Galápagos

CLINICAL STUDY PROTOCOL

Project Number:	GLPG1690
Study Number:	GLPG1690-CL-303
Study Title:	A Phase 3, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of GLPG1690 in addition to local standard of care for minimum 52 weeks in subjects with idiopathic pulmonary fibrosis.

Development Phase:	3	**Status:**	Final
CSP Version:	7.00	**Date:**	8-Jun-2020
Amendment 5			
EudraCT No.:	2018-001405-87		
CT.gov No.:	NCT03711162		
IND No.:	130687		
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** 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] SAE 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. Please refer to the study contact list in the investigator site file for the CRO medical contact details.

Sponsor Contact number:

[redacted]

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CLINICAL STUDY PROTOCOL HISTORY

CSP / Amendment #	Date	Rationale Including General / Country Specific
CSP Version 7.00 / Amendment 5	08-Jun-2020	To implement the urgent safety measures (USMs) for protection of subjects during the Coronavirus disease (COVID-19) pandemic - General
CSP Version 6.00 / Amendment 4	17-Dec-2019	Update of the exclusion criteria, and addition of the possibility to receive investigational medicinal product (IMP) in an extension study - General
CSP Version 5.00 / Amendment 3	12-Nov-2019	Specification of IMP intake time for subjects taking nintedanib - General
CSP Version 4.00 / Amendment 2	11-Feb-2019	General
CSP Version 3.00 / Amendment 1	27-Oct-2018	Changes to accommodate requests made under the Voluntary Harmonization Procedure (VHP)
CSP Version 2.00 / Update 1	01-Jun-2018	Minor edits and edits based on ad hoc IB update – General
CSP Version 1.00	27-Apr-2018	Initial Protocol Version – General

SUMMARY OF CHANGES

Amendment 5 (General)

The overall reason for this amendment: is to implement the urgent safety measures (USMs) for protection of study subjects during the Coronavirus disease (COVID-19) pandemic. These were detailed in the USM letter dated 07 May 2020 and sent to investigators, Competent Authorities, Ethics Committees, and Institutional Review Boards.

The USMs are introduced due to the exceptional situation generated by the COVID-19 pandemic. The objective of these USMs is to limit the risk of exposure to COVID-19 infection to ensure the safety and well-being of study subjects.

The USMs are:

- phone visits or televisits as alternative to on-site visits;
- collection of study assessments at the subject's home or other remote location (if possible and available);
- extension of visit windows;
- additional guidance for on-site visits;
- direct-to-patient (DTP) shipment of investigational medicinal product (IMP) and other supplies to the subject's home;
- additional guidance on the decision for continuation of IMP after missed visits.

In addition:

- Exclusion criterion 15 has been amended to include all lower respiratory tract infections requiring treatment, rather than those requiring antibiotic treatment.
- Clarification has been added that the investigator will be responsible for managing COVID-19 infected subjects.
- Exclusion criterion 5 was modified to clarify that subjects are permitted to take stable doses of immunosuppressive medication for reasons other than treatment of idiopathic pulmonary fibrosis (IPF).
- The possibility was added to perform source data review remotely when access to hospitals is restricted.
- The international nonproprietary name, ziritaxestat, was added.

The changes made to the clinical study protocol (CSP) GLPG1690-CL-303 Version 6.00 (17-Dec-2019) are listed below, with a brief rationale of each change and the applicable sections.

If a randomized subject is not able to attend a scheduled study visit on site for any COVID-19 related reason, then the investigator should perform a phone call or use a virtual platform such as Skype, Facetime, etc., to evaluate safety and assess well-being of the study subject.

Subject visits at home or at a remote location (other than the investigational site) can be considered at the investigator's discretion.

Applicable Sections:

Section 4.1 Clinical Study Design

Section 6 Clinical Study Assessments

Section 6.1.1 Alternative Timing and Assessment Procedures for Subjects who, due to any Covid-19-related Reason, Cannot Perform the Study Procedures

Section 6.11.1 Schedule of Activities: Screening and First 52 Weeks of Study Treatment

Section 6.11.2 Schedule of Activities: After 52 Weeks of Study Treatment

Amendment 5 (General)
To allow for the flexibility of obtaining safety and efficacy data when subjects are unable or unwilling to complete the study procedures due to any COVID-19-related issue, the visit windows for Visits 5, 6, 7, 8, 10, and 11 may be increased to ±7 days and the visit windows for Visit 9 and Visit 12 may be increased to ±28 days. **Applicable Sections**: Section 4.1 Clinical Study Design Section 6 Clinical Study Assessments Section 6.1.1 Alternative Timing and Assessment Procedures for Subjects who, due to any Covid-19-related Reason, Cannot Perform the Study Procedures Section 6.11.1 Schedule of Activities: Screening and First 52 Weeks of Study Treatment
At all times, the intent should be to ensure that study subjects can continue to take IMP without interruptions, if safe and deemed appropriate by the investigator. Guidance on when IMP should be interrupted and on re-start is provided. **Applicable Section:** Section 6.1.1 Alternative Timing and Assessment Procedures for Subjects who, due to any Covid-19-related Reason, Cannot Perform the Study Procedures
Information on the assessments/activities that should be performed (if possible) is provided for the on-site visits, for the home (or remote other location) visits, and for the phone/televisits. **Applicable Sections:** Section 4.1 Clinical Study Design Section 6 Clinical Study Assessments Section 6.1.1 Alternative Timing and Assessment Procedures for Subjects who, due to any Covid-19-related Reason, Cannot Perform the Study Procedures Section 6.4 Subject Diary Card Section 6.5.1.1 Spirometry Section 6.5.1.2 DLCO Section 6.5.1.3 Arterial Oxygen Saturation Section 6.5.3 Quality of Life Section 6.5.4 Functional Exercise Capacity Testing: 6MWT Section 6.6. Safety Assessments Section 6.6.5 Electrocardiogram Section 6.7 Pharmacokinetic Assessments Section 6.8 Pharmacodynamic Assessments Section 6.9.1 Disease-specific Biomarker Evaluations Section 6.11.1 Schedule of Activities: Screening and First 52 Weeks of Study Treatment Section 6.11.2 Schedule of Activities: After 52 Weeks of Study Treatment

Amendment 5 (General)
Exclusion criterion 15 has been amended to exclude all lower respiratory tract infections requiring treatment (rather than those requiring antibiotic treatment) within 4 weeks prior to screening and/or during the screening period. This is to exclude subjects with suspected or confirmed COVID-19 lower respiratory tract infections. A clarification has been added that the investigator will be responsible for managing COVID-19 infected subjects, and that the decision to continue or interrupt IMP for subjects with confirmed or suspected cases of COVID-19 infection is at the investigator's discretion. Guidance for reporting of suspected and confirmed COVID-19 cases in randomized subjects has been added. **Applicable Sections:** Section 4.1.2 Guidance for Dose Modification in Case of Adverse Events Section 4.4 Potential Risks and Benefits Section 4.5.2 Exclusion Criteria
Exclusion criterion 5 was modified to clarify that subjects are permitted to take stable doses of immunosuppressive medication for reasons other than treatment of idiopathic pulmonary fibrosis (IPF). The rationale is to ensure that subjects who are on immunosuppressives due to conditions other than IPF (such as post solid organ transplants and inflammatory bowel disease) are not excluded from the study. **Applicable Section:** Section 4.5.2 Exclusion Criteria
If a randomized subject is not able to attend a scheduled study visit on site for any COVID-19 related reason, IMP and other supplies can be shipped via DTP shipment to the study subject when required due to the COVID-19 situation as per ICH-GCP principles. **Applicable Sections:** Section 5.3 Packaging, Labelling, and Distribution Section 6.1.1 Alternative Timing and Assessment Procedures for Subjects who, due to any Covid 19-related Reason, Cannot Perform the Study Procedures Section 6.4 Subject Diary Card
The possibility was added to perform source data verification remotely. **Applicable Section:** Section 10.5.1 Monitoring
The international nonproprietary name, ziritaxestat, has been added. **Applicable Section:** Section 2.1.1 Physical, Chemical, Pharmaceutical Properties, and Formulations

Amendment 4 (General)
The overall reason for this amendment: is an update of the exclusion criteria, and addition of the possibility to receive investigational medicinal product (IMP) in an extension study.
The changes made to the clinical study protocol (CSP) GLPG1690-CL-303 Version 5.00 (12 Nov 2019), are listed below, with a brief rationale of each change and the applicable sections.
The information on GLPG1690 has been updated according to Edition 6 of the Investigator's Brochure (28-Jun-2019). **Applicable Sections**: Section 2 Introduction
The possibility of IMP being offered to eligible subjects in an extension study has been added. **Applicable Section:** Section 4.1 Clinical Study Design
Additional clarification is given with relation to study visits for subjects who permanently discontinue IMP but remain in the study. Subjects will still be encouraged to complete all following visits and evaluations as originally planned per protocol. If not possible to complete all visits, preference should be given to complete: • the first scheduled visit after their Early Treatment Discontinuation (ETD) • the Week 26 visit (if not done before IMP discontinuation) • the Week 52 visit (if not done before IMP discontinuation) • after Week 52, visits every 24 weeks up to End of Study Assessments (EoSA), as described in Section 6.11.2 **Applicable Sections:** Section 4.1 Clinical study design Section 4.5.4 Treatment Discontinuation, Subject Withdrawal, and Study Termination
For subjects still taking IMP and who had their last scheduled visit more than 6 weeks before the date that the last subject reaches 52 weeks into the study (Visit 12), the timing of the End of Study Treatment (EoST) visit has been reduced from 4 weeks to 2 weeks after the last subject reached 52 weeks. **Applicable sections:** Section 4.1 Clinical Study Design Section 6.1 Timing of assessments

Amendment 4 (General)
For a subset of subjects who complete the EoST visit (i.e. still on treatment at that time), an additional blood sample for pharmacodynamic (PD) assessment will be drawn at the follow-up (FU) visit. The purpose of these samples is to gather additional data on the lysophosphatidic acid (LPA) C18:2 levels and as needed to establish an LPA C18:2 time course after the last dose of IMP. The follow up visit will be scheduled 4 weeks after EoST/EoSA visit (visit at clinical center or phone call, depending whether only vital status or also a PD FU blood sample needs to be collected). **Applicable Sections:** Section 6.1 Timing of assessments Section 6.8 Pharmacodynamic Assessments Section 6.11 Schedule of activities
The required procedures for repetition an ECG in the case of abnormal findings were clarified. **Applicable Sections:** Section 4.5.4 Treatment Discontinuation, Subject Withdrawal, and Study Termination Section 6.6.5 Electrocardiogram
The stratification of randomization by standard of care treatment has been further clarified. Recruitment may be stopped earlier in one (or more) strata to maintain the balance as indicated, while the other strata continue to recruit. **Applicable Sections:** Section 4.6.1 Randomization
The following exclusion criteria have been modified for clarification. • Exclusion criterion 8 was modified to allow patients with implantable cardiovascular devices (e.g. pacemaker) affecting the QT interval time to be enrolled in the study, based upon investigator judgment following cardiologist consultation if deemed necessary, and only after discussion with the medical monitor. • Exclusion criterion 22 was extended to exclude patients with a history of nintedanib-related increase in liver function tests of greater than 5 x the upper limit of normal (ULN). • Exclusion criterion 25 was modified to add the restriction for patients previously exposed to investigational antibody therapy. • Exclusion criterion 29 was added to include laboratory findings suggestive of cholestasis. This is in alignment with the existing instructions on findings that would lead to discontinuation of treatment. The screening assessments to be performed at Visit 2 that are listed in Section 6.1 were updated for assessment of exclusion criterion 29. **Applicable Section:** Section 4.5.2 Exclusion criteria Section 6.1 Timing of Assessments

