy of GLPG1205 treatment in subjects with IPF on pulmonary function as evaluated by FVC compared to placebo over 26 weeks.

3.2. SECONDARY OBJECTIVES

- To evaluate the safety and tolerability of GLPG1205 treatment compared to placebo over 26 weeks.
- To evaluate the impact of GLPG1205 treatment compared to placebo on time to any major events (whichever occurs first) defined as:
  - Mortality (all cause and respiratory-related)
  - Hospitalization (all-cause and respiratory-related)
- To evaluate the changes from baseline in functional exercise capacity measured by the 6MWT, in IPF subjects treated with GLPG1205 compared to placebo at Week 26.
- To evaluate the changes in quality of life measures in IPF subjects treated with GLPG1205 compared to placebo over 26 weeks.
- To evaluate the PK of GLPG1205, nintedanib and pirfenidone in IPF subjects.

3.3. OTHER OBJECTIVES

[redacted]

4. INVESTIGATIONAL PLAN

4.1. ENDPOINTS

4.1.1. Primary Endpoint

- Change from baseline in FVC (mL) over 26 weeks compared to placebo.

4.1.2. Secondary Endpoints

- Safety and tolerability changes over time (baseline to 26 weeks).
- Time to any of major events (whichever occurs first) defined as:
  - Death (all-cause and respiratory-related)
  - First hospitalization (all-cause and respiratory-related)
- Change from baseline 26 weeks in functional exercise capacity, assessed by the 6MWT at Week 26.
- Change from baseline until 26 weeks in quality of life measures, assessed by the St. George's Respiratory Questionnaire (SGRQ) total score and domains and proportion of SGRQ responders.
- Plasma concentrations of GLPG1205, nintedanib and pirfenidone.

4.1.3. Other Endpoints

[redacted]

4.2. OVERALL STUDY DESIGN

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

Approximately 60 eligible subjects with a centrally confirmed IPF diagnosis are planned to be randomized in a 2:1 ratio to GLPG1205 100 mg q.d. taken as 2 capsules, or matching placebo q.d. administered for 26 weeks on top of local standard of care. Standard of care is defined as receiving nintedanib, pirfenidone or neither nintedanib nor pirfenidone.

Individual dose reductions of GLPG1205 will be allowed once in case of intolerance or toxicity at the discretion of the investigator (Section 5.2). Subjects may have their dose of IMP reduced from 100 mg (2 capsules) q.d. to 50 mg (1 capsule) q.d. for the remainder of the study. Should the intolerance or toxicity continue, IMP may be discontinued, and the subject may be withdrawn from the study (refer to Section 4.3.5).

During the course of the study (post randomization) further adaptations of the treatment with nintedanib or pirfenidone due to e.g. intolerance or initiation of either nintedanib or pirfenidone is allowed based on the medical needs of the individual as judged by the investigator.

Enrolled subjects will come to the clinical study center at screening, Day 1 (baseline), Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, Week 26, and, if applicable (i.e. for

early IMP discontinuation), the end of treatment visit (EOT). In addition, a follow-up visit will be planned 4 weeks after the last administration of IMP (i.e. Week 30/EoS). The end of the study is reached when the last follow-up visit as planned according the schedule of activities (Section 6.10) of the last subject is performed.

Subjects who stop IMP early need to be encouraged to complete the EOT and follow-up visit for safety assessments and pulmonary function, but will not be obliged to do so.

To enhance the safety of the subjects and integrity of the study data, an Independent Data Monitoring Committee (IDMC) will be implemented and clinical endpoint adjudication will be performed (see Section 8 for additional information).

For the in- and exclusion criteria please refer to Section 4.3.2, "Inclusion Criteria" and Section 4.3.3, "Exclusion Criteria".

A schematic diagram of clinical study design is provided (Figure 1).

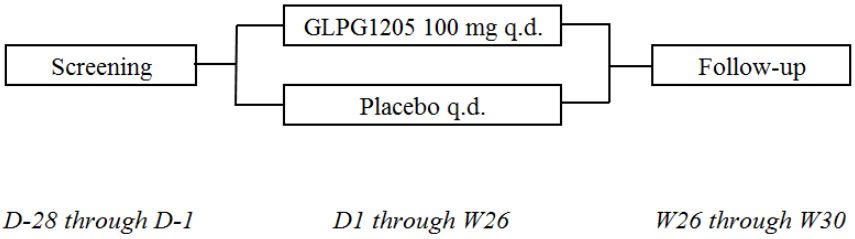


Figure 1 GLPG-1205-CL-220 Study Design

The subjects will be in the study for a duration of approximately 34 weeks: up to 4 weeks of screening, 26 weeks of treatment, and 4 weeks of follow-up.

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

4.3. STUDY POPULATION

4.3.1. Sample Size

Approximately 60 subjects are planned to be randomized into the study. In principle, it is aimed to achieve a balanced study population with regards to the background standard of care.

For the justification of sample size, including assumptions and power considerations please refer to Section 7.1 "Determination of Sample Size".

4.3.2. Inclusion Criteria

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

1. Signed informed consent form (ICF) obtained prior to any study-related procedures and/or assessments performed.
2. Males or females of non-child-bearing potential, aged ≥40 years on the day of signing the ICF.

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

- No menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level >40 IU/L
- Permanently surgically sterile (bilateral oophorectomy, i.e. surgical removal of ovaries, bilateral salpingectomy or hysterectomy, i.e. surgical removal of uterus)

3. Criterion modified per amendment.

   3.1 A diagnosis of IPF within 5 years prior to the screening visit as per applicable American Thoracic Society (ATS)/European Respiratory Society (ERS)/Japanese Respiratory Society (JRS)/Latin American Thoracic Association (ALAT) guideline [6, 24]. Subjects receiving local standard of care for the treatment of IPF, defined as either pirfenidone or nintedanib at a stable dose for at least 8 weeks before screening, and during screening; or neither pirfenidone nor nintedanib (for any reason). A stable dose is defined as the highest tolerated dose. Prednisone at steady dose ≤10 mg/day or equivalent glucocorticoid dose is allowed (stabilized 4 weeks prior to screening and continued without variation of dose or regimen). Supportive care like supplemental oxygen or pulmonary rehabilitation is allowed.

4. Criterion modified per amendment.

   4.1 Chest HRCT historically performed within 12 months prior to the screening visit and according to the minimum requirements for IPF diagnosis by central review (see Appendix 1) based on subject's HRCT only (if no lung biopsy [LB] available), or based on both HRCT and LB (with application of the different criteria in either situation). If an evaluable HRCT <12 months is not available, a HRCT can be performed at screening to determine eligibility, according to the same requirements as the historical HRCT.

5. Criterion modified per amendment.

   5.1 Meeting all of the following criteria at screening and during the screening period:

   a. FVC ≥50% predicted of normal
   b. Disease progression, defined as a decline of FVC (% predicted or mL) at the investigator's discretion, during the 9 months prior to the screening period and confirmed at the screening visit
   c. Diffusing capacity for the lungs for carbon monoxide (DLCO) ≥30% predicted of normal (corrected for hemoglobin) (see Section 6.4.4)
   d. Ratio of forced expiratory volume in one second (FEV_1) to FVC ≥0.70

6. Criterion modified per amendment.

   6.1 In a stable condition and suitable for study participation based on the results of a medical history, physical examination, vital signs, 12-lead ECG, and laboratory evaluation. Stable condition is based on the clinical judgment of the investigator, co-morbidities should be treated according to the local applicable guidelines. Concomitant medication for chronic co-morbidities should be stabilized from 4 weeks before screening and during the screening period (stable defined as no clinically relevant change according to the investigator's judgement).

7. Estimated minimum life expectancy of 12 months for non-IPF related disease in the opinion of the investigator.

8. Male subjects with female partners of child bearing potential are willing to comply with the contraceptive methods described in the protocol (see Section 4.3.4.1) prior to the first dose of the IMP, during the clinical study, and for at least12 weeks after the last dose of the IMP.
9. Criterion modified per amendment.

   9.1 Able to walk at least 150 meters during the 6MWT at screening; without having a contra-indication to perform the 6MWT (see Appendix 3), or without a condition putting the subject at risk of falling during the test (at investigator's discretion). The use of a cane is allowed, the use of a stroller is not allowed at all under any circumstances.
10. Able to understand the importance of adherence, and willing to comply to study treatment, study procedures and requirements as per study protocol, including the concomitant medication restrictions.

4.3.3. Exclusion Criteria

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

1. Known hypersensitivity to any of the IMP ingredients or a history of a significant allergic reaction to any drug as determined by the investigator (e.g. anaphylaxis requiring hospitalization).
2. Criterion modified per amendment.

   2.1 Current immunosuppressive condition (e.g. human immunodeficiency virus [HIV] infection, congenital, acquired, medication induced, organ transplantation).
3. Criterion modified per amendment.

   3.1 Positive blood testing for hepatitis B surface antigen (HB_S Ag) or hepatitis C virus antibody (if positive, confirmed by hepatitis C virus (HCV) RNA positivity). *Note:* Subjects with a resolved hepatitis A at least 3 months prior to first dosing of the IMP can be included.
4. 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, and squamous cell carcinoma of the skin if fully resected).
5. Criterion modified per amendment.

   5.1 Clinically significant abnormalities detected on 12-lead ECG of either rhythm or conduction, including prolongation of QTc or known long QTc syndrome. For any interval measurements e.g. when deciding if QT interval corrected for heart rate using Fridericia's formula [QTcF] is >450 ms [male], OR >460 ms [female], when triplicate ECG are performed (baseline), a single outlier value per interval should be considered (i.e. worst case scenario). Of note, a first-degree heart block will not be considered as a significant abnormality.
6. Criterion deleted per amendment.
7. Acute IPF exacerbation within 3 months prior to screening and during the screening period (see Appendix 2).
8. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the screening period.

9. Interstitial lung disease associated with known primary diseases (e.g. sarcoidosis, amyloidosis), exposures (e.g. radiation, silica, asbestos, coal dust), and drugs (e.g. amiodarone).
10. History of lung volume reduction surgery or lung transplant.
11. Unstable cardiovascular, pulmonary (other than IPF) or other disease within 6 months prior to screening or during the screening period (e.g. coronary heart disease, heart failure, stroke).
12. Any other clinical condition or circumstance that in the opinion of the investigator may make him or her unsuitable for inclusion or unable to complete the study or comply with study procedures and requirements.
13. Criterion modified per amendment.

    13.1 Moderate to severe hepatic impairment (Child-Pugh B or C) and/or abnormal liver function test (LFT) at screening, defined as aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) and/or bilirubin 1.5x and/or gamma glutamyl transferase (GGT) 3x upper limit of normal (ULN) range. Retesting is allowed once for abnormal LFT.

14. Criterion modified per amendment.

    14.1 Abnormal renal function defined as estimated creatinine clearance <30 mL/min using Cockcroft-Gault equation. Retesting is allowed once.

15. Criterion modified per amendment.

    15.1 Underwent major surgery within 3 months prior to screening or who has major surgery planned during the study period. Note: being on a lung transplant list is allowed.

16. Hemoglobin level <10 g/dl. Retesting is allowed once.
17. Criterion modified per amendment.

    17.1 Subject participating in a drug, device or biologic investigational research study, concurrently with the current study, within 12 weeks or 5-half-lives of the agent , whichever is longer, prior to screening, or prior participation in an investigational drug antibody/biologic study within 6 months prior to screening.