Amendment 4 (General)
The description of the high-resolution computed tomography (HRCT) evaluation process for assessing eligibility has been removed from Section 4.1 and Section 6.1, and is now described and clarified in Appendix 1. **Applicable sections:** Section 4.1 Clinical study design Section 4.2.2 Clinical study design rationale Section 6.1 Timing of assessments Appendix 1 HRCT/biopsy central review criteria
Events meeting the following defined criteria must be reported as a serious adverse event (SAE) and IMP must be discontinued: • AST or ALT ≥8xULN • AST or ALT ≥3xULN with signs of severe liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥1.5xULN or International Normalized Ratio [INR] >1.5) The investigations and steps to be taken by the investigator have been described in Section 4.5.4. In addition, an optional review of safety data associated with liver function tests has been added. **Applicable Sections:** Section 4.5.4 Treatment Discontinuation, Subject Withdrawal, and Study Termination Section 8.3 Additional optional independent review of safety data Section 9.1.5. Clinical laboratory abnormalities and other abnormal assessments as adverse events or serious adverse events Appendix 9 Algorithm for elevated liver function tests
The collection of history of progression of disease, as defined by a relative decline in the forced vital capacity (FVC) of at least 10% of the predicted value, during the 1 year prior to screening has been included. **Applicable Section:** Section 6.3 Initial Subject and disease characteristics
Suboxone was removed from the list of known strong Cytochrome P450 (CYP) CYP3A4 inhibitors because its constituents, naloxone and bupenophine are not known to be strong inhibitors. Azelastine was removed from the list of known potent P-glycoprotein (P-gp) inhibitors in Appendix 6 because it is primarily used as a nasal spray to treat allergic rhinitis and as eye drops for allergic conjunctivitis, therefore the risk of drug-drug interaction is negligible. **Applicable Section:** Appendix 5 Known strong CYP3A4 inhibitors Appendix 6 Known potent P-gp inhibitors

Amendment 4 (General)
It was clarified that decisions on eligibility for rescreening, permitted comedications, and discontinuation of treatment in case of worsening of IPF can be taken on a case-by-case basis by the investigator and in case of doubt can be discussed with the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available). **Applicable Sections:** Section 4.5.3.2 Prior and concomitant medications Section 6.3 Initial subject and disease characteristics
The timing when vital status should be collected for subjects who withdraw from the study has been clarified. **Applicable Sections:** Section 4.5.4 Treatment discontinuation, subject withdrawal, and study termination Section 6.11 Schedule of Activities
A table has been added to clarify the PK sampling times. **Applicable Section:** Section 6.7 Pharmacokinetic Assessments
Typographical corrections were made to Appendices 3 and 4. Further clarifications and corrections have been made throughout the protocol.

Amendment 3 (General)
The overall reason for this amendment: is to add new data from the GLPG1690-CL-113 drug-drug interaction study on interaction of GLPG1690 with nintedanib, and to change the IMP intake time for all subjects taking nintedanib to approximately 4 hours after the morning nintedanib dose.
The changes made to the CSP GLPG1690-CL-303 Version 4.00 (11 Feb 2019), are listed below, with a brief rationale of each change and the applicable sections.
Subjects taking nintedanib are recommended to take the daily dose of IMP at or after lunch, i.e. approximately 4 hours after the morning dose of nintedanib. All subjects taking nintedanib will be asked to indicate via a tick box on the diary card for each record of IMP whether the IMP administration was approximately 4 hours after the nintedanib morning dose. **Applicable Sections:** Section 4.4 Potential Risks and Benefits Section 5.2 Dosage and Administration Section 6.4 Subject Diary Card

Amendment 3 (General)
For subjects taking nintedanib at screening and randomization, until they stop taking nintedanib, the pharmacokinetic sample window after nintedanib intake and before IMP intake at Visits 4, 5, 6,7, 8, 10, and 11, and every 12 weeks after Visit 12 (week 52) has been changed from 2-5 hours to 2-6 hours after nintedanib morning dose. **Applicable Sections:** Section 6.1 Timing of Assessments Section 6.7 Pharmacokinetic Assessments Section 6.11 Schedule of Activities
For all subjects on nintedanib, the blood sampling at Visits 3, 9, and 12 can be performed after the ECG assessment and before the oxygen saturation test. **Applicable Section:** Section 6.1 Timing of Assessments
The following administrative changes have been made throughout the protocol. – The study physician has been changed – The Investigator's Brochure version has been updated to Edition 6

Amendment 2 (General)
The overall reason for this amendment: is to change and clarify inclusion criteria regarding diagnosis and background standard of care medication for idiopathic pulmonary fibrosis, to clarify screening procedures, to include new drug-drug interaction information for investigational medicinal product (IMP) with pirfenidone and nintedanib, and to update the information and guidance reflecting new data from nonclinical fertility studies. Additionally, the multiple testing approach as recommended in Health Authority feedback has been included in the statistical analysis section.
An 'other' (exploratory) objective has been added to evaluate the impact of GLPG1690 treatment on Health Resource Utilization parameters by patients with idiopathic pulmonary fibrosis (IPF). **Applicable Sections:** Section 1 Summary Section 3.3. Other objectives Section 4.3.3 Other endpoints Section 6.5.4 Health resource utilization Section 7.3.4 Analyses of efficacy parameters

Amendment 2 (General)

The following clarifications and corrections have been made:

- The liver function test (LFT) threshold at Visit 3 that would lead to IMP discontinuation for aspartate aminotransferase [AST] and alanine aminotransferase [ALT] has been corrected in Section 4.1.2 from ≥1.5 x to <3 x upper limit of normal (ULN) to ≥1.5x ULN, and is now in line with exclusion criterion 22 and Section 4.6.4.
- Figure 2 depicting the dose modification strategy has been updated for clarification.
- The statement that IMP should not be administered to subjects with moderate to severe renal impairment has been corrected to only include severe renal impairment, in line with exclusion criterion 23.

Applicable Sections:

Section 4.1.2 Guidance for dose modification

Section 4.1.2 Guidance for dose modification in case of adverse events

Section 4.4 Potential risks and benefits – special populations

Subject Eligibility. The clinical diagnostic requirements have been clarified and corrected.

- Inclusion criterion 4: Diagnosis of IPF should be made using the guideline current at the time of diagnosis.
- The reference to the ATS/ERS/JRS/ALAT diagnostic criteria 2011 has been corrected, and reference to the latest ATS/ERS/JRS/ALAT diagnostic criteria of 2018 has been added (Raghu G, Remy-Jardin M, Myers JL, et al. American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Society. "Diagnosis of Idiopathic Pulmonary Fibrosis. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline." Am J Respir Crit Care Med. 2018 Sep 1;198(5):e44-e68).
- Subjects with typical and probable usual interstitial pneumonia – idiopathic pulmonary fibrosis (UIP-IPF) pattern on high-resolution computed tomography (HRCT) will be eligible unless a historical lung biopsy, if available, is not in accordance with this diagnosis. Indeterminate UIP-IPF pattern on HRCT will need confirmation through review of historical lung biopsy, if available.
- The interval of 6 weeks before a patient can be rescreened was replaced by an interval determined at the investigator's discretion, taking into account the inclusion and exclusion criteria. Rescreening with the purpose to repeat a HRCT scan, is not allowed.
- The instructions for screening assessments have been clarified.

Applicable Sections:

Section 4.2.2 Clinical study design rationale

Section 4.5.1 Inclusion criteria

Section 6.1 Timing of assessments

Section 6.3 Initial subject and disease characteristics

Amendment 2 (General)
Eligibility Criteria: Stability of Standard of care before enrolment Inclusion criterion 6: has been updated to require stability of standard of care treatment prior to randomization. – Subjects receiving local standard of care for the treatment of IPF, defined as either pirfenidone or nintedanib at a stable dose for at least 2 months before start of screening, and during screening; or neither pirfenidone or nintedanib (for any reason). A stable dose is defined as the highest dose tolerated by the subject during those two months. **Applicable Sections:** Summary Section 4.5.1 Inclusion criteria 4.5.3.2 Prior and concomitant medications
The oxygen titration test requirements at Visit 2 for the 6-Minute Walk Test have been clarified; the oxygen saturation (SpO_2) during the walk has been clarified to ≥83% with 6 L O_2/minute or ≥88% with 0, 2 or 4 L O_2/minute (instead of ≥83% with 6 L O_2/minute or ≥88% with ~~≤4~~ L O_2/minute). **Applicable Sections:** Section 4.5.1 Inclusion criteria Section 6.5.4 6-Minute Walk Test Section 6.3 Initial subject and disease characteristics
Eligibility criteria: Exclusion criteria – Exclusion criterion 5 has been modified to exclude only a current immunosuppressive condition. – Exclusion criterion 6, detailing hepatitis test requirements, has been modulated because GLPG1690 is not known to have immunosuppressant action and the risk for hepatitis reactivation is considered to be low. The following changes have been made: • Hepatitis C virus (HCV) antibody testing will, if positive, be 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 screening of the IMP can be screened." – Exclusion criterion 14: the definition of an acute exacerbation has been added into the criterion together with a cross-reference to the existing Appendix 11 detailing the definition. – Exclusion criterion 20: "A gastric perforation within 3 months prior to screening or during screening" has been added to this criterion as gastric perforation is a reported adverse drug reaction to nintedanib. – Exclusion criterion 21 was updated with the following text to comply with French law (Articles L.1121-5 to L.1121-8 and L.1122-1-3, French Public Health Code), and to harmonize with Study GLPG1690-CL-304.: "as well as any subjects falling into any of the categories of persons listed by applicable law and regulations as protected persons for which participation in a study is prohibited or subject to restrictions." – Exclusion criterion 22 excluding patients with liver function test abnormalities, has been modified to include also patients with moderate or severe hepatic impairment (Child-Pugh B or C). **Applicable Sections:**

Amendment 2 (General)
Section 4.5.2 Exclusion criteria
The information on fertility has been updated with the results of nonclinical male and female fertility studies in rats. The recommendation for males to store sperm before taking part in the study has been removed, and replaced with guidance for male subjects to withdraw if they intend to father a child. **Applicable Sections:** Section 4.4 Potential risks and benefits Section 4.5.3.1.2 Precautions for sexual intercourse: male subjects
Interactions – The information on interaction with transporters in nonclinical studies has been updated. – The clinical safety and clinical pharmacokinetics sections have been updated based on recent data from two drug-drug interaction studies, one study with itraconazole and voriconazole, and one study with pirfenidone and nintedanib. Increased exposures of nintedanib, one of the standard of care treatments for IPF, was observed when coadministered with GLPG1690. – Additional PK sampling has been introduced to assess nintedanib levels. – A population PK analysis for nintedanib and pirfenidone has been added in the Statistical methods section. **Applicable Sections:** Section 2.1.3 Nonclinical pharmacokinetics and product metabolism Section 2.2.1 Clinical Safety Section 2.2.2 Clinical Pharmacokinetics Section 4.4 Potential risks and benefits Section 6.1 Timing of assessments Section 6.3 Initial subject and disease characteristics Section 6.4 Subject diary card Section 6.7 Pharmacokinetic assessments Section 6.11 Schedule of activities Section 7.3.6 Pharmacokinetics and Pharmacodynamics
The QTcF thresholds leading to discontinuation have been clarified, and the following has been added: – "If a normal QTcF is reported during the visit, but the central cardiologist reports it as abnormal (any of the two criteria above), then the IMP should be discontinued as soon as possible" **Applicable Sections:** Section 4.5.4 Treatment discontinuation, subject withdrawal, and study termination

Amendment 2 (General)
The list of clinical laboratory tests has been revised – Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) have been added to the hematology parameters to reflect the standard panel of investigations typically used in the IPF patient population. – If creatine kinase (CK) is elevated, then CK-muscle/brain (CK-MB) is to be measured, to monitor for muscle breakdown indicative of coronary heart disease. – Amylase and lipase have been added to monitor risk of pancreatitis, a reported risk/ adverse drug reaction for nintedanib. **Applicable Section:** Section 6.6.2 Clinical laboratory evaluations
Statistical analysis – The description of the statistical analysis of efficacy has been updated, to describe the determination of sample size multiple testing approach and multiplicity adjustment. – The proportion of St. George's Respiratory Questionnaire (SGRQ) responders and the proportion of subjects with hospitalization analysis was changed from Fisher exact test to a logistic regression model – The derivation of the IPF-specific version of St. George's Respiratory Questionnaire (SGRQ-I) (using 34 of the 50 test items) has been removed from the protocol (Yorke J, Jones P, and Swigris J. Development and validity testing of an IPF specific version of the St. George's Respiratory Questionnaire. Thorax, 2010;65(10):921 926). Some SGRQ items in SGRQ-I have weaker measurement properties than others when applied to patient populations other than the one for which SGRQ was developed. SGRQ-I has some missing components when derived from SGRQ. – The analysis for the health resource utilization parameters has been described **Applicable Sections:** Section 6.5.3 Quality of Life Section 7.1 Determination of sample size Section 7.3.4 Analyses of efficacy parameters
The non-exhaustive list of strong CYP3A4 inducers and potent P-gp inducers has been modified. Phenobarbital was removed because it is already included within the barbiturate group, and glucocorticoids (prednisone or equivalent) at > 10mg/day was specified, because high doses of glucocorticoids have been reported to be potential CYP3A4 inducers. Instructions for subjects to avoid double-strength grapefruit juice, which is potentially a potent CYP3A4 inhibitor have been added. **Applicable Section** Section 4.5.3.3 Food and beverage restrictions Appendix 4 Known strong CYP3A4 inducers and potent P-gp inducers
Voriconazole, a strong CYP3A4 inhibitor, has been added to the non-exhaustive list of strong CYP3A4 inhibitors in Appendix 5. **Applicable Section** Appendix 5 Known strong CYP3A4 inhibitors

Amendment 1
The overall reason for this amendment: Changes to accommodate requests made under the Voluntary Harmonization Procedure (VHP)
Clarification of definition of End of Trial for reporting purposes **Applicable Sections:** Section 4.1 Clinical Study Design Subheading 4.1.1 added with clarified definition of end of trial Additional subheading 4.1.2 added for the subsection on Guidance for dose modification in case of adverse events
The protocol was amended to require discontinuation when the criteria of liver enzymes AST or ALT ≥ 1.5 x ULN and / or total bilirubin ≥ 1.5 x ULN is met at Visit 3, **Applicable Sections:** Section 4.1.2, Section 4.5.4, Appendix 9
Reference to description of highly effective contraception/preventive exposure measures in Section 4.5.3.1 Precautions for Sexual Intercourse added to Inclusion criterion 11. **Applicable Section:** Section 4.5.1 Inclusion Criteria
Exclusion Criteria 2 and 21 combined into revised exclusion criterion 2 Replacement of exclusion criterion 21 with criterion to comply with the [redacted] **Applicable Section:** Section 4.5.2 Exclusion Criteria
Discontinuation to be mandatory for specified safety findings. **Applicable Section:** Section 4.5.4, Subsection: Discontinuation of IMP The wording “should be discontinued” was replaced by “will be discontinued”.
Specification that statistical testing will be 2-sided. **Applicable Sections:** Section 7.1, Section 7.3.4
Rationale for the sample size was added. **Applicable Section:** Section 7.1
Clarification of the planned pooled data analysis of the two identical studies, GLPG1690-CL-303 and GLPG1690-CL-304 **Applicable Section:** Section 7.3.4
The language related to the Declaration of Helsinki was updated to conform with EU Directives 2001/20/EC and 2005/28/EC **Applicable Sections:** Section 10

Amendment 1
The procedure for collection of informed consent of a patient unable to read and/or write was amended to comply with the [redacted] **Applicable Section:** Section 10.4.2

Update 1
Minor edits and edits based on ad hoc IB update – General

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviations

$\%FEV_1$	percent predicted forced expiratory volume in 1 second
%FVC	percent predicted forced vital capacity
6MWT	6-Minute Walk Test
AE	adverse event
ALAT	Latin American Thoracic Association
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AT1	angiotensin II receptor type 1
ATC	Anatomical Therapeutic Classification
ATS	American Thoracic Society
ATX	autotaxin
AUC	area under the plasma concentration-time curve
$AUC_{0-\infty}$	area under the concentration-time curve from time 0 to infinity
AUC_{0-24h}	area under the plasma concentration-time curve from time 0 to 24 hours
BLM	Bleomycin
BCRP	breast cancer resistance protein
b.i.d.	bis in die, twice daily
BSEP	bile salt export pump
BW	body weight
C_{Cr}	estimated creatinine clearance, calculated according to Cockcroft-Gault calculation
CEAC	clinical endpoint adjudication committee
CK	creatine kinase
C_{max}	maximum observed plasma concentration
COVID-19	Coronavirus disease
CRO	contract research organization
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CTGF	connective tissue growth factor
CYP	cytochrome P450
DBP	diastolic blood pressure

DDI	drug-drug interaction
DLCO	diffusing capacity of the lung for carbon monoxide
DTP	direct-to-patient
ECG	Electrocardiogram
E_{max}	maximum effect (expressed as a percentage reduction from baseline)
ENPP1/2	ectonucleotide pyrophosphatase/phosphodiesterase 1 or 2
eCOA	electronic clinical outcome assessment
EoSA	end of study assessments
EoST	end of study treatment
EQ-5D	EuroQOL 5-Dimensions Questionnaire
EQ-5D-3L	3-level version of EuroQOL 5-Dimensions Questionnaire
EQ VAS	EuroQOL visual analogue scale
ERS	European Respiratory Society
ETD	early treatment discontinuation
FAS	full analysis set
FC	food consumption
FDA	(United States) Food and Drug Administration
FEF_{25-75}	forced expiratory flow between 25% and 75% of exhaled volume
FEV_1	forced expiratory volume in 1 second
FIH	first-in-human
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GMP	Good Manufacturing Practices
GLP	Good Laboratory Practice
GGT	gamma glutamyl transferase
Hb	hemoglobin
HIV	human immunodeficiency virus
HMA	Heads of Medicines Agencies
HRCT	high-resolution computed tomography
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration (concentration resulting in 50% inhibition)
IC_{80}	80% inhibitory concentration (concentration resulting in 80% 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
I_{max}	predicted maximum concentration in the portal vein
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
K-BILD	King's Brief Interstitial Lung Disease
LB	lung biopsy
LC-MS/MS	liquid chromatography with tandem mass spectrometry
LCQ	Leicester Cough Questionnaire
LFT	liver function test
LPA	lysophosphatidic acid
LPC	lysophosphatidylcholine
LPD	lysophospholipase D
MCID	Minimal Clinical Important Difference
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
NOAEL	no observed adverse effects level
OATP	organic anion transporting polypeptide
OCT1	organic cation transporter 1
PD	pharmacodynamic(s)
PDE	Phosphodiesterase
P-gp	P-glycoprotein
PK	pharmacokinetic(s)
PLA	phospholipase A
PLC	phospholipase C
q.d.	quaque die, once daily

QTc	corrected QT interval
QTcF	QT interval corrected for heart rate using Fridericia's formula
QTcV	QT interval corrected for heart rate using Van de Water's formula
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SGRQ	St. George's Respiratory Questionnaire
SpO_2	oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse event
TGFβ	transforming growth factor β
t_{max}	time to maximum observed plasma concentration
UGT	uridine 5'-diphospho-glucuronosyltransferase
UIP-IPF	usual interstitial pneumonia – idiopathic pulmonary fibrosis
ULN	upper limit of the normal range
VAS	Visual Analogue Scale
V_{ss}	volume of distribution at steady state
WBC	white blood cell
WHO	World Health Organization
WOCBP	women of child bearing potential

Definition of Terms

BMI	weight (kg) / (height [m])^2
C_{Cr}	estimated creatinine clearance, calculated according to Cockcroft-Gault calculation: C_{Cr} (in mL/min) = [(140-age) x weight]/[72 x S_{Cr}] (x 0.85 for women), with S_{Cr} = serum creatinine in mg/dL, age in years and weight in kg
QTcF	QT interval corrected for heart rate using Fridericia's formula: $QTcF = QT/RR^{1/3}$, with RR = mean interval duration between consecutive RR peaks
QTcV	QT interval corrected for heart rate using Van de Water's formula: $QTcV = QT - 0.087\ (60/HR - 1)$, with HR = heart rate

1. SUMMARY

Objectives:

Primary Objective

- To evaluate the efficacy of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with idiopathic pulmonary fibrosis (IPF) as evaluated by the rate of decline of forced vital capacity (FVC) over a period of 52 weeks

Secondary Objectives

Key Secondary Objectives

- To evaluate the impact of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF on:
  - disease progression defined as deterioration of FVC or all-cause mortality at 52 weeks
  - respiratory-related hospitalization until the end of the study
  - changes in quality of life (measured by St. George's Respiratory Questionnaire [SGRQ] total score) at 52 weeks

Other Secondary Objectives

- To evaluate the efficacy of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF as evaluated by the rate of decline of FVC until the end of the study
- To evaluate the impact of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF on:
  - disease progression defined as deterioration of FVC or all-cause mortality until the end of the study
  - changes in quality of life (measured by SGRQ total score) until the end of the study
  - all-cause non-elective hospitalization until the end of the study
  - respiratory-related mortality until the end of the study
  - lung transplant until the end of the study
  - acute IPF exacerbation until the end of the study
  - all-cause mortality or lung transplant until the end of the study
  - all-cause mortality, or lung transplant, or qualifying for lung transplant until the end of the study
  - all-cause mortality, deterioration of FVC, or respiratory-related hospitalization until the end of the study
  - all-cause mortality or respiratory-related hospitalizations until the end of the study
- To evaluate the effect of two doses of GLPG1690 in addition to local standard of care compared to placebo on the changes from baseline in FVC at 52 weeks and until the end of the study
- To evaluate the safety and tolerability of two doses of GLPG1690 in addition to local standard of care compared to placebo until the end of the study

- To evaluate changes compared to placebo in subjects with IPF in:
  - cough-related quality of life (measured by the Leicester Cough Questionnaire [LCQ] and by the Visual Analogue Scale [VAS] Cough and Urge to Cough) at 52 weeks and until the end of the study
  - quality of life (measured by EuroQOL 5-Dimensions Questionnaire [EQ-5D] and King's Brief Interstitial Lung Disease [K-BILD] total score and domains over time) at 52 weeks and until the end of the study
- To evaluate the pharmacokinetics (PK) of GLPG1690, pirfenidone, and nintedanib (as appropriate) in subjects with IPF at 52 weeks and until the end of the study
- To evaluate the effect of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF on the changes in functional exercise capacity measured by the 6-Minute Walk Test (6MWT) at 52 weeks and until the end of the study
- To evaluate the effect of two doses of GLPG1690 in addition to local standard of care compared to placebo on the diffusing capacity of the lung for carbon monoxide (DLCO) at 52 weeks and until the end of the study

Other Objectives

- To evaluate the change in target biomarkers/pharmacodynamics (PD) in blood and/or clinical endpoints that may be relevant to GLPG1690 mechanism and/or clinical outcome, compared to placebo and compared to baseline
- To evaluate the change in disease-specific biomarkers in blood, compared to placebo and compared to baseline
- To assess the relationship between mutational status and clinical outcome and/or biomarker level
- To evaluate the effect on oxygen saturation (SpO_2) compared to baseline
- To evaluate the impact on Health Resource Utilization parameters

Design:

This clinical Phase 3 study is a randomized, double-blind, parallel-group, placebo-controlled multicenter study designed to evaluate the efficacy and safety of two doses (200 mg once daily [q.d.] and 600 mg q.d.) of orally administered GLPG1690 in addition to local standard of care for at least 52 weeks in adult subjects with a centrally confirmed diagnosis of IPF. Local standard of care for IPF is defined as receiving either pirfenidone or nintedanib at a stable dose for at least two months before screening, and during screening; or neither pirfenidone or nintedanib (for any reason). A stable dose is defined as the highest dose tolerated by the subject during those two months. A total of approximately 750 subjects with confirmed diagnosis of IPF will be randomized in a 1:1:1 ratio to receive GLPG1690 600 mg q.d., GLPG1690 200 mg q.d., or matching placebo (i.e. 250 subjects in each treatment group). Subjects will have their end of study treatment and follow-up visit planned when the last subject has reached his or her Week 52 visit.