18. Criterion modified per amendment.

    18.1 Use any of the following therapies within 4 weeks before screening and during screening, or planned during the study:

    a. Warfarin
    b. Imatinib
    c. Endothelin receptor antagonists (e.g. ambrisentan, bosentan and macitentan)
    d. Azathioprine
    e. Cyclophosphamide
    f. Cyclosporine A
    g. Methotrexate
    h. Sildenafil
    i. Prednisone at steady dose >10 mg/day or equivalent

19. Criterion modified per amendment.

19.1 Use any of the following therapies within 5 half-lives before screening and during screening, or planned during the study

a. medications which are known BCRP substrates (see Appendix 5)
b. medications which are known dual CYP3A4 and CYP2C19 inhibitors (see Appendix 8)
c. medications which are known to be CYP3A4 or CYP2C19 strong inducers (see Appendix 9)

20. Current alcohol or substance abuse in the opinion of the investigator.

4.3.4. Prohibition and Restrictions

4.3.4.1. Precautions for Sexual Intercourse

Highly effective contraceptive measures for males must be documented in the source documents.

Non-vasectomized male subjects with female partners of childbearing potential must be willing to use a condom from the time of the first dose of IMP, during the clinical study, and for at least 12 weeks after the last dose of IMP, in addition to having their female partner use one of the following forms of contraception:

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

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

In case where the female partner of a male subject has undergone documented surgical sterilization (bilateral oophorectomy, i.e. surgical removal of ovaries, bilateral salpingectomy or hysterectomy, i.e. surgical removal of uterus) that was performed more than 1 year before screening, then the subject is not required to use an additional form of contraception.

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

No sperm donation is allowed from first dose of the clinical study during the clinical study until 12 weeks after the last dose.

4.3.4.2. Prior and Concomitant Medications

Concomitant therapies taken for the long-term treatment of preexisting chronic conditions can continue during the study provided they are in accordance with the inclusion and exclusion criteria (see Section 4.3.2 and Section 4.3.3, respectively). All concomitant medicines must be locally approved and administered at a dose that is considered standard-of-care for the treated indication. It is required that these medications be stabilized prior to study entry and if

possible continued without clinically relevant changes (at the discretion of the investigator) during the study.

In a case where additional concomitant medication needs to be administered or dose adjustments for IPF and other 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. As such, adaptation or initiation of treatment with nintedanib or pirfenidone (both post randomization) or other non-excluded concomitant medications are allowed throughout the study based on the medical need of the individual patient.

Note: Subjects receiving either pirfenidone or nintedanib have to be on a stable dose for at least 8 weeks before screening, and during screening. A stable dose is defined as the highest tolerated dose.

All decisions on the start and stop of the intake of nintedanib or pirfenidone or the need for dose adjustments during the study will be made by the investigator and recommendations of the respective local SmPCs should be followed, as done in normal clinical practice.

In vitro assays indicated an inhibition by GLPG1205 of the drug transporters BCRP and OCT2, at a concentration being equivalent to human exposure of 100 mg GLPG1205. Preliminary in vivo data from a clinical drug-drug interaction study assessing the effect of GLPG1205 on OCT2 and BRCP probe substrates show that there is only clinically relevant inhibition of BCRP by GLPG1205 (approximately 3 fold exposure increase), therefore inclusion of subjects with stable chronic illness on stable medications which are transported by known BCRP is not allowed and known BRCP substrates are prohibited during the study. A (non-exhaustive) list of BCRP substrates is provided in Appendix 5.

Inclusion of patients with stable chronic illness on stable medications which are transported by OCT2 transporters (less than 2 fold exposure increase observed) should be decided on a case-by-case basis, taking into account the medical history, concomitant medication of the patient and benefit/risk profile. The CRO's medical monitor or sponsor's medical lead can be contacted when deemed necessary by the investigator, specifically for medication with a narrow therapeutic index and/or a risk of (un)predictable AEs. This is specifically to be done for medication that is transported by OCT2 and has the risk to prolong QT interval. A (non-exhaustive) list of OCT2 substrates is provided in Appendix 6.

Statins have different pathways involved in their disposition (either via metabolic enzymes and/or via transporters) and since it cannot be ruled out that GLPG1205 could interfere with some of those pathways (leading to cumulative net effect difficult to predict from in vitro studies) and to date, no in vivo clinical drug-drug interaction studies have been conducted yet, there is a need to further monitor subjects who may be on statin background therapy. Monitoring of liver function tests and creatine kinase (CK) is implemented during the study as per local guidance for statins in clinical practice.

The use of medication known to prolong QT interval during the study needs to be based on a benefit-risk evaluation by the investigator, e.g. in the case of atrial fibrillation. In other situations (e.g. the initiation of macrolides or fluoroquinolones in case of a lower respiratory tract infection), when a medication known to prolong or potentially prolonging QT is indicated, IMP can be interrupted after clinical assessment of the subject's profile, including the baseline QTcF and how this has changed over time. If the investigator elects to continue IMP, additional

monitoring will be performed as per investigator's judgment. A non-exhaustive list of medication known to prolong QT interval is provided in Appendix 10.

All medications that are not allowed in accordance with the inclusion and exclusion criteria should not be used during the study.

It is highly recommended that the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available) are consulted before the initiation of new medications, in particular medication known to prolong QT interval, and medication known to be transported by OCT2 transporters.

All concomitant therapies, as well as their changes occurring during the study are to be recorded on the relevant case report form (CRF) page(s), along with the reason for and details of therapy use. All prior surgeries will be recorded on the relevant CRF page(s).

4.3.4.3. Food and Beverage Restrictions

The comparison of exposures to GLPG1205 achieved after oral administration of GLPG1205 as a capsule in fed or fasted state (GLPG1205-CL-102) indicates that food has no influence on exposure, therefore there is no food restriction in the current study.

4.3.4.4. Other Prohibitions and Restrictions

No blood donation is allowed during the study.

4.3.5. Removal of Subjects from Therapy or Assessments

A subject may be withdrawn from the clinical study at any time without the subject's consent if the investigator or sponsor determines that it is not in the best interest of the subject to continue participation. In such case, the reason for withdrawal will be documented in the source documents, and the subject will be asked to complete the EOT visit and follow-up visit for safety assessments and pulmonary function.

Study treatment should be discontinued by the investigator (preferably after discussion with the CRO medical monitor, for any of the following conditions:

- Life-threatening AE or a SAE that places the subject at immediate risk
- Serious infections (those requiring parenteral antimicrobial therapy and/or hospitalization)
- Arrhythmia or conduction abnormality, including but not limited to prolonged QT interval corrected for the heart rate using Fridericia's formula (QTcF), where the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 Grade 3 or higher (i.e. QTcF ≥501 ms or an increase from baseline (Visit 2) in QTcF of >60 ms) on at least 2 separate ECGs at the same visit
- Increase in liver function tests:
  - AST and/or ALT elevations >8x ULN: IMP treatment should be withheld and the LFTs should be repeated. IMP should be discontinued if the results are confirmed
  - AST and/or ALT elevations >3x ULN and <8xULN: IMP treatment should be withheld. If LFTs do not return to normal within 2 weeks then the IMP should be discontinued. If LFTs return to normal within 2 weeks then IMP could be restarted with close monitoring (e.g. repeat testing twice per week for the first 2 weeks then

weekly for the following month). In the event LFTs become abnormal at any subsequent point during the study (i.e. after rechallenge) then the IMP should be discontinued.

- AST and/or ALT elevations >3x ULN and total bilirubin level (TBL) >2xULN or international normalized ratio (INR) >1.5: IMP treatment should be withheld and the LFTs should be repeated. IMP should be discontinued if the results are confirmed.
- AST and/or ALT elevations >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%): IMP treatment should be withheld, LFT repeated and IMP discontinued if LFT confirmed or if symptoms and signs persist

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

The investigator may also decide to discontinue IMP (preferably after discussion with the CRO medical monitor, who may consult and must inform the sponsor's study physician) for any of the following reasons:

- Use of concurrent therapy that was not permitted
- Noncompliance with the IMP treatment
- Noncompliance with the clinical study procedures (e.g. missing more than 2 visits)
- Serious or severe AEs
- Worsening of disease condition, which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study (e.g. rescue medication)
- In case of interruption of IMP for cumulatively >30 days

Every effort should be made to keep subjects in the study and on treatment. However, the investigator can consider stopping the treatment with IMP, preferably after consultation with the sponsor's study physician, in case of concerns about the subject's safety, major protocol noncompliance, serious or severe AEs or worsening of the disease condition, which in the investigator's opinion needs an alternative treatment approach not being covered in the clinical study (e.g. rescue medication).

When IMP is discontinued, the subject will be requested to return for the EOT and EOS Visits to allow safety Follow- up.

Subjects will be informed prior to clinical study entry that they are allowed to withdraw from the clinical study. At any time and for any reason, a subject's participation in the clinical

study may terminate at his/her request without prejudice to his/her future medical care. The subject will be encouraged to share the reason(s) for withdrawal so this can be documented in the source documents, and to complete the EOT visit and follow-up visit for safety assessments and pulmonary function, but will not be obliged to do so.

Subjects who withdraw from the clinical study without contact with the site (lost to follow-up) should be contacted by the site so that their health status can be assessed and documented in the source documents. The site should make every effort to understand whether the subject is alive, including checking the medical records, contacting general practitioner or relatives, if necessary. All attempts (at least 3) must be documented in the source documents.

Subjects who drop out before the first administration of the IMP will be replaced. Subjects who stop taking IMP for any reason will not be replaced.

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

4.4. MEASURES TO MINIMIZE BIAS

4.4.1. Randomization

At screening, subjects will be assigned a subject identification number using a centralized electronic system (interactive web response system [IWRS]). When subjects are confirmed to be eligible for the clinical study, the subject will be randomized in a 2:1 ratio to GLPG1205 or placebo. Allocation of each subject to a given treatment will be done via IWRS and will be stratified for background standard of care (subjects receiving nintedanib, pirfenidone, or neither nintedanib nor pirfenidone).

4.4.2. Blinding and Unblinding

This is a randomized, double-blind study. The subject, investigator, clinical study coordinator and the entire clinical study team, will remain blinded to treatment assignment.

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

The blind can be broken only if the investigator deems it necessary for the safety of a subject. The investigator is encouraged to discuss considerations to break the blind with the CRO medical monitor, whenever possible and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he or she feels rapid emergency unblinding is necessary but is required to inform the sponsor in a timely fashion after unblinding has occurred, without disclosing the treatment allocation to the team.

The blind can be broken by the investigator via IWRS.

All subjects who are unblinded while on the clinical study will be withdrawn at the moment of unblinding, with the reason for unblinding given as the reason for withdrawal from the clinical study. If an AE leads to unblinding, the AE will be given as the reason for unblinding, and the AE will be followed up as described in Section 9.3.1. All subjects who are unblinded should, where possible, complete the EOT visit and the follow-up visit, 4 weeks after EOT.

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

An unblinded review of data will be performed on a regular basis by an IDMC. See Section 8 for further details.

An interim analysis may be performed in order to allow sponsor planning of following clinical studies, while maintaining the blind at an individual subject level. All efforts will be made to restrict the access to results so that personnel involved with the study conduct remains blinded to the extent possible. See Section 7.3.2 for further details.

5. INVESTIGATIONS MEDICINAL PRODUCTS

5.1. IDENTITY OF THE INVESTIGATIONS MEDICINAL PRODUCTS

The chemical name of GLPG1205 is 9-cyclopropylethynyl-2-((S)-1-[1,4]dioxan-2-lmethoxy)-6,7-dihydro-pyrimido[6,1-a]isoquinolin-4-one.

GLPG1205 will be provided as an oral hard gelatin capsule containing 50 mg of G321605 (active ingredient) or a matching placebo. Both active and placebo capsule will be identical in appearance, shape, smell and taste.

5.2. DOSAGE AND ADMINISTRATION

The following doses will be tested:

- GLPG1205 100 mg q.d. (as 2 capsules of 50 mg)
- Matching placebo q.d. (as 2 capsules)

The IMP is to be taken q.d. at approximately the same time every morning with or without food. Subjects will be instructed to swallow the capsules of GLPG1205 or placebo as a whole with a glass of water and to not chew the drug prior to swallowing. At the baseline visit, IMP will be administered on site after predose assessments have been completed. On all other visit days subjects also need to take their IMP on site. If subjects are taking pirfenidone or nintedanib then these must also be taken on site at Visit 2, Visit 4 and Visit 8 in order to perform appropriate PK sampling (see Section 6.6).

If a subject misses a dose (e.g. because he/she forgot to take the medication), he/she should take the missed dose within 5 hours after the planned intake time. If IMP is not taken within 5 hours after the planned time, the missed dose should be skipped. For each dose taken, the time, date and number of capsules taken should be recorded in the subject's diary card. During each visit, the investigator will record a summary of IMP intake data in the CRF.

In case of an AE at least possibly related to GLPG1205 as per the investigator's judgement requiring dose reduction, or in the case of intolerance to or toxicity of the IMP, subjects may have their dose of IMP reduced from 2 capsules q.d. (100 mg) to 1 capsule q.d. (50 mg) for the remainder of the study. Should the intolerance or toxicity continue, IMP may be discontinued, and the subject may be withdrawn from the study.

In the event of temporary interruption of IMP due to e.g. an AE, IMP can be re-introduced at the investigator's discretion, depending on the reason for interruption. The investigator should inform the medical monitor immediately of interruption or events leading to interruption in order to help with subject retention.

5.3. PACKAGING, LABELING AND DISTRIBUTION

An IMP kit will consist of 3 Alu/Alu blisters, each containing 12 capsules, packaged in an outer box and labeled with a clinical study-specific label. Each IMP kit contains medication to cover 2 weeks of treatment, including spares. All manufacturing, packaging, and labeling operations will be performed according to Good Manufacturing Practice for Medicinal Products and the relevant regulatory requirements.

The distribution will only occur after the required local documentation is obtained including clinical study approval by Competent Authorities and the Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs), documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae) and the signed and dated study agreement and financial agreement.

Addendum for IMP Distribution:
Direct-to-patient (DTP) shipment of IMP due to Coronavirus disease 19 (COVID-19) pandemic

In case a subject is not able to visit the site for IMP resupply, DTP shipment of IMP can be implemented. DTP IMP shipment will follow the ICH GCP principles and be in compliance with national legislation. DTP IMP shipment will occur from an investigational site to the subject by a logistics provider in a traceable and preferably temperature-controlled manner and will be documented adequately. The patient will be asked to return any unused IMP and empty IMP packages by a logistics provider or during the next on-site visit.

5.4. STORAGE

Sites are to store the IMP (GLPG1205 and matching placebo) supplies in a secure area below +30°C (may not be frozen) until dispensed. Sites will be required to monitor the storage temperature by using at least a min-max temperature-recording device and to keep a minimum to maximum temperature log that is to be completed each working day in order to establish a record of compliance with these storage conditions. The investigator will instruct subjects on how the IMP should be stored at home after it is dispensed.

5.5. TREATMENT COMPLIANCE AND DRUG ACCOUNTABILITY

The pharmacist or designated clinical study personnel will maintain a log of the total amount of IMP received at site, amount dispensed to the subject, and the amount of IMP returned by the subject to the site. Drug supplies for each subject will be inventoried and accounted for

throughout the clinical study. At the end of the treatment period these records will be checked against the inventory by the study monitor. All clinical supplies will be stored in locked facilities.

Subjects will be given a diary card at every visit in the treatment period starting at Visit 2 (Day 1) to record the following:

- From Day 1 through Week 26, subjects will be asked to record the date, time and number of capsules taken
- From Day 1 through Week 26, subjects will be asked to record changes in concomitant medication regimen, including new medicines not captured in medication history, use of bronchodilators, use of pirfenidone or nintedanib, and any other concomitant medication used as well as any emerging AE.

Subjects will be instructed to bring their diary card and to return any unused IMP and empty IMP packages at each visit during the treatment period and/or EOT visit. A summary of the diary card data will be entered in the CRF by the designated site personnel. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure proper subject dosing.

Subjects with a poor compliance (<80% or >120%) will be retrained by the study site. If study drug compliance remains <80% or >120% between study visits, the subject will be evaluated for potential discontinuation. Any discontinuation should be done in consultation with the medical monitor.

Upon sponsor approval all unused IMP and empty IMP packages should be returned to the drug supplier/drug depot or will be destroyed at the site. In case of destruction by the site or the supplier/drug depot, an acceptable destruction process should be in place and a destruction certificate should be provided to the sponsor.

6. CLINICAL STUDY ASSESSMENTS

Every effort should be made to ensure that CSP-required tests and procedures are completed as described (see Section 6.10). To avoid inter-observer variability, every effort should be made to ensure that all safety and efficacy evaluations are completed by the same individual who made the initial baseline determinations.

6.1. TIMING OF ASSESSMENTS

The study assessments will be undertaken at time points as specified in the schedule of activities in Section 6.10. Screening assessments need to be performed within 28 days before Day 1 and may be split into multiple days or visits. A window of ±2 days is allowed for Visit 3 and 4, a window of ±4 days is allowed for Visit 5, 6, 7, 8 and 10; and a window of ±6 days is allowed for Visit 9. All visits should preferably be performed in the morning.

If an on-site Visit 9 cannot be performed at the scheduled timepoint due to factors related to the COVID-19 pandemic, the visit window and the study medication intake period can be either extended up to +56 days or shortened up to -28 days, to allow flexibility in scheduling the visit. For more details and other visits see Section 6.1.1.

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

- Laboratory values for liver function tests, creatinine clearance, and hemoglobin can be retested once
- Lost or invalid blood or urine samples

Rescreening: in case of screening failure, subjects are allowed to be rescreened once, with an interval of at least 6 weeks. Subjects confirmed not to have a diagnosis of IPF by central reading may not be rescreened. If rescreened, the subject must be reconsented. The subject will be assigned a new subject number which will be linked to the first screening number.

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

During all visits the following should be taken into account with respect to timing of assessments (if applicable):

- SGRQ is recommended to be performed prior to any other visit-related procedures
- 12-lead ECG and vital signs are to be performed before spirometry
- Spirometry*, physical examination, 12-lead ECG and vital signs are to be performed before blood/urine sampling
- Spirometry* is to be performed preferably at approximately the same time every visit

Screening assessments need to be performed with the following considerations:

- Spirometry* can be repeated once at another screening visit (within the same planned screening period) if acceptability and repeatability criteria as specified by ATS/ERS/JRS/ALAT are not met as confirmed by central spirometry reader
- Safety blood/urine samples for clinical laboratory evaluations and physical examination, vital signs, 12-Lead ECG need to be available at the latest on Day -1
- Repeat spirometry can only proceed if IPF diagnosis per HRCT/LB is confirmed (according to the criteria in Appendix 1)
- For sites that do not have a DLCO machine and need to refer to another site, it is recommended to perform the DLCO only once IPF diagnosis per HRCT/LB is confirmed (according to the criteria in Appendix 1)
- If there is no historical HRCT available, a new HRCT needs to be planned and performed. Only if for logistic reasons it is not possible to perform a new HRCT within the planned screening period and after approval of the medical monitor it is allowed to extend the screening period with maximum 2 weeks

During the baseline visit (Visit 2) the following should be taken into account with respect to the timing of assessments:

- At baseline (Visit 2) all assessments are to be performed prior to dosing
- Spirometry* can be repeated once if confirmation acceptability and repeatability criteria as specified by ATS/ERS/JRS/ALAT are not met. This repeat spirometry must be performed before randomization
- [redacted]

* Spirometry assessments should be performed prebronchodilator. Prebronchodilator 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 hours prior to the spirometry assessment AND
  - withheld their long-acting bronchodilator (e.g. salmeterol, formoterol) for ≥12 hours and other longer-acting agents (e.g. indacaterol, tiotropium) for ≥24 hours prior to the spirometry assessment

In case the subject is on bronchodilators, he/she can use the bronchodilator after spirometry assessments [redacted]

Safety assessments should be repeated at other time points and additional assessments made if clinically indicated.

6.1.1. Description of Visits

Visit 1 (screening visit)

The following procedures and assessments (to be performed within 28 days before Day 1 and may be split into multiple days or visits) will be performed during screening:

1. Signing ICF
2. Provide subject participation card
3. Assign a subject identification number
4. Initial subject and disease characteristics (send chest HRCT [historical or plan new] and LB [if available] for central review, demographics, medical history/concurrent illnesses, alcohol consumption and smoking habits; check inclusion/exclusion criteria)
5. Physical examination (including weight and height)
6. AE assessment and concomitant medication (including verification of stable dose pirfenidone or nintedanib, if applicable)
7. 12-lead ECG
8. Vital signs (supine systolic blood pressure [SBP], diastolic blood pressure [DBP], heart rate, oral or tympanic body temperature, and respiratory rate)
9. Spirometry (and submit data to central reader)
10. Safety blood sampling for clinical laboratory evaluations (hematology, coagulation, clinical chemistry, serology, and if applicable FSH test and pregnancy test)
11. Safety urine sampling for clinical laboratory evaluations (urinalysis)
12. DLCO
13. 6MWT
14. Repeat spirometry if acceptability and repeatability criteria as specified by ATS/ERS/JRS/ALAT are not met after confirmation by central spirometry reader (after IPF diagnosis per HRCT/LB is confirmed according to the criteria in Appendix 1)
15. Schedule all visit days with the subject

The following procedures and assessments will be performed during the dosing period and follow-up:

Visit 2 (baseline visit):

Subjects who are taking nintedanib or pirfenidone, should bring these to the site for onsite dosing.

1. Check inclusion/exclusion criteria
2. SGRQ
3. Physical examination
4. AE assessment and concomitant medication
5. 12-lead ECG (triplicate)
6. Vital signs (supine SBP, DBP, heart rate, oral or tympanic body temperature, and respiratory rate)
7. Spirometry (and submit data to central reader)
8. Predose PK blood sample (for GLPG1205, and if applicable nintedanib or pirfenidone concentration analysis)
9. Safety blood sampling for clinical laboratory evaluations (hematology, coagulation and clinical chemistry)
10. Safety urine sampling for clinical laboratory evaluations (urinalysis)
11. [redacted]
12. [redacted]
13. 6MWT
14. [redacted]
15. Repeat spirometry if acceptability and repeatability criteria as specified by ATS/ERS/JRS/ALAT are not met after confirmation by central spirometry reader
16. Randomization if all in- and exclusion criteria are met)
17. Dispense subject diary and provide instructions on IMP intake, timing and storage
18. Dispense IMP
19. Dosing IMP and if applicable nintedanib or pirfenidone on site

Visit 3, 5, 6, and Visit 7 (if applicable)

Subjects who are taking nintedanib or pirfenidone can do this at home or on site according to their normal routine.