Rationale:

Disease-modifying drugs such as pirfenidone and nintedanib have been shown to have a beneficial effect on the rate of decline in lung function (as measured by FVC over 1 year) and show a trend in favor of a reduction in mortality in patients with mild to moderate IPF. However, the residual decline of FVC over 1 year remains substantial. Therefore, there remains a considerable unmet medical need. In a proof-of-concept Phase 2a study, FVC values remained stable in the majority of subjects after 12 weeks of treatment with GLPG1690 600 mg q.d. Moreover, 12 weeks of treatment with GLPG1690 600 mg q.d. was

generally well tolerated. The current Phase 3 study is the next step in the clinical development of GLPG1690, evaluating the efficacy and safety of two doses of orally administered GLPG1690 (200 mg q.d. and 600 mg q.d.) compared to placebo in subjects with IPF in addition to local standard of care.

Endpoints:

Primary Endpoint

- Rate of decline of FVC (in mL) over a period of 52 weeks

Secondary Endpoints

Key Secondary Endpoints

- Disease progression defined as the composite endpoint of first occurrence of ≥10% absolute decline in percent predicted forced vital capacity (%FVC) or all-cause mortality at 52 weeks
- Time to first respiratory-related hospitalization until the end of the study
- Change from baseline in the SGRQ total score at 52 weeks

Other Secondary Endpoints

- Rate of decline of FVC (in mL) until the end of the study
- Disease progression defined as the composite endpoint of first occurrence of ≥10% absolute decline in %FVC or all-cause mortality until the end of the study
- Change from baseline in the SGRQ total score until the end of the study
- Time to first all-cause non-elective hospitalization until the end of the study
- Time to respiratory-related mortality until the end of the study
- Time to lung transplant until the end of the study
- Time to first acute IPF exacerbation until the end of the study
- Time to all-cause mortality or lung transplant until the end of the study
- Time to all-cause mortality, or lung transplant, or qualifying for lung transplant until the end of the study
- Time to all-cause mortality, ≥10% absolute decline in %FVC, or respiratory-related hospitalizations until the end of the study
- Time to all-cause mortality or respiratory-related hospitalizations until the end of the study
- FVC analyses at 52 weeks and until the end of the study:
    - absolute and relative change from baseline of FVC and %FVC
    - absolute categorical change of %FVC until the end of the study: decrease by >5, increase by >5, and change within ≤5
    - absolute categorical change of %FVC until the end of the study: decrease by >10, increase by >10, and change within ≤10
- Safety and tolerability over time until the end of the study
- Changes from baseline in cough-related quality of life, assessed by the LCQ total score and domains over time, and the VAS Cough and Urge to Cough, at 52 weeks and until the end of the study
- Changes from baseline in quality of life, assessed by the EQ-5D, K-BILD total score and domains over time, at 52 weeks and until the end of the study

- Plasma concentration of GLPG1690, pirfenidone, and nintedanib (as appropriate) at 52 weeks and until the end of the study
- Change from baseline in functional exercise capacity, assessed by the 6MWT distance, at 52 weeks and until the end of the study
- Change from baseline in DLCO (corrected for hemoglobin [Hb]) at 52 weeks and until the end of the study

Other Endpoints

- Changes in target biomarkers/PD in blood over time compared to baseline until the end of the study
- Changes in disease-specific biomarkers in blood over time compared to baseline until the end of the study
- Efficacy and biomarker endpoints by genotype subgroups
- Change from baseline in Borg scale before and after 6MWT at 52 weeks and until the end of the study
- Change from baseline in SpO_2 until the end of the study
- Health Resource Utilization parameters until the end of the study

2. INTRODUCTION

For details of GLPG1690, refer to the Investigator's Brochure (IB) (Edition 6, 28-Jun-2019) and any relevant updates/addenda/errata.

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

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, severely debilitating, and ultimately lethal lung disease predominantly affecting elderly male smokers or ex-smokers with a median age of 65 to 70 years [5]. 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) [4, 12, 14, 18, 28].

The estimated IPF prevalence ranges from 14.0 to 27.9 cases per 100,000 population in the United States and from 1.3 to 23.4 cases per 100,000 population in Europe (data from 1990-2011). The estimated IPF incidence in these studies ranges from 6.8 to 8.8 cases per 100,000 population in the United States and from 0.2 to 7.4 cases per 100,000 population in Europe [8, 22, 31, 38].

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. Consequently, these treatments are standard of care for many patients. Pirfenidone (antifibrotic, anti-inflammatory, and antioxidant treatment marketed as e.g. Esbriet®; indicated in adults for the treatment of mild to moderate IPF), was the first drug to be licensed specifically for IPF. Phase 3 studies demonstrated that the drug improved progression-free survival and slowed the decline in forced vital capacity (FVC). Moreover, pirfenidone may have a mortality benefit [13, 23, 34, 37]. The drug was approved in the European Union in 2011 and in the United States in 2014. Nintedanib (tyrosine kinase inhibitor marketed as e.g. Ofev®; indicated in adults for the treatment of IPF), was initially developed as an anticancer agent. In Phase 3 studies, it significantly reduced the decline in FVC compared with placebo. A trend towards a reduced death rate was also observed; however, the studies were not designed to detect differences in mortality [32]. The drug was approved in the United States in 2014 and in the European Union in 2015. Both treatments appear to slow disease progression but are frequently associated with side effects potentially limiting their use in clinical practice [7, 24, 29].

There thus remains a considerable unmet medical need for the investigation and development of novel IPF treatments targeting disease-relevant pathways.

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

Mode of Action

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

ATX, also known as ectonucleotide pyrophosphatase/phosphodiesterase 2 (ENPP2) or lysophospholipase D (LPD), is a ~120 kDa protein that belongs to the ENPP family of enzymes. ATX is the only ENPP enzyme with LPD activity and is responsible for the hydrolysis of lysophosphatidylcholine (LPC) to produce the bioactive lipid lysophosphatidic acid (LPA). The term LPA covers several chemical species able to activate LPA receptors depending on the nature of the fatty acid side chain on the glycerol backbone. The most abundant LPA species in human plasma is LPA C18:2 with a fatty acid side chain of 18 carbon atoms including two unsaturated bonds [2]. Literature data have identified the ATX/LPC axis as the main source of LPA in blood [36, 39].

Several publications suggest a role for ATX in the control of disease-affected lung function through effects on lung epithelial cells, fibroblasts, and smooth muscle cells [17]. In general, inflammatory conditions in the lung are often described as associated with increased ATX and LPA levels. Studies related to IPF indicated an increase in LPA levels in the bronchoalveolar lavage fluid of patients [35], an increase of ATX levels in human fibrotic lung [25], and an elevation of LPA C22:4 in exhaled breath condensate of patients [20]. Further, LPA1 knock-out and inhibitor studies revealed a key role for LPA in fibrotic processes in lung and were complemented by studies using cell-specific knock-out mice lacking ATX in bronchial epithelial cells and macrophages. These mice were shown to be less sensitive to models of lung fibrosis [25]. The role of LPA in lung remodeling relates to the effects of LPA on both lung fibroblasts (through LPA1) and epithelial cells (through LPA2). It has been demonstrated that LPA2 plays a key role in the activation of transforming growth factor β (TGFβ) in epithelial cells under fibrotic conditions [40].

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

2.1. BACKGROUND - NONCLINICAL STUDIES

2.1.1. Physical, Chemical, Pharmaceutical Properties, and Formulations

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

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

2.1.2. Pharmacology

2.1.2.1. Primary and Secondary Pharmacology

GLPG1690 is an ATX inhibitor (50% inhibitory concentration [IC_{50}] of 131 nM and 224 nM in biochemical assays with human enzyme and mouse enzyme, respectively). The LPA production after human plasma incubation was inhibited by GLPG1690 with an IC_{50} of 242 nM, demonstrating the low impact of plasma protein binding on the activity of the compound. The compound was selective over related enzymes like ENPP1, phosphodiesterase (PDE)4 and PDE5, and phospholipase A (PLA) and phospholipase C (PLC). Moreover,

GLPG1690 showed no inhibition in a panel of kinases. In a Cerep diversity panel (98 targets including receptors and ion channels), only three targets displayed more than 50% inhibition at 10 µM, namely angiotensin II receptor type 1 (AT1) (83%), sigma receptor (79%), and 5-lipoxygenase (68%). Follow-up studies showed GLPG1690 to be a weak antagonist of AT1 receptor with an IC_{50} of 5.4 µM (cell assay), a weak ligand of sigma 2 receptor with an IC_{50} of 1.5 µM, and inactive (IC_{50} >10 µM) on sigma 1 receptor. At high concentrations of GLPG1690, inhibition of AT1 and sigma receptors has been found. This may be associated with hypotension. However, no adverse events (AEs) were observed in a hemodynamic study in the dog. For more details refer to the IB (Edition 6, 28-Jun-2019) and any relevant updates/addenda/errata.

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

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

The efficacy of GLPG1690 in a prophylactic bleomycin (BLM) 21-day mouse model of lung fibrosis, measured as the reduction in lung weight and Ashcroft score, was similar to that of the pirfenidone comparator. Significant reduction of collagen I deposit in the lung was observed in the GLPG1690 group only. After GLPG1690 treatment, the increase of LPA levels in bronchoalveolar lavage fluid after BLM exposure was reduced for several LPA species. In therapeutic BLM studies in mice and rats, GLPG1690 showed similar effects as nintedanib as evidenced by its positive effects on lung weight, Ashcroft score, collagen I deposit, and/or lung function. In addition, the efficacy of GLPG1690 in the tobacco smoke challenge model in mice, measured as the capacity to reduce inflammatory cell recruitment to the lungs, was indicative of the anti-inflammatory capacity of GLPG1690. This is seen as relevant, as inflammation is an important component in the pathophysiology of IPF.

2.1.2.2. Safety Pharmacology

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

2.1.3. Nonclinical Pharmacokinetics and Product Metabolism

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

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

In rat, [^{14}C]-GLPG1690 was widely distributed throughout the body. Highest concentrations of radioactivity were observed in contents of the gastrointestinal (GI) tract, glandular tissues, liver, and uveal tract. GLPG1690 and/or its metabolites exhibited some affinity for melanin-containing tissues, like uveal tract and meninges.

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

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

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

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

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

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

In addition, GLPG1690 demonstrated a strong time-dependent, irreversible inhibition potential against CYP2C8-mediated metabolism. This could likely lead to a pronounced interaction with a sensitive CYP2C8 probe substrate (increased exposure) if co-administered with a GLPG1690 dose of 600 mg q.d. in human.

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

2.1.4. Toxicology

2.1.4.1. General Toxicology

A comprehensive toxicology program has been conducted with GLPG1690. This program includes Good Laboratory Practice (GLP) oral repeat-dose toxicity studies of up to 26 weeks in rats and 39 weeks in dogs, embryofetal development studies in rats and rabbits, fertility studies in male and female rats, non-TgrasH2 mice preliminary studies, preliminary carcinogenicity

studies, and in vivo and in vitro genotoxicity studies. Additional toxicology studies conducted include phototoxicity studies and dose-range finding studies in rats and dogs.