1. SGRQ (Visit 6)
2. Physical examination (Visit 3 and 6)
3. AE assessment and concomitant medication
4. 12-lead ECG (Visit 3 and 6, single)
5. Vital signs (supine SBP, DBP, heart rate, oral or tympanic body temperature, and respiratory rate)
6. Spirometry (Visit 5, 6 and 7)
7. PK blood sample (Visit 6: predose sample for GLPG1205, and if applicable postdose sample for nintedanib or pirfenidone concentration analyses)
8. Safety blood sampling for clinical laboratory evaluations (hematology, coagulation and clinical chemistry)
9. [redacted]

10. [redacted]
11. Safety urine sampling for clinical laboratory evaluations (urinalysis)
12. Dosing IMP on site
13. Dispense subject diary and provide instructions on IMP intake, timing and storage
14. Collect subject diary
15. Dispense IMP
16. Collect returned IMP and review IMP compliance

Visit 4 and Visit 8 (if applicable)

Subjects who are taking nintedanib or pirfenidone, should bring these to the site for onsite dosing.

1. Physical examination
2. AE assessment and concomitant medication
3. 12-lead ECG (Visit 8, single)
4. Vital signs (supine SBP, DBP, heart rate, oral or tympanic body temperature, and respiratory rate)
5. Spirometry
6. Predose PK blood sample (for GLPG1205, and if applicable nintedanib or pirfenidone concentration analysis)
7. Safety blood sampling for clinical laboratory evaluations (hematology, coagulation and clinical chemistry)
8. [redacted]
9. [redacted]
10. Safety urine sampling for clinical laboratory evaluations (urinalysis)
11. Dosing IMP and if applicable nintedanib or pirfenidone on site
12. Postdose PK blood sample (±2 hour postdose sample for GLPG1205, and if applicable nintedanib or pirfenidone concentration analyses)
13. Dispense subject diary and provide instructions on IMP intake, timing and storage
14. Collect subject diary
15. Dispense IMP
16. Collect returned IMP and review IMP compliance

Addendum for Visit 3 to Visit 8:
Alternative approach due to COVID-19 pandemic

If a study participant cannot conduct a study visit on site, the investigator will follow an alternative visit approach to ensure the safety of the subject and will conduct a remote visit (e.g., phone call, virtual visit) or home visit, to evaluate the safety of the patient, and to decide whether continuation in the study is justifiable.

The investigator should at least discuss the following items and collect the following information as much as possible:

- the subject's general condition
- information on any adverse events (changes of ongoing or new events)
- information on study medication intake
- information on standard of care medication intake
- information on concomitant medication intake
- completion of subject diary pages and Quality of Life Questionnaire by the study subject.

The investigator should consider local laboratory testing, physical examination, vital signs and ECG, whenever possible. These local data will not become part of the clinical database. These results should be stored as part of the source documentation at the clinical site to be available as necessary. In case any of the results are deemed clinically significant by the investigator, the corresponding AE needs to be reported in the eCRF.

Visit 9/EOT and Visit 10/EOS (if applicable)

Subjects who are taking nintedanib or pirfenidone can do this at home or on site according to their normal routine.

1. SGRQ (Visit 9/EOT)
2. Physical examination (including weight)
3. AE assessment and concomitant medication
4. 12-lead ECG (single)
5. Vital signs (supine SBP, DBP, heart rate, oral or tympanic body temperature, and respiratory rate)
6. Spirometry
7. PK blood sample (Visit 9: predose sample for GLPG1205, and if applicable postdose sample for nintedanib or pirfenidone concentration analyses; Visit 10/EOS: for GLPG1205, and if applicable also for nintedanib or pirfenidone concentration analyses)
8. Safety blood sampling for clinical laboratory evaluations (hematology, coagulation and clinical chemistry)
9. [redacted]
10. [redacted]
11. Safety urine sampling for clinical laboratory evaluations (urinalysis)
12. Dosing IMP on site (Visit 9)
13. [redacted]
14. 6MWT [redacted] (Visit 9/EOT)
15. [redacted]
16. Collect subject diary (Visit 9/EOT)
17. Collect returned IMP and review IMP compliance (Visit 9/EOT)
18. Repeat spirometry if acceptability and repeatability criteria as specified by ATS/ERS/JRS/ALAT are not met after confirmation by central spirometry reader

Addendum for Early treatment discontinuation Visit (EOT)
Alternative approach due to COVID-19 pandemic

In case of an early treatment discontinuation, the following EOS visit, planned regularly 28 days after the last IMP intake, can occur either earlier by up to 7 days or later up to 28 days to enable the conduct of the EOS Visit on site (for more details see below in the Visit 10/EOS addendum). In addition:

- if the decision to discontinue the treatment was made during an on-site visit, and without any safety findings or ongoing AEs, the EOS Visit may be performed remotely.

- if the decision to discontinue the treatment was not made during an on-site visit, or in case of any safety observations or ongoing AEs, an EOS Visit on site is required to monitor the safety of the subject. In addition, remote or home unscheduled visits should be conducted at least every 14 days, until the on-site EOS Visit can be performed.

Addendum for Visit 9:
Alternative approach due to COVID-19 pandemic

- If Visit 9 cannot be conducted on site according to the original schedule of activities (Section 6.10; see also Section 6.1, "Timing of Assessments") due to the COVID-19 pandemic, the treatment period can be extended up to +56 days or shortened up to -28 days to enable the conduct of Visit 9 on site.
- If the study treatment is prolonged beyond the originally planned Visit 9 date, remote (e.g., telephone contact, virtual contact) or home unscheduled visits should be conducted at the originally planned visit date, and thereafter at least every 14 days, to closely monitor the patient's safety until the on-site visit can be performed.
- If no on-site visit is possible within the 56 days of treatment prolongation, then a remote or home visit should be planned and conducted within the extended Visit 9 window. However, every effort should be made to perform the end of study (EOS) Visit 10 on site. If this is not feasible the medical monitor or sponsor should be contacted.

Addendum for Visit 10/EOS:
Alternative approach due to COVID-19 pandemic

- If Visit 10 cannot be conducted on site according to the original schedule of activities (Section 6.10; see also Section 6.1, "Timing of Assessments") due to COVID-19 pandemic, the visit window can be extended up to +28 days or shortened up to -7 days to enable the conduct of Visit 10 on site.
- If the Visit 10 window is extended, a remote or home unscheduled visit 28 days after last IMP intake should be conducted and thereafter at least every 14 days, until the on-site visit can be performed.
- If within the +28 days of Visit 10 window prolongation no on-site visit is possible, and Visit 9/EOT was performed on site without relevant findings and/or safety concerns,

then Visit 10 may be performed remotely or at home within the respective visit window.

- If, however, Visit 9/EOT was conducted remotely or at home, or if relevant findings and/or safety concerns were reported, then Visit 10 will have to be performed on site. If this is not feasible the investigator shall contact the medical monitor or sponsor.

6.2. UNSCHEDULED VISITS

If the subject has taken a bronchodilator before spirometry, the visit should be rescheduled within the defined visit window to allow spirometry assessment without bronchodilator.

[redacted] This extra site visit needs to be performed within the defined visit window and the subject should take his/her medication until the day of the last assessment.

Safety assessments should be repeated at other time points and additional assessments made if clinically indicated. If needed additional visits (on site, remote, or home visit) to assess safety should be conducted.

Addendum for Remote Unscheduled Visits:
Approach due to COVID-19 pandemic

In case of visit window extensions beyond the originally planned visit dates for Visit 9 or Visit 10, unscheduled remote or home visits are to be conducted as described in Section 6.1.1.

6.3. INITIAL SUBJECT AND DISEASE CHARACTERISTICS

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

At Visit 1, the subject's historical HRCT and LB (if available) will be sent for review to confirm IPF diagnosis (according to the criteria in Appendix 1). If there is no evaluable historical HRCT available, a chest HRCT needs to be planned and performed. Only if for logistic reasons it is not possible to perform a new HRCT within the planned screening period and after approval of the medical monitor it is allowed to extend the screening period with maximum 2 weeks (see also Section 6.1). The radiation exposure during this scan is presented in Appendix 7.

A 12-lead ECG will be recorded, vital signs (SBP and DBP, heart rate, oral or tympanic body temperature, and respiratory rate) will be measured, and safety blood and urine sampling will be done. Subjects should rest for at least 5 minutes in the supine position before the ECG recording, blood pressure and heart rate measurement. DLCO and 6MWT will be assessed to check eligibility (see also Section 6.4.4 and Section 6.4.5). DLCO can only proceed if IPF diagnosis per HRCT/LB is confirmed.

Spirometry will be performed at the study center to assess pulmonary function. If the acceptability and repeatability criteria for spirometry results (see Section 6.4.1) are not met

and confirmed by central reader, one repeat spirometry can be done during the screening period (according to the criteria in Appendix 1).

6.4. EFFICACY ASSESSMENTS

All efficacy assessments will be performed at the visits specified in the schedule of activities in Section 6.10 (see also Section 6.1, "Timing of Assessments").

6.4.1. Pulmonary Function by Spirometry

Spirometry will be performed at the study center to assess pulmonary function.

Pulmonary function will be measured in a standardized manner, using standardized equipment, and results will be transmitted electronically preferably during the visit (required to do so at first spirometry at baseline [Visit 2]) and evaluated by a central reader.

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

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

The '2012 Global Lung Function Initiative Equations' will be used to calculate the predicted values [25].

6.4.2. Quality of Life

The SGRQ is a 50-item paper 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),
- 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.

6.4.3. Clinical Endpoints

The time to any of the following clinical endpoints (whichever is first) will be evaluated:

- Death (all-cause and respiratory-related)
- First hospitalization (all-cause and respiratory-related)

Clinical endpoint adjudication will be performed by an independent expert (or his/her back-up) who will review and adjudicate these endpoints in a blinded manner (refer to Section 8.2).

6.4.4. Diffusing Capacity for the Lungs for Carbon Monoxide

DLCO will be assessed using a method in compliance with the current ATS/ERS/JRS/ALAT guideline on DLCO measurements [26] and corrected for hemoglobin using the following formula:

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

(Hb = hemoglobin expressed in g/dL)

At screening, DLCO must meet the following criteria [26]: DLCO corrected for hemoglobin ≥30% predicted of normal. 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 current ATS/ERS/JRS/ALAT guideline on DLCO measurements [26] and the prediction formula appropriate for that method.

[redacted]

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

6.4.5. Functional Exercise Capacity Testing: 6-Minute Walk Test

A 6MWT will be performed at the study center to assess pulmonary function. The 6MWT will be performed based on the ATS recommendations [27] and at baseline visit (Visit 2) and Visit 9 / EOT [redacted] Contraindications for performing the 6MWT are provided in Appendix 3.

[redacted]

6.5. SAFETY ASSESSMENTS

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

6.5.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at their last follow-up visit.

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

6.5.2. Clinical Laboratory Evaluations

The following clinical laboratory safety tests will be performed:

- Hematology: hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), hemoglobin, red blood cell count, white blood cell count, white blood cell differential count (absolute and relative), red blood cell differential count / morphology (if indicated) and platelets
- Coagulation: INR, thromboplastin time and partial thromboplastin time
- Clinical chemistry: glucose, urea, creatinine, uric acid, sodium, potassium, calcium, chloride, phosphorus, AST, ALT, GGT, TBL, alkaline phosphatase, lactate dehydrogenase, CK including isotypes (if needed), total serum bile acid, albumin, total proteins, triglycerides, cholesterol (total, high density lipoprotein, low density lipoprotein), and brain natriuretic peptide
- Urinalysis: dipstick: pH, glucose, proteins, blood, leukocytes; microscopic examination of the sediment for cellular elements, casts, crystals, microorganism, miscellaneous elements if indicated
- Serology/blood: Hepatitis B surface antigen and HCV antibody (if positive confirmed by HCV RNA polymerase chain reaction assay), and HIV 1 and 2 antibodies at screening. Positive hepatitis and HIV results should be reported by the investigator as required by local law
- FSH test for females at screening to confirm menopause if applicable
- Pregnancy test for females: serum beta human chorionic gonadotropin at screening

The clinical laboratory evaluations will be performed at visits specified in the schedule of activities in Section 6.10 (see also Section 6.1, "Timing of Assessments"). Reference ranges will be supplied by the central laboratory. At the discretion of the investigator, when following up adverse events, additional laboratory parameters may be tested, and additional samples taken.

Clinical laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Only clinically significant laboratory test abnormalities as judged by the principal investigator should be recorded as AEs.

During screening one retest of the following lab values is allowed: AST, ALT, bilirubin, alkaline phosphatase, GGT, creatinine and hemoglobin.

The total amount of blood to be taken during the clinical study for scheduled laboratory assessments will not exceed 306 mL. This also includes sampling for PK, [redacted]

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

6.5.3. Physical Examination

Physical examinations will be conducted by a physician, trained physician's assistant, or nurse practitioner as acceptable according to local regulation at visits specified in the schedule of activities in Section 6.10 (see also Section 6.1, "Timing of Assessments"). The person conducting the physical examination will document this in the subject's medical records. Clinically significant abnormal findings should be recorded as AEs. At screening the physical examination will include height and weight, and weight should be measured at Visit 9/EOT and Visit 10/EOS.

6.5.4. 12-lead Electrocardiogram

At the time points specified in the schedule of activities Section 6.10 (see also Section 6.1, "Timing of Assessments"), a 12-lead ECG will be recorded and results will be sent for central reading. ECG recordings will be performed before blood/urine sampling and after subjects rested for 5 minutes in supine position. In case an indwelling catheter is used, ECGs may be recorded after blood sampling, provided that there is at least 30 minutes between catheter insertion and the ECG recording. When catheter insertion would fail, the 12-lead ECG needs to be taken before the venipuncture and at least 30 minutes after the failed attempt. Triplicate ECGs will be performed at baseline (Visit 2) only within a time span of 6 minutes, with an approximate 3-minute interval between ECGs. Parameters to be recorded include the following: heart rate, PR interval, QRS interval, uncorrected QT interval, morphology and rhythm analysis (QTcF will be derived during the statistical analysis). ECG parameter normal ranges are presented in Appendix 4. QTcF will be considered as normal if ≤450 ms (male) and ≤460 ms (female), while subjects experiencing a prolongation of QTcF to ≥501 ms or an increase from baseline >60 ms should be discontinued from IMP (see Section 4.3.5). Immediately after recording, the ECGs will be reviewed by the investigator on clinical significant abnormalities. This immediate review during the visit needs to be documented in the subject's source. After receipt of the central report, also all flagged ECG abnormalities need to be assessed by the investigator on clinical relevance. All clinically significant abnormal ECG values should be recorded as AEs.

6.5.5. Vital Signs

Vital signs (SBP and DBP, heart rate, oral or tympanic body temperature and respiratory rate) will be recorded in a standardized manner (i.e. after the subject has rested in a supine position for 5 minutes; consistent way of measuring body temperature: all measurements per subject oral or tympanic) at visits specified in the schedule of activities in Section 6.10 (see also Section 6.1, "Timing of Assessments"). Vital sign parameter normal ranges are presented in Appendix 4. Clinically significant abnormal values should be recorded as AEs.

6.5.6. Other Safety Assessments

Not applicable

6.6. PHARMACOKINETIC ASSESSMENTS

Blood samples for the PK assessment should be collected on the visits specified in the schedule of activities in Section 6.10 (see also Section 6.1, "Timing of Assessments"). In total 8 blood samples will be used for analysis of GLPG1205, nintedanib and pirfenidone in plasma (other analytes, such as metabolites, may be determined if deemed appropriate).

Samples will be collected as follows:

- Visit 2: 1 predose sample to be collected before dosing with IMP and if applicable with pirfenidone or nintedanib
- Visit 6 and 9: 1 predose sample to be collected before dosing with IMP and if applicable after dosing with pirfenidone or nintedanib
- Visit 4 and 8:
  - 1 predose sample to be collected before dosing with IMP and if applicable with pirfenidone or nintedanib
  - 1 postdose sample to be collected ±2 hours after dosing with IMP and if applicable with pirfenidone or nintedanib
- Visit 10/EOS: 1 sample (no IMP dosing)

The exact date and time of blood collection will be recorded in the CRF, as well as the exact date, number of capsules and time of IMP intake on site. For subjects on standard of care the date actual dose and time of nintedanib or pirfenidone intake (intake at home or intake at site) is also recorded.

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

Concentrations of GLPG1205, nintedanib and pirfenidone in plasma samples will be determined using validated liquid chromatography-tandem mass spectrometry analytical methods by the bioanalytical laboratory in charge of these analyses.

[redacted]

[redacted]

6.8. OTHER ASSESSMENTS

[redacted]

6.9. SAMPLE MANAGEMENT

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

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

Blood Samples for PK [redacted]

After the end of the study (e.g. when the last follow-up visit as planned according the schedule of activities of the last subject is performed), all biological samples obtained during the clinical study may be stored for a period of maximum 5 years, after which the samples will be destroyed. The sample storage period will be in accordance with the IRB/EC-approved ICF and applicable laws (e.g. health authority requirements).

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

No characterization of human genetic material (genes, DNA, RNA) will be undertaken on these samples. If research is performed on genetic material of the samples then this can only be performed in context of the described CSP [redacted] and the data obtained may in no case be used for the purpose of identification or re-identification of subjects.

[redacted]

Lung Biopsy

If a LB is available for central IPF diagnosis then this biopsy is sent by the clinical center to the central reading vendor, if allowed by local regulations. Once the central reading (HRCT or HRCT+LB) is done and the results are acceptable the LB is shipped back to the clinical center.

6.10. SCHEDULE OF ACTIVITIES

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

EVENT	SCR	TREATMENT PERIOD									FU
Study visit	**1**[1]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**EOT**	**10/ EOS**
Study week (W) or day (D) ± days (d)	**D-28 to D-1**	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W12 ±4d**	**W16 ±4d**	**W20 ±4d**	**W26[6] ±6d**		**W30[7] ±4d**
Informed consent (Section 6.3 and Section 10.4.2)	✓										
Dispense subject participation card (Section 10.2.4)	✓										
Send HRCT (historical or new[2]) for central review (Section 6.3)	✓										
Send LB (if available) for central review (Section 6.3)	✓										
Demographics (Section 6.3)	✓										
Medical history/concurrent illnesses (Section 6.3)	✓										
Alcohol consumption and smoking habits (Section 6.3)	✓										
Inclusion/exclusion criteria (Section 6.3)	✓	✓									
Physical examination (Section 6.5.3)	✓[3]	✓	✓	✓		✓		✓	✓[3]	✓[3]	✓[3]
12-Lead ECG (Section 6.5.4)	✓	✓	✓			✓		✓	✓	✓	✓
Vital signs (Section 6.5.5)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[1] Screening assessments need to be performed within 28 days before Day 1 and may be split into multiple days or visits.
[2] If there is no historical HRCT available, a new HRCT needs to be planned and performed. Only if for logistic reasons it is not possible to perform a new HRCT within the planned screening period and after approval of the medical monitor it is allowed to extend the screening period with maximum 2 weeks.
[3] At screening include height and weight; at Visit 9/EOT and Visit 10/EOS include weight.

EVENT	SCR	TREATMENT PERIOD									FU
Study visit	**1**[1]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**EOT**	**10/ EOS**
Study week (W) or day (D) ± days (d)	**D-28 to D-1**	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W12 ±4d**	**W16 ±4d**	**W20 ±4d**	**W26**[6] **±6d**		**W30**[7] **±4d**
Spirometry (Section 6.4.1)	✓[4]	✓[4]		✓	✓	✓	✓	✓	✓[4]	✓	✓
SGRQ (Section 6.4.2)		✓				✓			✓	✓	
Clinical laboratory tests (hematology, coagulation, clinical chemistry, urinalysis) (Section 6.5.2)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Serology (Section 6.5.2)	✓										
FSH test (Section 6.5.2)	✓										
Pregnancy test (Section 6.5.2)	✓										
PK blood samples (Section 6.6)		✓		✓		✓		✓	✓		✓
[redacted]											
[redacted]											
DLCO (Section 6.4.4)	✓[redacted]	[redacted]									
6MWT (Section 6.4.5)	✓	✓							✓	✓	
[redacted]											

[4] Spirometry can be repeated once if acceptability and repeatability criteria as specified by ATS/ERS/JRS/ALAT are not met after confirmation by central reader.

[5] [redacted]

[6] In case Visit 9 cannot be performed on site within the visit window due to the COVID-19 pandemic, the study medication intake and the corresponding time window for Visit 9 can be extended up to +56 days or shortened up to -28 days.

[7] In case Visit 10 cannot be performed on site within the visit window due to the COVID-19 pandemic, the corresponding time window for Visit 10 can be extended up to +28 days or shortened up to -7 days.

EVENT	SCR	TREATMENT PERIOD									FU
Study visit	**1[1]**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**EOT**	**10/ EOS**
Study week (W) or day (D) ± days (d)	**D-28 to D-1**	**D1**	**W2 ±2d**	**W4 ±2d**	**W8 ±4d**	**W12 ±4d**	**W16 ±4d**	**W20 ±4d**	**W26[6] ±6d**		**W30[7] ±4d**
Randomization (Section 4.4.1)		✓									
Dispense subject diary (Section 5.5)		✓	✓	✓	✓	✓	✓	✓			
Collect subject diary (Section 5.5)			✓	✓	✓	✓	✓	✓	✓	✓	
Dispense IMP (Section 5.5)		✓	✓	✓	✓	✓	✓	✓			
Collect returned IMP and review IMP compliance (Section 5.5)			✓	✓	✓	✓	✓	✓	✓	✓	
Dose IMP (Section 5.2)		daily throughout the treatment period									
Concomitant medication (4.3.4.2)	throughout the study										
AE assessment (Section 6.5.1)	throughout the study										

6MWT=6-Minute Walk Test; AE=adverse event; D=Day; d=days; DLCO=diffusing capacity for the lungs for carbon monoxide; ECG=electrocardiogram; EOS=end of study; EOT=end of treatment visit; [redacted]; FSH=follicle stimulating hormone; FU=follow-up; HRCT=high-resolution computed tomography; IMP=investigational medicinal product; [redacted] PK=pharmacokinetic; SAE=serious adverse event; SCR=screening; SGRQ=St George's Respiratory Questionnaire; LB= lung biopsy; W=Week

7. STATISTICAL METHODS

All statistical methods shall be detailed in a statistical analysis plan (SAP) that will be finalized before treatment unblinding and data analysis. All data collected in this clinical study will be documented using summary tables, figures, and/or subject data listings.