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

In repeat oral dose toxicity studies in dogs, the dose-limiting effects consisted of decreased white blood cell (WBC) count and FC, emesis and BW loss, associated with poor clinical conditions at doses ≥100 mg/kg/day in the 13- and 39-week GLP studies, respectively. . QT prolongation, which was considered non-adverse, was also observed in repeat oral dose toxicity studies in dogs (4-, 13-, and 39-week studies).. Additional findings in dogs consisted of adverse altered sperm parameters and inflammatory cell infiltrates in the liver and minimal bile duct hyperplasia at 150/100 mg/kg/day (in the 13-week GLP toxicity study). The safety margins obtained from the mean (AUC) exposures at the NOAEL for dogs in the 39-week study when compared with the highest clinical dose currently being tested in healthy subjects (600 mg q.d. Study GLPG1690-CL-116) was 31-fold.

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

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

GLPG1690 showed no genotoxic effects in vitro or in vivo.

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

2.2. BACKGROUND - CLINICAL STUDIES

2.2.1. Clinical Safety

As of the safety data cut-off date of IB Edition 6, in clinical pharmacology studies, GLPG1690 had been administered to 85 healthy subjects as single doses (dose range: 20 to 1500 mg), to 96 healthy subjects in repeated doses (dose range: 100 to 1000 mg for either 7 or 14 days).

Administration of GLPG1690 was considered safe and well tolerated during these studies. No deaths, serious treatment-emergent adverse events (TEAEs), or TEAEs leading to investigational medicinal product (IMP) discontinuation were reported after dosing with GLPG1690. All GLPG1690 TEAEs were at most moderate in severity. In Study GLPG1690-CL-109, one SAE (ECG repolarization abnormality) was reported after a single dose of nintedanib, but before dosing with GLPG1690 (IMP).

The safety profile of single doses of nintedanib and pirfenidone in Study GLPG1690-CL-109 both alone and in combination with GLPG1690 was consistent with the respective nintedanib and pirfenidone prescribing information.

An additional DDI study (GLPG1690-CL-113) evaluated the effect of multiple oral doses of GLPG1690 on the safety and tolerability of nintedanib 150 mg twice daily (b.i.d.) under different dosing conditions; i.e. the GLPG1690 dose and the timing of GLPG1690 administration versus the nintedanib morning intake. Subjects received 150 mg nintedanib b.i.d. on Days 1 and 7, and GLPG1690 200 mg q.d. 0 (i.e. concomitantly) or 2 hours after nintedanib morning intake time, or 600 mg q.d. 0, 2, or 4 hours after the nintedanib morning intake time on Days 3 to 9. Cohorts 1 and 2 evaluated the morning and evening PK of nintedanib (150 mg b.i.d.) when administered alone and when the morning dose was administered simultaneously with GLPG1690 200 mg (in Cohort 1) or 600 mg (in Cohort 2). Cohorts 3 and 4 evaluated the morning and evening PK of nintedanib 150 mg b.i.d. when administered alone and in combination with GLPG1690 200 mg or 600 mg administered 2 h or 4 h after the nintedanib morning dose (i.e., 600 mg 2 h [Cohort 3a]; 600 mg 4 h [Cohort 3b] or 200 mg 2 h [Cohort 4a]).

There were no serious adverse events and all TEAEs were at most moderate in severity. There was one TEAE (herpes zoster) that led to discontinuation of treatment in the cohort that received GLPG1690 200 mg at the same time as the nintedanib morning dose. GLPG1690 at doses of 200 mg and 600 mg q.d. was well-tolerated.

The frequency of TEAEs was generally similar between cohorts and treatments. The frequency of diarrhea adverse events was higher in most cohorts after nintedanib alone than after GLPG1690 alone. In contrast to the previous DDI study (GLPG1690-CL-109), the incidence of diarrhea events did not increase when nintedanib was administered with GLPG1690.

Administration of oral doses of GLPG1690 600 mg q.d. for 12 weeks in 17 subjects with IPF was well tolerated (Phase 2a study GLPG1690-CL-202). No deaths were reported. Serious TEAEs were experienced by one subject in the GLPG1690 600 mg q.d. group (cholangiocarcinoma, led to permanent discontinuation) and by two subjects in the placebo group (atrioventricular block second degree in one subject, led to permanent discontinuation; and lower respiratory tract infection, urinary tract infection, and acute kidney injury in the other subject). None of these serious TEAEs were considered related to IMP according to the investigator. No notable differences were observed in the incidences of treatment-emergent

abnormalities between subjects with IPF treated with GLPG1690 600 mg q.d. or placebo. The majority of TEAEs were mild to moderate in severity.

2.2.2. Clinical Pharmacokinetics

Single (up to 1,500 mg) and multiple ascending oral doses of GLPG1690 (up to 1,000 mg q.d.) for 14 days were assessed in healthy male subjects under fed conditions. GLPG1690 was rapidly absorbed with a median time to maximum plasma concentration (t_{max}) of 0.5-2 h. Steady state exposure of GLPG1690 increased approximately in proportion with the dose between 300 to 1,000 mg total daily. Excretion of unchanged GLPG1690 in human urine was low (<1.8% in 24 hours [h] based on unchanged GLPG1690) and rapid. There was no impact on the urinary 6β-OH-cortisol/cortisol ratio after repeated dosing suggesting a lack of CYP3A4 induction by GLPG1690.

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

Food decreased the rate of absorption of GLPG1690 given as tablet (as expected by delay in gastric emptying), but there was no clinically relevant difference in the bioavailability of GLPG1690. A higher between-subject variability was observed in fasted state, with 4 subjects out of 12 having 5- to 10-fold lower exposure than the other subjects. The rate of elimination was not impacted by food. The mean terminal half-life ($t_{1/2}$) after a single 600 mg dose as tablets was approximately 11 h.

After q.d. dosing with the strong CYP3A4/potent P-gp inducer rifampin for 10 days, GLPG1690 (600 mg q.d.) exposure was decreased (by 6.0- and 9.3-fold for maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve from time 0 to 24 h [AUC_{0-24h}], respectively) without any significant change in the apparent rate of elimination.

Exposure of GLPG1690, as measured by area under the concentration-time curve from time 0 to infinity ($AUC_{0-\infty}$), was 3- and 4-fold greater when administered in combination with itraconazole and voriconazole, respectively, than when GLPG1690 was administered alone. Maximum exposure (C_{max}) of GLPG1690 increased slightly following administration of GLPG1690 in combination with itraconazole or voriconazole compared with administration of GLPG1690 only (C_{max} values were 1.4-fold greater following administration in combination with itraconazole or voriconazole). This increase is unlikely to be clinically significant. GLPG1690 can therefore be classified as a moderately sensitive substrate of CYP3A4 as it demonstrated an increase in AUC of ≥2 to <5-fold with strong index inhibitors. Comparison of the plasma profiles showed no impact on the apparent rate of elimination of GLPG1690.

The potential impact of GLPG1690 600 mg on the PK of single doses of pirfenidone and nintedanib was evaluated. Exposure of pirfenidone and its metabolite 5-carboxypirfenidone, as measured by C_{max}, $AUC_{0-\infty}$, and terminal elimination half-life ($t_{1/2}$) was not affected when administered in combination with GLPG1690, compared to when pirfenidone was administered alone. Exposure of nintedanib, as measured by C_{max}, $AUC_{0-\infty}$ was approximately 2-fold greater when administered in combination with GLPG1690, than when GLPG1690 was administered alone. Nintedanib $t_{1/2}$ was not affected by coadministration of GLPG1690.

As described in Section 2.2.1, the additional study GLPG1690-CL-113 evaluated the effect of multiple oral doses of GLPG1690 on the PK of nintedanib 150 mg b.i.d. (the indicated dose in the prescribing information) under different dosing conditions (GLPG1690 dose and time of GLPG1690 dose versus the nintedanib morning dose).

As observed in the previous GLPG1690-CL-109 study, when GLPG1690 was administered at the same time as the morning dose of nintedanib, an interaction was again observed, i.e., the nintedanib exposure was increased when administered in combination with GLPG1690 compared to nintedanib alone. The magnitude of the effect on nintedanib exposure was dependent on the dose of GLPG1690 (200 mg or 600 mg once daily [q.d.]) and time difference between nintedanib and GLPG 1690 administration.

When GLPG1690 200 mg was administered at the same time as the morning dose of nintedanib, the maximum observed plasma concentration after the morning nintedanib dose ($C_{max0-11}$) increased from 22.9 (nintedanib administered alone) to 39.4 µg/L (1.7 fold), and the area under the plasma concentration-time curve after the morning nintedanib dose (AUC_{0-11}) increased from 117.3 to 199.4 h·µg/L (1.7 fold) respectively. With GLPG1690 600 mg, the increase in nintedanib $C_{max0-11}$ was from 24.7 (nintedanib administered alone) to 52.6 µg/L (2.1 fold) and in AUC_{0-11} from 118.6 to 263.8 h·µg/L (2.2 fold).

When the 600 mg GLPG1690 dose was administered 2 hours and 4 hours later than the morning dose of nintedanib, the interaction was decreased as compared to when administered concomitantly. With the 2-hour interval the increase in nintedanib $C_{max0-11}$ was from 30.8 to 49.2 µg/L (1.6 fold) and in AUC_{0-11} from 152.0 to 251.8 h·µg/L (1.7 fold). With the 4-hour interval the increase in nintedanib $C_{max0-11}$ was from 30.8 to 37.5 µg/L (1.3 fold) and in AUC_{0-11} from 152.0 to 244.0 h·µg/L (1.6 fold).

Similarly, when the 200 mg GLPG1690 dose was administered 2 hours later than the morning dose of nintedanib, the increase in nintedanib $C_{max0-11}$ was from 28.2 to 32.8 µg/L (1.2 fold) and in AUC_{0-11} from 141.2 to 186.3 h·µg/L (1.3 fold).

2.2.3. Clinical Pharmacodynamics

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

The sustained effect on LPA C18:2 was also confirmed by area under the effect-time curve for the percentage reduction from baseline and maximum effect (expressed as a percentage reduction from baseline) (E_{max}).

GLPG1690 induced a fast and sustained reduction in plasma LPA C18:2 levels in subjects with IPF, indicative for target engagement. At the follow-up visit, the mean LPA C18:2 level was back to baseline levels, indicating that the inhibitory effect of GLPG1690 on the target is reversible. The profiles of plasma LPA C18:2 levels after single doses of pirfenidone or nintedanib whether administered alone and in combination with multiple doses of GLPG1690 were similar over time.