7.1. DETERMINATION OF SAMPLE SIZE

The aim of this proof-of-concept study is to show a trend in treatment difference for the primary endpoint (change from baseline in FVC over 26 weeks), therefore no formal sample size calculation was performed. In the following paragraph, the variability of the estimated treatment difference for the proposed sample size of 60 subjects is illustrated.

Consider 40 and 20 evaluable subjects in the GLPG1205 and placebo arm, respectively, and an aim of a 50:50 balanced study population being either on nintedanib/pirfenidone or neither. Further, assume for FVC change from baseline at Week 26 a common standard deviation of 200 mL, a true treatment difference of 50 mL in the population receiving nintedanib or pirfenidone and a true treatment difference of 80 mL in the population receiving neither nintedanib nor pirfenidone. Under these assumptions and taking into account 10% dropout, the probability to observe a treatment effect of more than 40 mL in the total study population is 67% and the probability to observe a treatment effect of more than 20 mL is 78%.

Approximately 60 subjects are planned to be randomized into the study.

7.2. POPULATION FOR ANALYSES

7.2.1. All Screened Subjects

All subjects who signed an ICF.

7.2.2. All Randomized Subjects

All subjects who were randomized into the clinical study.

7.2.3. Full Analysis Set

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

7.2.4. Per-Protocol Set

All full analysis set subjects who did not have a major protocol deviation impacting the efficacy results (as defined in a protocol deviation plan). If needed, the determination of the per-protocol population will be finalized and documented prior to database lock and unblinding.

7.2.5. Pharmacokinetic Analysis Set

Subset of the safety set, selecting all subjects who have available and evaluable plasma concentration data (e.g. excluding all protocol deviations or AEs that may have an impact on the PK analysis).

[redacted]

7.3. STATISTICAL ANALYSES

7.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, standard deviations or standard error, as appropriate, median, minimum, and maximum for continuous variables, and the number and percentage per category for categorical data. In addition to tabulated descriptive statistics, graphical data displays may be used to summarize the data. Unless otherwise noted, inferential statistics will be interpreted at the 2-sided 5% significance level.

7.3.2. Interim Analysis

An unblinded review of data will be performed on a regular basis by an IDMC. See Section 8 for further details. No premature study termination is planned for favorable treatment effect reason. Accordingly, no adjustment of alpha level for testing is performed for this exploratory study.

In addition, given the exploratory nature of the study, an interim analysis may be performed in order to allow sponsor planning of following clinical studies, while maintaining the blind at an individual subject level. There is no plan to terminate the study earlier based on this potential interim analysis. It is acknowledged that the sponsor may be unblinded at the time the interim analysis will take place. However, all efforts will be made to restrict the access to results so that personnel involved with the study conduct remains blinded to the extent possible.

7.3.3. Analyses of Demographics and Baseline Characteristics

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, concomitant therapies, and use of clinical study medication and compliance will be analyzed descriptively and/or listed.

7.3.4. Analyses of Efficacy Parameters

All efficacy parameters (spirometry, clinical endpoints, quality of life, [redacted]) will be analyzed descriptively in the full analysis set unless otherwise specified.

7.3.4.1. Primary Efficacy Endpoint Analysis

The change from baseline in FVC at 26 weeks will be analyzed using an analysis of covariance (ANCOVA) model including treatment, sex and stratum as categorical covariates

and age, height and baseline FVC value as continuous covariates. Subgroup analysis may be performed for background treatment.

As a sensitivity analysis, a random coefficient regression model (random slopes and intercepts) including treatment, sex and stratum as categorical fixed effects and time, age and height as continuous fixed effects, will be used to analyze the rate of decline in FVC. The treatment effect will be determined by using estimated slopes for each study group on the basis of the time-by-treatment interaction term from the mixed model. All available FVC values from baseline to Week 26 will be used including FVC measurements at the follow-up visit for subjects who discontinue the study medication prematurely and do not complete the study visits through Week 26.

Furthermore, sensitivity analyses including multiple imputation methods may be performed using all randomized subjects to assess the impact of missing data on the primary efficacy analysis.

7.3.4.2. Secondary Efficacy Endpoints Analyses

The % predicted FVC change from baseline will be analyzed using a similar model as the one described for the primary analysis.

The proportions of subjects who have an absolute decline of 10 percentage points or more in % predicted FVC or who die will be analyzed using logistic regression.

Treatment effect on time to death (all cause and respiratory-related) / hospitalization (all cause and respiratory-related), whichever occurs first, will be assessed using the log-rank test. Kaplan-Meier estimates will be derived for probability of death (all cause and respiratory-related) / hospitalization (all cause and respiratory-related) (whichever occurs first) over time and displayed graphically.

SGRQ total score and domains will be analyzed using descriptive statistics of actual values and changes from baseline at all time points. The proportion of SGRQ responders (defined as absolute change from baseline at all time points, in SGRQ total score ≤-4 points) will also be tabulated.

SGRQ responders and proportion of subjects with hospitalization will be described and tested for treatment differences using a Fisher's exact test.

[redacted] More detail will be provided in the SAP.

7.3.5. Analyses of Safety Data

All safety analyses will be performed using the full analysis set (Section 7.2.3). All safety data collected on or after the first dose of IMP administration up to the last follow-up visit after the last dose of IMP, unless specified otherwise, will be displayed in listings of individual data and/or summarized by treatment group according to the IMP received. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs.

7.3.5.1. Extent of Exposure

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

7.3.5.2. Adverse Events

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

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

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

Summaries (number and percentage of subjects) of TEAEs by System Organ Class and Preferred Term will be provided by treatment group. TEAEs will also be summarized by causal relationship to IMP or standard of care and by severity. In addition, TEAEs leading to premature discontinuation or dose reduction of IMP will be summarized. All AEs, non-treatment-emergent AEs, SAEs, AEs leading to hospitalization, AEs leading to death, deaths, AEs leading to discontinuation of IMP/standard of care and AEs leading to temporary stop or dose-reduction of IMP/standard of care will be listed.

7.3.5.3. Clinical Laboratory Evaluations

Laboratory assessments and their changes from baseline will be analyzed descriptively by treatment group.

7.3.6. Pharmacokinetic Analyses

Observed GLPG1205, nintedanib and pirfenidone plasma concentrations will be analyzed using a population PK approach to characterize the PK profile of GLPG1205 in IPF subjects and determine the covariates which might influence the PK in this population.

[redacted]

8. DATA MONITORING

8.1. INDEPENDENT DATA MONITORING COMMITTEE

To enhance the safety of the subjects, an IDMC consisting of independent recognized international experts will be convened to regularly review the accumulating unblinded safety data for the clinical study. The IDMC will provide a recommendation to the sponsor on clinical study continuation, suggestions for clinical study adaptation(s) or early termination. Ultimately, the final decision, to continue, adapt or early terminate the study, remains with the sponsor. The specific responsibilities, composition, meeting formats and details of output provided for the meetings of the IDMC are outlined in detail in the IDMC Charter.

8.2. CLINICAL ENDPOINT ADJUDICATION

Clinical endpoint adjudication will be performed by an experienced chest physician (and a back-up) and governed by a Charter which will be set up to perform, on a regular basis, a blinded adjudication of all cause and respiratory-related death and of all cause and respiratory-related hospitalization during the clinical study. The adjudication of these events will be performed in a blinded fashion for the purpose of data analysis (to enhance the integrity of the study data), and not for monitoring of subject safety. This objective data adjudication will reduce variation in outcome reporting and observer bias.

9. SAFETY REPORTING

9.1. DEFINITIONS OF ADVERSE EVENTS, AND SERIOUS ADVERSE EVENTS

9.1.1. Adverse Events

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

An AE can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related. AEs may also include pre- or posttreatment complications that occur as a result of CSP-specified procedures, worsening of the targeted disease, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting events

that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

9.1.2. Serious Adverse Events

An SAE is defined as an AE that, results in the following:

- Death.
- Life-threatening (Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.).
- In-subject hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- Medically significant (medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed in the definition above).

9.1.3. Unlisted (Unexpected) Adverse Event/Reference Safety Information

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

9.1.4. Adverse Events of Special Interest

Not applicable.

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

Laboratory abnormalities without clinical significance based on the investigator's judgement, are not considered AEs or SAEs. However, laboratory abnormalities (e.g. clinical chemistry, hematology and urinalysis) or other abnormal (clinical study specific) assessments (e.g. ECG, radiography, vital signs) that require medical or surgical intervention, are associated with signs and/or symptoms, lead to IMP interruption, modification, or discontinuation must be recorded as an AE or SAE if they meet the definition as described in Sections 9.1.1 and 9.1.2, respectively. If the laboratory abnormality is part of a syndrome, the syndrome or diagnosis is to be reported (e.g. anemia instead of decreased hemoglobin).

9.2. ASSESSMENT OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

9.2.1. Assessment of Causality

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

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

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

9.2.2. Assessment of Severity

The severity of AEs should be graded using CTCAE Version 5.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in the table below.

Table 1 Grading of Adverse Event Severity

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

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

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

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

9.2.3. Outcome

Each AE must be rated by choosing among:

- Recovered/Resolved
- Recovered/Resolved with sequelae
- Recovering/Resolving
- Not recovered/Not resolved
- Fatal
- Unknown

9.3. INVESTIGATOR REQUIREMENTS AND INSTRUCTIONS FOR REPORTING ADVERSE EVENTS / SERIOUS ADVERSE EVENTS /PREGNANCIES TO THE SPONSOR

9.3.1. Adverse Events

The AE reporting period for safety surveillance begins when the subject signs the ICF and ends at the subject's follow-up visit (the last follow up visit after the last dose of IMP). In this period, all new AEs regardless of cause or relationship, derived by spontaneous, unsolicited reports of subjects, by observation and by routine open questioning (such as "How do you feel?") need to be recorded in the CRF.

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

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

If the AE meets the criteria for seriousness, the SAE form must be completed and sent to the sponsor within 24 hours (see Section 9.3.2 here after).

9.3.2. Serious Adverse Events

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

Any SAEs that occur after the post treatment follow-up visit but within 30 days of the last dose of IMP(s), regardless of causality, should also be reported. Investigators are not obligated to actively seek SAEs after the CSP-defined follow up period, however, if the investigator learns of any SAEs that occur after clinical study participation has concluded and the event is deemed relevant to the use of IMP(s), he/she should promptly document and report the event to the sponsor at any time by using the SAE form.

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

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

Follow-up and outcomes should be reported and documented in the source documents for all subjects that experience an SAE. It is important that the information provided on the SAE form matches the information recorded on the CRF for the same event. In case an AE is ongoing at the time of the last follow-up visit, only the SAE form is to be updated, not the CRF.