3. CLINICAL STUDY OBJECTIVES

3.1. PRIMARY OBJECTIVE

- To evaluate the efficacy of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF as evaluated by the rate of decline of FVC over a period of 52 weeks

3.2. SECONDARY OBJECTIVES

3.2.1. Key Secondary Objectives

- To evaluate the impact of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF on:
    - disease progression defined as deterioration of FVC or all-cause mortality at 52 weeks
    - respiratory-related hospitalization until the end of the study
    - changes in quality of life (measured by St. George's Respiratory Questionnaire [SGRQ] total score) at 52 weeks

3.2.2. Other Secondary Objectives

- To evaluate the efficacy of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF as evaluated by the rate of decline of FVC until the end of the study
- To evaluate the impact of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF on:
    - disease progression defined as deterioration of FVC or all-cause mortality until the end of the study
    - changes in quality of life (measured by SGRQ total score) until the end of the study
    - all-cause non-elective hospitalization until the end of the study
    - respiratory-related mortality until the end of the study
    - lung transplant until the end of the study
    - acute IPF exacerbation until the end of the study
    - all-cause mortality or lung transplant until the end of the study
    - all-cause mortality, or lung transplant, or qualifying for lung transplant until the end of the study
    - all-cause mortality, deterioration of FVC, or respiratory-related hospitalization until the end of the study
    - all-cause mortality or respiratory-related hospitalizations until the end of the study
- To evaluate the effect of two doses of GLPG1690 in addition to local standard of care compared to placebo on the changes from baseline in FVC at 52 weeks and until the end of the study
- To evaluate the safety and tolerability of two doses of GLPG1690 in addition to local standard of care compared to placebo until the end of the study
- To evaluate changes compared to placebo in subjects with IPF in:

  - cough-related quality of life (measured by the Leicester Cough Questionnaire [LCQ] and by the Visual Analogue Scale [VAS] Cough and Urge to Cough) at 52 weeks and until the end of the study
  - quality of life (measured by EuroQOL 5-Dimensions Questionnaire [EQ-5D] and King's Brief Interstitial Lung Disease [K-BILD] total score and domains over time) at 52 weeks and until the end of the study
- To evaluate the PK of GLPG1690, pirfenidone, and nintedanib (as appropriate) in subjects with IPF at 52 weeks and until the end of the study
- To evaluate the effect of two doses of GLPG1690 in addition to local standard of care compared to placebo in subjects with IPF on the changes in functional exercise capacity measured by the 6-Minute Walk Test (6MWT) at 52 weeks and until the end of the study
- To evaluate the effect of two doses of GLPG1690 in addition to local standard of care compared to placebo on the diffusing capacity of the lung for carbon monoxide (DLCO) at 52 weeks and until the end of the study

3.3. OTHER OBJECTIVES

- To evaluate the change in target biomarkers/PD in blood and/or clinical endpoints that may be relevant to GLPG1690 mechanism and/or clinical outcome, compared to placebo and compared to baseline
- To evaluate the change in disease-specific biomarkers in blood, compared to placebo and compared to baseline
- To assess the relationship between mutational status and clinical outcome and/or biomarker level
- To evaluate the effect on oxygen saturation (SpO_2) compared to baseline
- To evaluate the impact on Health Resource Utilization parameters

4. INVESTIGATIONAL PLAN

4.1. CLINICAL STUDY DESIGN

This clinical Phase 3 study is a randomized, double-blind, parallel-group, placebo-controlled multicenter study designed to evaluate the efficacy and safety of two doses (200 mg q.d. and 600 mg q.d.) of orally administered GLPG1690 in addition to local standard of care for at least 52 weeks in adult subjects with a centrally confirmed diagnosis of IPF. Local standard of care for IPF is defined as receiving either pirfenidone or nintedanib at a stable dose for at least two months before screening, and during screening; or neither pirfenidone or nintedanib (for any reason). A stable dose is defined as the highest dose tolerated by the subject during those two months. A total of approximately 750 subjects with confirmed diagnosis of IPF will be randomized, 250 subjects in each treatment group (GLPG1690 600 mg q.d., GLPG1690 200 mg q.d., or matching placebo).

The diagnosis of IPF will be confirmed by central reading of the chest high-resolution computed tomography (HRCT) and by central review of the available lung biopsy (LB), if required, based on the Fleischner White Paper [15] as described in Section 6.3 and Appendix 1.

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

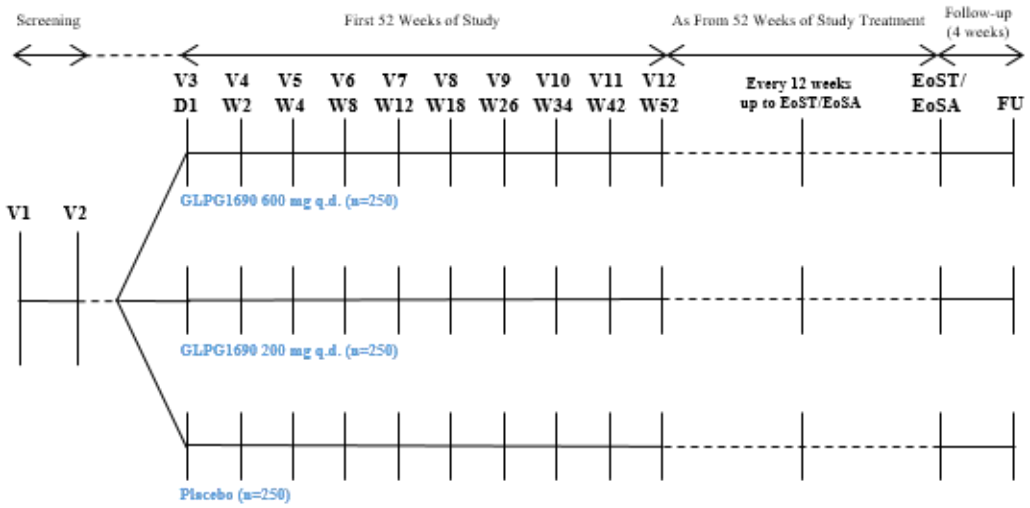

Figure 1: Schematic Study Overview

D=Day, EoST/EoSA=end of study treatment/end of study assessments, FU=follow-up, V=Visit, W=Week.

Enrolled subjects will come to the clinical study center at screening (two visits from Day -28 to Day -1). Visit 2 of screening can only take place after confirmed IPF diagnosis on HRCT and LB (if applicable) (for details, refer to Section 6.3 and Appendix 1).

For the in- and exclusion criteria, please refer to Section 4.5.1 and Section 4.5.2, respectively.

At Visit 3, eligible subjects will be randomized in a 1:1:1 ratio to receive GLPG1690 600 mg q.d., GLPG1690 200 mg q.d., or matching placebo for at least 52 weeks. Randomization will be stratified for background local standard of care for treatment of IPF.

Subjects will come to the clinical study center on Day 1 (baseline), Weeks 2, 4, 8, 12, 18, 26, 34, 42, 52, and every 12 weeks thereafter. Additional unscheduled visits are allowed if, in the investigator's opinion, further evaluation (clinical, laboratory, or other) is needed.

When the last subject reaches 52 weeks (Visit 12), subjects still taking IMP and who had a scheduled visit at the clinical study center within 6 weeks before this date will be contacted by their investigator (phone call) to discontinue IMP within 7 days after this date. Then the last scheduled visit will be documented as the end of study treatment (EoST) visit. These subjects will be invited to their follow-up visit scheduled at the clinical study center 4 weeks after their last dose of IMP (±7 days). For subjects still taking IMP and who had their last scheduled visit more than 6 weeks before the date that the last subject reaches 52 weeks into the study (Visit 12), a scheduled visit will be planned within 2 weeks of this date for an EoST visit, followed by a follow-up visit 4 weeks later (visit at clinical center or phone call). Note that these subjects will continue IMP intake until their EoST visit.

For subjects who, for any Coronavirus disease (COVID-19)-related reason, cannot perform study procedures, extended visit windows, the possibility to conduct phone/televisits and home (or other remote location) visits, and alternative assessment procedures are detailed in Section 6.1.1.

Subjects who discontinue IMP early (early treatment discontinuation [ETD]), with the exception of patients lost to follow-up and patients who withdraw consent, will be encouraged to complete all following visits and evaluations as originally planned per protocol.

In particular, the subject will be requested if at all possible to attend:

- the first scheduled visit after their Early Treatment Discontinuation (ETD)
- The Week 26 visit (if not done before IMP discontinuation)
- the Week 52 visit (if not done before IMP discontinuation)
- after Week 52, visits every 24 weeks up to End of Study Assessments (EoSA), as described in Section 6.11.2

For procedures in case of ETD, refer to Section 4.5.4. In the exceptional case that a clinical study center visit cannot be attended, a phone call by the investigator will be made to evaluate safety, in combination with scheduled clinical study center visits.

Each subject will have a screening period of maximum 28 days. The duration of study treatment for individual subjects will vary from 52 weeks for the last enrolled subject to e.g. 132 weeks for the first enrolled subject (assuming a recruitment period of 80 weeks, the actual duration will depend on the actual time to recruit subjects for the study). A follow-up visit (at the clinical study center or by phone call, decided by the investigator) is planned 4 weeks after the EoST/end of study assessment (EoSA) visit.

At the end of this study, treatment with IMP in an optional extension study (under a separate study protocol) may be offered to all eligible subjects, provided Independent Ethics Committee (IEC)/Institutional Review Board (IRB) and Competent Authority approvals for such an extension are granted.

To protect the safety and integrity of the study data, an independent data monitoring committee (IDMC) will be implemented, as well as a clinical endpoint adjudication committee (CEAC). Charters are in place for all committees. For additional information, refer to Sections 8.1 (for IDMC) and 8.2 (for CEAC).

For detailed information regarding dosage form, packaging, and labeling of the IMP, please refer to Sections 5.2 and 5.3.

4.1.1. Definition of End of Trial

The global end of trial will be reached when the last subject has completed the last follow-up visit (scheduled clinical study center visit or phone call), i.e. four weeks (±7 days) after the end of study treatment (EoST) or end of study assessments (EoSA) visit (Section 4.1 and Section 6.11.2).

4.1.2. Guidance for dose modification in case of adverse events

At any stage, the investigator can decide to permanently discontinue IMP for concerns regarding safety and tolerability, i.e. an AE, including clinically significant abnormal laboratory tests. For abnormal liver function tests (LFTs), specific guidance is described in Appendix 9.

For the subsequent management of these AEs, the investigator can reduce the dose, interrupt, or permanently discontinue the IMP. Down-titration will be a one-step process to the lowest reduced dose. Once the AE has stabilized or improved, the dose can be increased again (re-escalation). For the re-escalation from the lowest reduced dose, an intermediate reduced dose level is required (Figure 2).

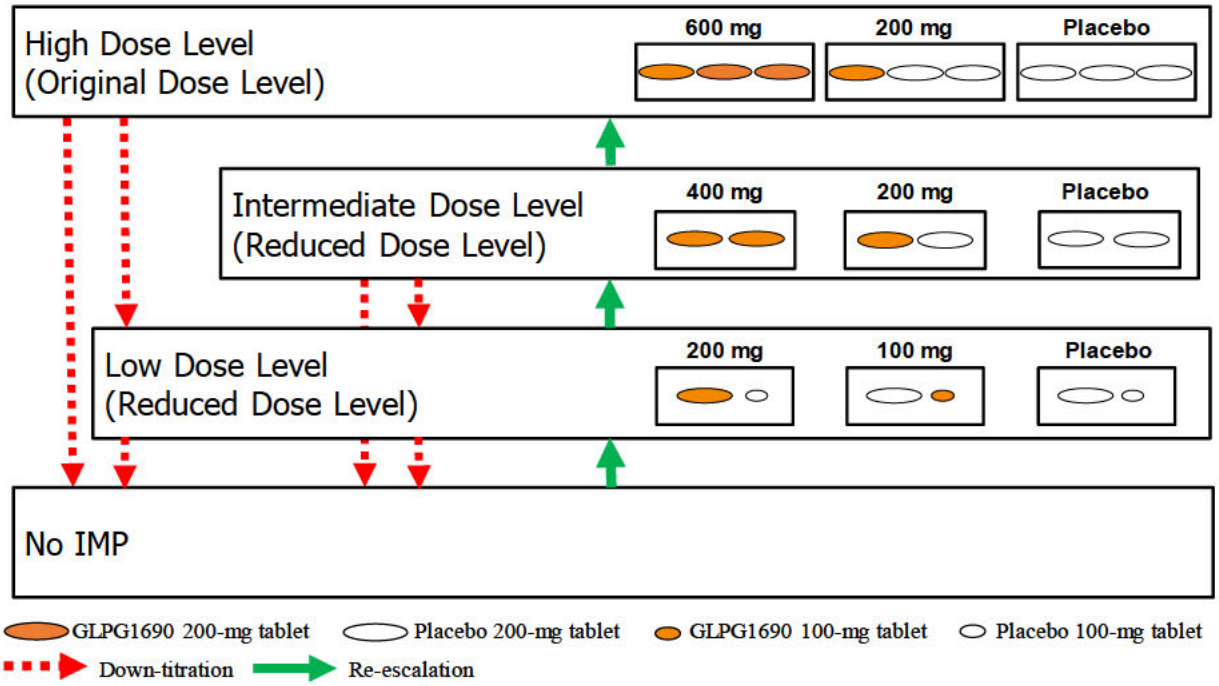

Figure 2: Study Drug Dose Modification: Down-titration and Re-escalation Steps

Tablet colors are for illustration purposes only

For all AEs, the investigator is advised to evaluate the concomitant medication, including local standard of care for the treatment of IPF, as part of the benefit-risk evaluation. The recommended duration of a different dose level or interruption for elevated LFTs is at least 2 weeks.

Elevated LFTs

At Visit 3 (randomization visit), blood samples are collected before IMP intake and the results of the laboratory tests will only be known after IMP intake. Therefore, if the LFTs are abnormal at this visit, the investigator needs to discontinue IMP (only if aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥1.5x upper limit of normal [ULN], total bilirubin ≥1.5xULN, and/or gamma glutamyl transferase [GGT] ≥3xULN). It is recommended to consult the contract research organization (CRO) medical monitor (as per study contact list) or sponsor's study physician (if the former is not available).

At any visit from Visit 4 onwards:

Continue as planned: AST or ALT ≥1.5x to 3xULN.

Discontinuation of IMP:

- AST or ALT >8xULN: permanently discontinue IMP with close observation*.
- AST or ALT ≥3xULN with signs or symptoms of severe liver damage**: permanently discontinue IMP with close observation*.
- AST or ALT ≥3xULN for more than 2 weeks.
- AST or ALT ≥3xULN during re-escalation (described below)

Down-titration to reduced dose level or interruption of IMP:

- AST or ALT ≥3x to 5xULN without signs of severe liver damage**:

  Down-titrate to low (reduced) dose level or interrupt IMP for at least 2 weeks (to be decided by the investigator, based on the subject's risk assessment).
- AST or ALT ≥5x to 8xULN without signs of severe liver damage**:

  Interrupt IMP for at least 2 weeks.

During these periods of at least 2 weeks: Re-test AST, ALT, alkaline phosphatase, total bilirubin, and eosinophils within 48 to 72 hours, approximately at 7 days, thereafter approximately at 14 days, and also assess signs of severe liver damage**. If local regulations allow, home visits can be performed if subjects cannot come to the clinical study center.

Re-escalation after each period of at least 2 weeks at any dose level:

- Remain on the highest tolerated dose at investigator's discretion. Monitoring of LFTs can return to the planned study assessments once the LFTs have stabilized at the highest tolerated dose level for 8 weeks.
- AST and ALT <3xULN:

  Re-escalate to the next dose level for at least 2 weeks, with regular LFT monitoring (weekly for the first 2 weeks, biweekly for the following weeks, or more frequently at investigator's discretion) and repeat re-escalation to next higher dose level every 2 weeks (or longer at investigator's discretion) if AST and ALT <3xULN.
- AST or ALT ≥3xULN:
  Discontinue IMP.

*Close observation is defined as:

- Monitor two to three times per week all of the following parameters: ALT, AST, alkaline phosphatase, total bilirubin, eosinophils, and International Normalized Ratio (INR). If local regulations allow, home visits can be performed if subjects cannot come to the clinical study center.
- Frequency of retesting can be reduced to once a week or less if abnormalities stabilize or the IMP has been discontinued; however, monitoring might still be needed more frequently taking into consideration the standard of care and/or changes to this.
- Re-query history of symptoms, prior and concurrent diseases, concomitant medication and non-prescription medicines, herbal, dietary supplements, alcohol use, recreational drug use, special diets.
- Rule out all of the following: acute viral hepatitis, auto-immune hepatitis, alcoholic hepatitis, non-alcoholic fatty hepatitis, hypoxic/ischemic hepatitis, biliary tract disease, and cholestasis.
- Re-query exposure to environmental chemical agents.
- Consider gastro-enterology or hepatology consultations.

** Signs of severe liver damage:

- Increase of liver transaminases is accompanied by appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%), and/or
- Total bilirubin ≥1.5x ULN, or
- INR >1.5.

Each blinded treatment kit will have blisters for the high (original) dose level, intermediate (reduced) dose level, and low (reduced) dose level, allowing the clinical study center to modulate the IMP dose for a particular subject, even without knowing the original treatment allocation (also see Section 5.2).

The Investigator will be responsible for managing COVID-19 infected subjects and the decision to continue or interrupt IMP for subjects with confirmed or suspected cases of COVID-19 infection is at the investigator's discretion. Guidance on continuation of IMP and requirements for assessments conducted during the COVID-19 pandemic are provided in Section 6.1.1.

4.2. CLINICAL STUDY RATIONALE

Since 2010, disease-modifying drugs such as pirfenidone and nintedanib are indicated for patients with IPF and available in most parts of the world. These drugs have been shown to have a beneficial effect on the rate of decline in lung function (as measured by FVC over 1 year) and show a trend in favor of a reduction in mortality [32]. Both drugs have received conditional recommendation for use in the American Thoracic Society (ATS) / European Respiratory Society (ERS) / Japanese Respiratory Society (JRS) / Latin American Thoracic Association (ALAT) 2015 guidelines [29].

However, the residual decline of FVC over 1 year remains substantial, with a further decline of FVC over 52 weeks of 125 mL and 114 mL in INPULSIS I and II (nintedanib) [33], respectively, and around 200 mL in the ASCEND study (pirfenidone) [13].

Additional therapies targeting different disease pathways could potentially prove to be more effective by further preventing the decline in FVC with an acceptable safety profile [41].

In the proof-of-concept Phase 2a study GLPG1690-CL-202, FVC values remained stable in the majority of subjects on GLPG1690 600 mg q.d. (+8 mL mean change from baseline). Moreover, 12 weeks of treatment with GLPG1690 600 mg q.d. was generally well tolerated (refer to Section 2.2.1).

The current Phase 3 study is a next step in the clinical development of GLPG1690, evaluating the efficacy and safety of two doses of orally administered GLPG1690 (200 mg q.d. and 600 mg q.d.) compared to placebo in subjects with IPF in addition to local standard of care.

The primary objective of the study is to evaluate the efficacy of GLPG1690 in addition to local standard of care on the rate of decline of FVC over a period of 52 weeks. FVC has been accepted as a clinically relevant efficacy measure in IPF, as a benefit in terms of FVC decline showed a trend toward decreased mortality [11].

Key secondary objectives are to evaluate the effect on disease progression defined as deterioration of FVC (expressed as categorical decline of ≥10% predicted FVC) or all-cause mortality, respiratory-related hospitalizations, and quality of life as measured by SGRQ total score.

All-cause and respiratory-related mortality have been chosen as other secondary objectives to provide supportive evidence that the treatment affects the disease. The effect on acute IPF exacerbation and patient-related outcomes such as quality of life, cough-related outcomes, and hospitalizations will also be evaluated. Safety and tolerability, GLPG1690, pirfenidone, and

nintedanib concentration, and PD of target engagement and diseases will be assessed as well. Disease-specific biomarkers will be evaluated throughout the study. Exercise capacity will be assessed through the 6MWT, as well as the diffusing capacity of the lung as evaluated by DLCO.

Refer to Sections 3 and 4.3 for a more detailed description of the objectives and endpoints, respectively.

4.2.1. Dose Rationale

Two doses of GLPG1690 (i.e. 200 mg and 600 mg) for oral administration q.d. have been selected to be evaluated for this Phase 3 study.

This selection is based on the observations made on efficacy, PD, PK, safety, and tolerability in the Phase 2a study (GLPG1690-CL-202), where GLPG1690 was evaluated as monotherapy versus placebo, as well as on the Phase 1 results in the healthy subject study (GLPG1690-CL-101). In addition, in the 21-day prophylactic BLM mouse model, the efficacy of GLPG1690 was reached (in terms of reduction of Ashcroft score) with an AUC of 11 µg.h/mL, corresponding to 26 µg.h/mL in humans after correction for plasma protein binding, predicting an efficacious dose of GLPG1690 in humans to be around 200 mg.

Consequently, a population PK and PK/PD model was developed in subjects with IPF to describe the exposure-response relationships of GLPG1690 and LPA C18:2 as PD biomarker using data from the FIH single and multiple ascending dose study, the drug-drug-interaction study with rifampin, and the GLPG1690-CL-202 study. Subsequent simulation suggests the anticipated therapeutic dose range to lie between 200 mg q.d. and 600 mg q.d., where the maximum reduction of LPA C18:2 is >80% and concentrations of GLPG1690 are maintained above the IC_{50} for at least 80% of the 24-hour dosing interval. Both doses also allow concentrations above 80% inhibitory concentration (IC_{80}) of LPA C18:2 to be attained for at least 60% of the dosing interval.

In conclusion, the selected doses are considered to provide sufficient confirmatory data on the benefit-risk of GLPG1690 in the treatment of subjects with IPF.

4.2.2. Clinical Study Design Rationale

This is a multicenter, randomized, double-blind Phase 3 study in subjects with IPF. The randomized double-blind study design was chosen as it is the most rigorous method to generate high-quality scientific data. 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 [10].

Subject eligibility

Subject eligibility criteria are similar to previous clinical studies in IPF, differing in the IMP being evaluated in addition to local standard of care for the treatment of IPF. Subjects clinically diagnosed with IPF based on ATS/ERS/JRS/ALAT guidelines [28, 29] are eligible for the

study, if complying with all the study in- and exclusion criteria. The disease typically affects elderly patients, so subjects ≥40 years are to be included.

The clinical diagnosis of IPF will be confirmed by central reading of the chest HRCT and by central review of a historical LB if available, if required, based on the Fleischner White Paper [15] as described in Section 6.3 and Appendix 1.

Refer to the in- and exclusion criteria in Sections 4.5.1 and 4.5.2, respectively, and to the prohibitions and restrictions in Section 4.5.3 for medications that are not allowed prior to or during the study.

Rationale for chosen endpoints

A rationale for the chosen endpoints is provided in Section 4.3.

Duration of the study

Each subject will have a screening period of maximum 28 days. The duration of study treatment for individual subjects will vary from 52 weeks for the last enrolled subject to e.g. 132 weeks for the first enrolled subject (assuming a recruitment period of 80 weeks, the actual duration will depend on the actual time to recruit subjects for the study). A follow-up visit (at the clinical study center or by phone call) is planned 4 weeks after the EoST/EoSA visit. This duration ensures long-term collection of efficacy and safety data in a blinded manner, and increases the probability of demonstrating an effect on clinical endpoints. Note that subjects who discontinue IMP early (ETD) will be encouraged to complete all following visits and evaluations as originally planned per protocol (refer to Section 4.5.4).

Dose modification in case of adverse events

For the management of AEs, the investigator can reduce, interrupt, or permanently discontinue IMP (see Section 4.1.2 and Section 4.5.4). This allows the subject to remain on the highest tolerated dose during the study.

4.3. ENDPOINTS

The rate of decline of FVC over a period of 52 weeks has been chosen as primary efficacy endpoint, as this has been recognized as a clinically relevant efficacy measure in IPF [11].

Key secondary endpoints are disease progression defined as deterioration of FVC (expressed as categorical decline of ≥10% predicted FVC) or all-cause mortality, respiratory-related hospitalizations, and quality of life as measured by SGRQ total score.

All-cause and respiratory-related mortality have been chosen as secondary endpoints to provide supportive evidence that the treatment affects the disease. Other (secondary) endpoints include acute IPF exacerbation and patient-related outcomes such as quality of life and cough-related outcomes, and hospitalizations. The safety and tolerability, concentration of GLPG1690, pirfenidone and nintedanib, and PD of target engagement and diseases will be assessed as well. Disease-specific biomarkers will be evaluated throughout the study. Exercise capacity will be assessed through the 6MWT, as well as the diffusing capacity of the lung as evaluated by DLCO.

4.3.1. Primary Endpoint

- Rate of decline of FVC (in mL) over a period of 52 weeks.