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

9.3.3. Pregnancy

All initial reports of pregnancies in partners of male subjects included in the clinical study must be recorded and documented in the source documents (after specific informed consent is provided, see Section 10.4.2). The investigator must report each pregnancy immediately after getting knowledge about this on the pregnancy form, and under no circumstances should this

exceed 24 hours following the knowledge of the pregnancy, as is indicated on Page 2 under "Emergency Contact Information".

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

9.4. SPONSOR REPORTING REQUIREMENTS

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

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

All concerned investigators will receive a safety letter notifying them of relevant SUSAR reports associated with any IMP(s). The investigator should notify the IEC/IRB of SUSAR reports as soon as is practical, where this is required by local regulatory agencies, and in accordance with the local institutional policy.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

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

10.1. SPONSOR'S RESPONSIBILITIES

10.1.1. Regulatory Approval / Notification

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

10.1.2. Clinical Study Closure Considerations

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

The end of clinical study declaration will be submitted to the regulatory authorities and IEC/IRB after the complete clinical study has ended in all participating centers, in all countries. This notification will also be submitted within 90 days of the end of the clinical study in a given country/member state or within the timelines required by the local regulations.

Reasons for the closure of an investigational site include but are not limited to:

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

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

- Safety concerns
- Sufficient data suggesting lack of efficacy

10.1.3. Indemnification

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

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

10.1.4. Insurance

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

10.1.5. Reporting

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

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

10.1.6. Publication

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

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

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

10.2. INVESTIGATOR'S RESPONSIBILITIES

10.2.1. Financial Disclosure

Not applicable.

10.2.2. Source Data and Data Capture

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

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

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

10.2.3. Archiving

The investigator shall maintain the clinical study specific documents as specified in Section 8 "Essential Documents for the Conduct of a Clinical Study" of the ICH GCP Guidelines and as

required by the applicable regulatory requirement(s). The investigator should take measures to prevent accidental or premature destruction of these documents.

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

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

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

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

10.2.4. Participation Cards

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

10.3. CONFIDENTIALITY

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

All information concerning the product and the sponsor’s operations (such as patent applications, 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 clinical study and will not use it for other purposes.

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

10.4. ETHICAL CONSIDERATIONS

10.4.1. Independent Ethics Committee / Institutional Review Board

This clinical study can only be undertaken after full approval of the CSP, informed consent, any other written information given to subjects, and subject recruitment materials has been obtained from the IEC/IRB. This approval document must be dated and clearly identify the clinical study and the related clinical study documents being approved, including the subject compensation programs, if applicable.

During the course of clinical study at least the following documents will be provided to the IEC/IRB per local requirements:

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

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

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

10.4.2. Informed Consent

The investigator or designated personnel must explain the clinical study and the implications of participation (e.g. objectives, methods, anticipated benefits, and possible risks) to potential subjects according to applicable regulations prior to any clinical study related activity. Subjects will be informed that their participation is voluntary and that they may withdraw from the clinical study at any time. They will be informed that choosing not to participate or to withdraw from the clinical study will not have an impact on the care the subject will receive for the treatment of his/her disease. 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 clinical study, consent should be appropriately recorded by means of the subject's personally dated signature (or, if applicable, by the signature of an independent witness who certifies the subject's consent in writing) and by the investigator’s signature. 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 clinical study, the subject will be informed in a timely manner by means of an updated ICF. This amended ICF will be signed and dated by the subject (or, if applicable,

by an independent witness) and the investigator to document the willingness of the subject to continue with the clinical study.

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

[redacted]

Pregnant partners who agree to that information will be gathered about her pregnancy and the birth and health of her baby will sign a specific ICF to participate in the data collection.

10.5. DATA QUALITY CONTROL / ASSURANCE

10.5.1. Monitoring

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

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

10.5.2. Audit and Inspection

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

REFERENCES

[1] Cordier JF and Cottin V. Neglected evidence in idiopathic pulmonary fibrosis: from history to earlier diagnosis, Eur Respir J 2013;183:916-23.

[2] Kim DS, Collard HR, King TE Jr. Classifications and natural history of the idiopathic interstitial pneumonias, Am Thorac Soc 2006;3:285-92.

[3] M. B. F. K. e. a. Collard HR, " Acute exacerbations of idiopathic pulmonary fibrosis," Am J Respir Crit Care Med 2007;176:636-43.

[4] Meltzer EB and Noble PW. Idiopathic pulmonary fibrosis, Orphanet J Rare Dis 2008;3:8.

[5] Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis, Am J Respir Crit Care Med 2011;183:431-40.

[6] Raghu G, Collard HR, Egan, JJ, et al. n official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management, Am J Respir Crit Care Med 2011;183:788-824.

[7] Thomeer M, Costabe U, Rizzato G, et al. Comparison of registries of interstitial lung diseases in three European countries, Eur Respir J Suppl 2001;32:114s-118s.

[8] Raghu G, Weycker D, Edelsberg J. et al. Incidence and prevalence of idiopathic pulmonary fibrosis, Am J Respir Crit Care Med 2006;174:810-6.

[9] Fernández PER, Daniels CE, Schroeder DR, et al. Incidence, prevalence, and clinical course of idiopathic pulmonary fibrosis: a population-based study, Chest 2010;137(1):129.37.

[10] Navaratnam V, Fleming KM, West J, et al. The rising incidence of idiopathic pulmonary fibrosis in the UK, Thorax 2011;66(6):462-7.

[11] G. Raghu, S. Chen, W. Yeh, B. Maroni, Q. Li, Y. Lee en H. Collard, „Idiopathic pulmonary fibrosis in US Medicare beneficiaries aged 65 years and older: incidence, prevalence, and survival, 2001-11," *Lancet Respir Med,* vol. 2(7), pp. 566-572, 2014.

[12] Spagnolo P, Del Giovane C, Luppi F, et al. Non-steroid agents for idiopathic pulmonary fibrosis (review), Cochrance Database Syst Rev 2010; Sep 8 CD003134.

[13] Taniguchi H, Ebina M, Kondoh Y, et al. Pirfenidone in idiopathic pulmonary fibrosis, Eur Respir J 2010;35:821-9.

[14] Noble PW, Albera C, Bradford WZ, et al. Pirfenidone in patients with idiopathic pulmonary fibrosis, Lancet 2011;377:1760-9.

[15] King TE, Bradford WZ, Castro-Bernardini S, et al. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis, N Eng J Med 2014;370:2083-92.

[16] Richeldi L, du Bois RM, Raghu G, et al. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis, N Engl J Med 2014;370:2071-82.

[17] Esbriet. Summary of Product Characteristics.

[18] Ofev. Summary of Product Characteristics.

[19] Raghu G, Rochwerg B, Zhang Y, et al. n official ATS/ERS/JRS/ALAT clinical practice guideline: treatment of idiopathic pulmonary fibrosis, Am J Respir Crit Care Med 2015;192:e3-e19.

[20] Gagnon L, Leduc M, Thibodeau JF, et al. A newly discovered antifibrotic pathway regulated by two fatty acid receptors: GPR40 and GPR84, Am J Pathol 2018 Feb;15:1-17.

[21] Parker J, et al. PBI-4050 is safe and well tolerated and shows evidence of benefit in ideopathic lung fibrosis, Am J Respir Crit Care Med 2017;195:A7606.

[22] Wuyts W, Antoniou K, Borensztajn K, et al. Combination therapy: the future of management for idiopathic pulmonary fibrosis?, Lancet Resp Med 2014;2:933-42.

[23] Nathan SD, Albera C, Bradford WZ, et al. Effect of continued treatmnet with pirfenidone following clinically meaningful declines in forced vital capacity: analysis of data from three phase 3 trials in patienst with ideopathic pulmonary fibrosis, Thorax 2016;71(5):429-35.

[24] G. Raghu, M. Remy-Jardin, J. Myers, L. Richeldi and C. Ryerson, "Diagnosis of Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT clinical practice guideline," *Am J Respir Crit Care Med,* vol. 198, pp. e44-e68, 2018.

[25] Quanjer PH, Stanojevic S, Cole TJ, et al. 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 Fu, Eur Respir J 2012; 40(6):1324-43.

[26] Macintyre N, Crapo RO, Johnson DC, et al. Standardisation of the single-breath determination of carbon monoxide uptake in the lung, Eur Respir J 2005;26(4):710-35.

[27] American Thoracic Society. ATS Statement: Guidelines for the Six-Minute Walk Test, Am J Respir Crit Care Med 2002;166:117.

[28] Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper, Lancet Respir Med 2018 Feb;6(2):138-54.

[29] H. Collard, C. Ryerson, T. Corte, G. Jenkins, Y. Kondoh en D. Lederer, „Acute exacerbation of idiopathic pulmonary fibrosis," *Am J Respir Crit Care Med,* vol. 194, pp. 265-275, 2016.

[30] du Bois R, Weycker D, Albera C, et al. Six-Minute-Walk Test in Idiopathic Pulmonary Fibrosis, Am J Respir Crit Care Med 2011;183:1231-7.

[31] USNRC, "United States Nuclear Refulatory Commission. Fact sheet on biological effects of radiation.," May 2017. [Online]. Available: https://www.nrc.gov/reading-rm/doc-collections/fact-sheets/bio-effects-radiation.html. [Accessed Mar 2018].

[32] WNA, "World Nuclear Association," Jul 2016. [Online]. Available: http://www.world-nuclear.org/info/safety-and-security/radiation-and-health/nuclear-radiation-and-health-effects/. [Accessed Mar 2018].

[33] Investigator Brochure GLPG1205 Edition 5 (March 2018).

[34] Misharin AV, Morales-Nebreda L, Reyfman PA, et al. Monocyte-derived alveolar macrophages drive lung fibrosis and persist in the lung, J Exp Med. 2017 Aug;214(8):2387-404.

[35] Byrne AJ, Maher TM, Lloyd CM. Pulmonary Macrophages: A new pathway in Fibrosing Lung Disease?, Trends in Mol Med 2016;22(4):303-16.

[36] [redacted]

[37] Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry, Eur Respir J 2005;26:319-38.

APPENDICES

Appendix 1 High-resolution Computed Tomography/Biopsy Central Review Criteria

All chest HRCTs and histopathology slides of lung biopsies (if available and indicated) will be centrally reviewed by two independent radiologists with adjudication by a third radiologist if indicated and one independent histopathologist to confirm the diagnosis of IPF and therefore eligibility of the subject for the study.

The diagnostic criteria for IPF, published as the Fleishner Society White Paper [28], will be used to determine eligibility of the subject for the study.

In case a historical lung biopsy is available, this will be used as complementary information and will allow confirmation of UIP-IPF in certain cases. An algorithm to be used by the radiologists and the histopathologist to determine eligibility is available in the relevant manual.

	Typical UIP CT pattern	Probable UIP CT pattern	CT pattern indeterminate for UIP	CT features most consistent with non-IPF diagnosis
Distribution	Basal predominant (occasionally diffuse), and subpleural predominant; distribution is often heterogeneous	Basal and subpleural predominant; distribution is often heterogeneous	Variable or diffuse	Upper-lung or mid-lung predominant fibrosis; peribronchovascular predominance with subpleural sparing
Features	Honeycombing; reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; absence of features to suggest an alternative diagnosis	Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis*; honeycombing is absent; absence of features to suggest an alternative diagnosis	Evidence of fibrosis with some inconspicuous features suggestive of non-UIP pattern	Any of the following: predominant consolidation, extensive pure ground glass opacity (without acute exacerbation), extensive mosaic attenuation with extensive sharply defined lobular air trapping on expiration, diffuse nodules or cysts

UIP=usual interstitial pneumonia. IPF=idiopathic pulmonary fibrosis. *Reticular pattern is superimposed on ground glass opacity, and in these cases it is usually fibrotic. Pure ground glass opacity, however, would be against the diagnosis of UIP or IPF and would suggest acute exacerbation, hypersensitivity pneumonitis, or other conditions.

Table 1: **Diagnostic categories of UIP based on CT patterns**

	Definite UIP-IPF	Probable UIP-IPF	Indeterminate for UIP-IPF	Features most consistent with an alternative diagnosis
General comments	Patients show features with all four criteria, and do not show features that might suggest an alternative diagnosis (eg, non-UIP)	Patients show either honeycomb fibrosis only, or a severe fibrosing process that falls short of showing all four criteria for definite UIP-IPF and do not show features that might suggest an alternative diagnosis	Patients show evidence of a fibrosing process but with features that are more in favour of either a non-UIP pattern, or UIP in a setting other than IPF	Patients show either a UIP pattern with ancillary features strongly suggesting an alternative diagnosis, or a non-UIP pattern (see cell below)
Specific criteria	Dense fibrosis causing architecture remodelling with frequent honeycombing; patchy lung involvement by fibrosis; subpleural or paraseptal distribution, or both; fibroblast foci at the edge of dense scars	Honeycomb fibrosis only or; dense fibrosis causing architecture remodelling with frequent honeycombing; patchy lung involvement by fibrosis; fibroblast foci at the edge of dense scars may or may not be present	Patients have less compelling histological changes than those classified by the final column (eg, occasional foci of centrilobular injury or scarring, rare granulomas or giant cells, only a minor degree of lymphoid hyperplasia or diffuse inflammation, or diffuse homogenous fibrosis favouring fibrotic non-specific interstitial pneumonia); these features, and the differential diagnoses they call to mind, become part of the multidisciplinary discussion and decision with regard to a multidisciplinary diagnosis of IPF, or not	Non-UIP pattern: patients with features of other fibrotic disorders—eg, fibrotic hypersensitivity pneumonitis, fibrotic non-specific interstitial pneumonia, fibrosing organising pneumonia, pleuroparenchymal fibroelastosis, pulmonary Langerhans cell histiocytosis, or smoking-related interstitial fibrosis; UIP pattern with ancillary features strongly suggesting an alternative diagnosis: eg, prominent diffuse alveolar damage or organising pneumonia (consider acute exacerbation of UIP), granulomas, (consider hypersensitivity pneumonitis, sarcoid, infection), marked interstitial inflammatory cell infiltrate away from areas of UIP (consider hypersensitivity pneumonitis)

UIP=usual interstitial pneumonia. IPF=idiopathic pulmonary fibrosis.

Table 2: **Histopathological criteria for UIP in IPF (UIP-IPF)**

Appendix 2 Definition of Acute Idiopathic Pulmonary Fibrosis Exacerbation

Definition and diagnostic criteria are defined as follows [29]:

Definition:

An acute, clinically significant respiratory deterioration characterized by evidence of new widespread alveolar abnormality.

Diagnostic criteria:

- Previous or concurrent diagnosis of IPF
- Acute worsening or development of dyspnea typically < 1 month duration
- Computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern
- Deterioration not fully explained by cardiac failure or fluid overload

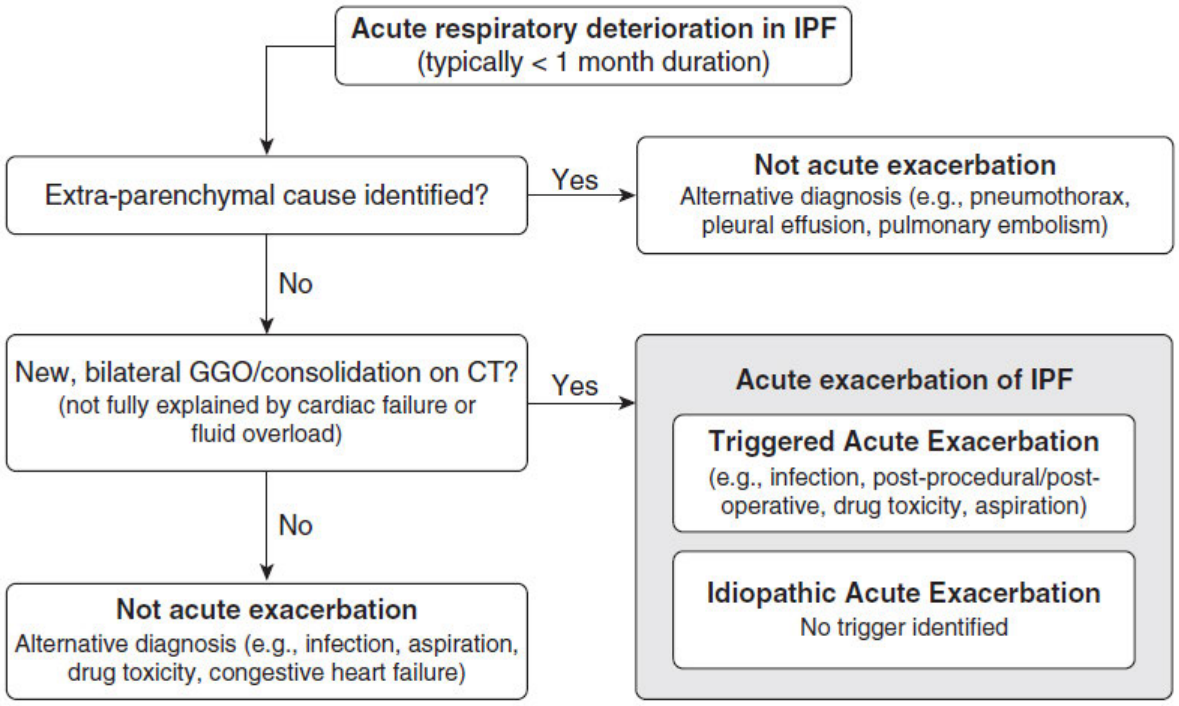


Figure 3. Proposed conceptual framework for evaluation of acute respiratory deterioration in idiopathic pulmonary fibrosis (IPF). Acute respiratory deterioration of IPF (defined as "typically <1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural effusion) or parenchymal. Parenchymal causes that demonstrate new bilateral ground-glass opacification (GGO)/consolidation on computed tomography (CT) that is not fully explained by cardiac failure or fluid overload are categorized as acute exacerbations of IPF, regardless of the presence or absence of a known trigger (e.g., infection). Acute exacerbations are further categorized as triggered acute exacerbation or idiopathic acute exacerbation, depending on whether an underlying trigger for acute exacerbation is found.

Appendix 3 Contraindications for 6-Minute Walk Test

Absolute contraindications:

- Unstable angina during the previous month [27]
- Myocardial infarction during the previous month [27]
- Oxygen saturation measured by pulse oximetry <88 % after 10 minutes of rest of breathing room air or at baseline oxygen flow rate [30].

Relative contraindications [27]

- Resting heart rate >120 beats per minute
- SBP >180 mmHg
- DBP >100 mmHg

Source: [27]

Appendix 4 Normal Ranges

NORMAL RANGES FOR VITAL SIGNS

Normal ranges applicable in supine position (after 5 minutes):

Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)	Oral/Tympanic temperature (°C)	Respiratory rate (RR) (breaths/minute)
90≤ SBP ≤150	45≤ DBP ≤90	50≤ HR ≤100	35.5≤ t° ≤37.5	12 ≤ RR ≤ 18

NORMAL RANGES FOR ECG PARAMETERS

Normal ranges applicable in supine position (after 5 minutes):

PR (ms)	QRS (ms)	QTcF (ms)	Heart rate (bpm)
120≤ PR ≤220	QRS ≤120	QTcF ≤450 (male) QTcF ≤460 (female)	50≤ HR ≤100

Appendix 5 Non-exhaustive List of Known Breast Cancer Resistance Protein Substrates

Substrate liability demonstrated in vitro:

4-methylumbelliferone sulfate
Daunorubicin
Doxorubicin
Estradiol-17beta-glucuronide
Estrone 3-sulfate
Hematoporphyrin
Imatinib
Methotrexate
Mitoxantrone
Pheophorbide A
Pitavastatin
Rosuvastatin
SN-38
SN-38 glucuronide
Sulfasalazine
Topotecan

In vivo substrates, from clinical studies:

Rosuvastatin
Pitavastatin
Topotecan

Appendix 6 Non-exhaustive List of Known Organic Cation Transporter 2 Substrates

Known OCT2 substrates:

Amantadine
Amiloride
Cimetidine
Dopamine
Epinephrine
Famotidine
Histamine
Lamivudine
Memantine
Metformin*
N-methylpyridinium
Norepinephrine
Prostaglandin E2
Prostaglandin F2alpha
Ranitidine
Serotonin
Tetraethylammonium
Varenicline*

* denotes drugs that can potentially be used for in vivo (clinical) studies of the designated transporter

Appendix 7 Exposure to Radiation

HRCT for IPF diagnosis

A chest scan for IPF diagnosis will expose a subject to approximately 4–5 mSv.

[redacted]

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 is of 3.1 mSv per year in the US and 2.4 mSv per year in Europe [31, 32].

Appendix 8 Non-exhaustive List of Medications Known to be Dual Inhibitors of CYP3A4 and CYP2C19 Enzymes

Medications known to be dual inhibitors of CYP3A4 and CYP2C19 are prohibited during the study. The following is a non-exhaustive list of these medications as guidance for the investigator.

- Chloramphenicol
- Cimetidine
- Fluvoxamine
- Ketoconazole
- Voriconazole

Appendix 9 Non-exhaustive List of Medications Known to be Strong Inducers of CYP3A4 or CYP2C19

Medications known to be strong inducers of CYP3A4 or CYP2C19 are prohibited during the study. The following is a non-exhaustive list of these medications as guidance for the investigator.

- Barbiturates
- Carbamazepine
- Modafinil
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Pioglitazone
- Rifabutin
- Rifampin
- St. John's Wort
- Norethindrone

Appendix 10 Non-exhaustive List of Medications Known to Prolong QT interval

Medications known to prolong QT interval are to be used with caution during the study. The following is a non-exhaustive list of these medications as guidance for the investigator.

- Disopyramide
- Dofetilide
- Flecainide
- Ibutilide
- Quinidine
- Sotalol

SIGNATURE PAGE – SPONSOR

Study Title: A Phase II randomized, double-blind, placebo-controlled, 26-week study to evaluate the efficacy, safety and tolerability of GLPG1205 in subjects with idiopathic pulmonary fibrosis

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

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

[redacted] MD		
Study Physician	Signature	Date

SIGNATURE PAGE – INVESTIGATOR

Study Title: A Phase II randomized, double-blind, placebo-controlled, 26-week study to evaluate the efficacy, safety and tolerability of GLPG1205 in subjects with idiopathic pulmonary fibrosis

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

Investigator Name	Signature	Date

Signature Page for glpg1205-cl-220-protocol 10923

Approval	[redacted] Translational Medicine Leader Translational Medicine 30-Apr-2020 17:48:03 GMT+0000

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