4.3.2. Secondary Endpoints

4.3.2.1. Key Secondary Endpoints

- Disease progression defined as the composite endpoint of first occurrence of ≥10% absolute decline in percent predicted forced vital capacity (%FVC) or all-cause mortality at 52 weeks
- Time to first respiratory-related hospitalization until the end of the study
- Change from baseline in the SGRQ total score at 52 weeks

4.3.2.2. Other Secondary Endpoints

- Rate of decline of FVC (in mL) until the end of the study
- Disease progression defined as the composite endpoint of first occurrence of ≥10% absolute decline in %FVC or all-cause mortality until the end of the study
- Change from baseline in the SGRQ total score until the end of the study
- Time to first all-cause non-elective hospitalization until the end of the study
- Time to respiratory-related mortality until the end of the study
- Time to lung transplant until the end of the study
- Time to first acute IPF exacerbation until the end of the study
- Time to all-cause mortality or lung transplant until the end of the study
- Time to all-cause mortality, or lung transplant, or qualifying for lung transplant until the end of the study
- Time to all-cause mortality, ≥10% absolute decline in %FVC, or respiratory-related hospitalizations until the end of the study
- Time to all-cause mortality or respiratory-related hospitalizations until the end of the study
- FVC analyses at 52 weeks and until the end of the study:
    - absolute and relative change from baseline of FVC and %FVC
    - absolute categorical change of %FVC until the end of the study: decrease by >5, increase by >5, and change within ≤5
    - absolute categorical change of %FVC until the end of the study: decrease by >10, increase by >10, and change within ≤10
- Safety and tolerability over time until the end of the study
- Changes from baseline in cough-related quality of life, assessed by the LCQ total score and domains over time, and the VAS Cough and Urge to Cough, at 52 weeks and until the end of the study
- Changes from baseline in quality of life, assessed by the EQ-5D, K-BILD total score and domains over time, at 52 weeks and until the end of the study
- Plasma concentration of GLPG1690, pirfenidone, and nintedanib (as appropriate) at 52 weeks and until the end of the study
- Change from baseline in functional exercise capacity, assessed by the 6MWT distance, at 52 weeks and until the end of the study

- Change from baseline in DLCO (corrected for hemoglobin [Hb]) at 52 weeks and until the end of the study

4.3.3. Other Endpoints

- Changes in target biomarkers/PD in blood over time compared to baseline until the end of the study
- Changes in disease-specific biomarkers in blood over time compared to baseline until the end of the study
- Efficacy and biomarker endpoints by genotype subgroups
- Change from baseline in Borg scale before and after 6MWT at 52 weeks and until the end of the study
- Change from baseline in SpO_2 until the end of the study
- Health Resource Utilization parameters until the end of the study

4.4. POTENTIAL RISKS AND BENEFITS

IPF is a chronic and progressive lethal lung disease for which two treatments (pirfenidone and nintedanib) are currently approved in the majority of countries. These treatments slow disease progression, but still with substantial loss of lung function measured by FVC, which is considered as a clinically important efficacy measure in IPF, because of the relationship between FVC and mortality trends [11] (for details, refer to Section 4.2). Additional beneficial effect on the progression of the disease is therefore an unmet medical need, together with an acceptable safety and tolerability profile.

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

Fertility/Embryotoxicity

The risk of treatment with GLPG1690 in adult subjects is primarily related to fertility, pregnancy, and lactation.

GLPG1690 induced reversible microscopic findings in the seminiferous tubules in the 13-week oral toxicity studies as well as reversible (complete or partially) changes in sperm parameters in rats and dogs, respectively. Male and female fertility studies showed that there are no effects of GLPG1690 on mating performance, fertility, or reproduction (litter size and embryofetal survival) in either male or female rats at the dose levels tested. However, there are no human data on the effect of GLPG1690 on fertility. As the effects on sperm and testis proved reversible and had no functional impact on animal fertility parameters, the risk of an impact on male fertility in adult subjects is considered low.

GLPG1690 showed teratogenic effects in both rats and rabbits, with induction of major external, skeletal, and visceral abnormalities at doses >10 mg/kg/day (rats) and >5 mg/kg/day (rabbits). No data have been generated in lactating women on excretion in milk. In view of the teratogenic effects seen in animals and limited knowledge of the possible effects of GLPG1690 on lactation at this stage of development, GLPG1690 should not be given to pregnant or lactating women. In addition, highly effective contraceptive measures/preventive exposure measures should be taken by women of childbearing potential (WOCBP) and in men to prevent pregnancy and to avoid the risk of exposure of the embryo or fetus.

QT interval prolongation

Subjects with long QT syndrome or QTcF >450 ms during screening will be excluded. The chronic use or initiation of medication known to prolong the QT interval needs to be evaluated on a case-by-case basis. Periodic ECG recording and monitoring with central reading will be implemented for the duration of the study. A list intended as guidance for the investigator is provided in Appendix 7.

Drug-drug interaction

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

Combination of GLPG1690 with pirfenidone or nintedanib

Pirfenidone is primarily metabolized in humans via CYP1A2 with minor contributions from other CYP isoenzymes. In vitro experiments showed that GLPG1690 was potentially a weak CYP1A2 inducer with a possible reduction of pirfenidone exposure of approximately 30%. Pirfenidone is a weak P-gp inhibitor and a weak CYP2C9, CYP2C19 or CYP1A2, CYP2D6, and CYP3A4 inhibitor. GLPG1690 is a P-gp substrate and has CYP3A4 involved in its metabolism, although it is expected to undergo a low first-pass effect after oral dosing.

No clinically relevant induction of CYP2B6 and CYP2C enzymes by GLPG1690 was observed in human hepatocytes. For CYP1A2 and CYP3A4, a potential weak induction could not be excluded at a GLPG1690 dose of 600 mg q.d. in human. However a recent clinical drug-drug-interaction (DDI) study conducted with pirfenidone (a CYP1A2 primary substrate) showed that GLPG1690 had no effect on pirfenidone exposure, indicating that GLPG1690 has no induction potential on CYP1A2 substrates. In addition, from the first in human study, urinary 6β-OH-cortisol/cortisol ratio was not impacted by q.d. or b.i.d. repeated dosing with GLPG1690 suggesting that GLPG1690 is not a CYP3A4 inducer.

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. In addition, the United States 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.

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 uridine 5'-diphospho-glucuronosyltransferase (UGT)1A1 or UGT2B7 activities and is a weak inhibitor of P-gp. GLPG1690 is P-gp substrate and has CYP3A4 involved in its metabolism although it is expected to undergo a low first-pass effect after oral administration.

Clinical DDI studies showed that exposure of nintedanib (150 mg single dose or b.i.d dose), as measured by C_{max}, and AUCs was approximately 2-fold greater when administered on the same day (b.i.d) as, and simultaneously with, GLPG1690 600 mg than when administered alone. The increased exposure of nintedanib was in the same order of magnitude to that observed with concomitant administration of ketoconazole (a P-gp and CYP3A4 inhibitor) and that did not warrant a contraindication in the nintedanib label, but a warning for monitoring tolerability.

The interaction (increased exposure of nintedanib) observed when GLPG1690 and nintedanib 150 mg b.i.d. were administered concomitantly was reduced when GLPG1690 was administered 2 or 4 hours after the nintedanib morning dose.

This clinical study protocol contains specific precautions and exclusions to manage use of GLPG1690 on top of standard of care (pirfenidone and nintedanib). The plasma concentrations of GLPG1690, pirfenidone and nintedanib will be collected. The potential for increased exposure to nintedanib when co-administered with GLPG1690, can be managed by separating the intake times of the morning dose of nintedanib and the IMP daily dose. It is therefore recommended that all subjects on nintedanib take IMP at or after lunch (approximately 4 hours after nintedanib morning intake); refer to Section 5.2. Additionally all subjects taking nintedanib will be evaluated by monitoring adverse events and managing them according to the guidance in the nintedanib prescribing information.

Management of adverse events

For the management of AEs, guidance for the investigator should be followed, as described in Section 4.1.2. As noted above, the investigator needs to evaluate the potential of increased exposure to nintedanib when coadministered with IMP by monitoring adverse events and managing them according to the guidance in the nintedanib prescribing information and the guidance provided in this protocol.

Details for capture of the suspected and confirmed cases of COVID-19 based on the symptoms and the confirmatory test, respectively, have been provided in data entry guidance issued to the sites, and will be included in the CRF completion guidelines.

All these cases, whether suspected or confirmed, should be documented in the CRF.

Clinical studies

GLPG1690 has been evaluated in several Phase 1 studies and in the GLPG1690-CL-202 study with patients. Administration of GLPG1690 was generally safe and well tolerated. In the GLPG1690-CL-202 study, FVC values remained stable in the majority of subjects on GLPG1690 600 mg q.d. (+8 mL mean change from baseline) when administered for 12 weeks (refer to Section 2.2.1).

Special populations

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

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

4.5. CLINICAL STUDY POPULATION

4.5.1. Inclusion Criteria

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

1. Able and willing to comply with the protocol requirements and signed the informed consent form (ICF) as approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB), prior to any screening evaluations.
2. Subject must be able and willing to comply with restrictions on prior and concomitant medication as described in Section 4.5.3.2.
3. Male or female subject aged ≥40 years on the day of signing the ICF.
4. Criterion modified per amendment.

   4.1 A diagnosis of IPF within 5 years prior to the screening visit, as per applicable ATS/ERS/JRS/ALAT guideline at the time of diagnosis [28, 29].
5. Chest HRCT historically performed within 12 months prior to the screening visit and according to the minimum requirements for IPF diagnosis by central review based on subject's HRCT only (if no LB available), or based on both HRCT and LB (with application of the different criteria in either situation) (see Appendix 1). If an evaluable HRCT <12 months prior to screening is not available, an HRCT can be performed at screening to determine eligibility, according to the same requirements as the historical HRCT.
6. Criterion modified per amendment.

   6.1 Subjects receiving local standard of care for the treatment of IPF, defined as either pirfenidone or nintedanib at a stable dose for at least two months before screening, and during screening; or neither pirfenidone or nintedanib (for any reason). A stable dose is defined as the highest dose tolerated by the subject during those two months.
7. The extent of fibrotic changes is greater than the extent of emphysema on the most recent HRCT scan (investigator-determined).
8. Meeting all of the following criteria during the screening period:
   - FVC ≥45% predicted of normal.
   - Forced expiratory volume in 1 second (FEV_1)/FVC ≥0.7.
   - DLCO corrected for Hb ≥30% predicted of normal (see Appendix 2).
9. Criterion modified per amendment.

   9.1 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 have been stable from 4 weeks prior to screening and during the screening period (stable defined as no clinically relevant change according to the investigator's judgment).
10. Estimated minimum life expectancy of at least 30 months for non-IPF related disease in the opinion of the investigator.
11. Male subjects and female subjects of childbearing potential agree to use highly effective contraception/preventive exposure measures (as described in Section 4.5.3.1) from the time of first dose of IMP (for the male subject) or the signing of the ICF (for the female

subject), during the study, and until 90 days (male) or 30 days (female) after the last dose of IMP.

12. Criterion modified per amendment.

    12.1 Able to walk at least 150 meters during the 6MWT at screening Visit 1; without having a contraindication to perform the 6MWT (see Appendix 10) or without a condition putting the subject at risk of falling during the test (investigator's discretion). The use of a cane is allowed, the use of a stroller is not allowed at all for any condition. At Visit 2, for the oxygen titration test, resting SpO_2 should be ≥88% with maximum 6 L O_2/minute; during the walk, SpO_2 should be ≥83% with 6 L O_2/minute or ≥88% with 0, 2 or 4 L O_2/minute.

13. Able to read and complete the EQ-5D, SGRQ, LCQ, K-BILD questionnaire, and VAS by themselves.
14. 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 (described in Section 4.5.3.2).

4.5.2. Exclusion Criteria

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

1. Investigator or other study staff or relative thereof who is directly involved in the conduct of the study.
2. Any clinical condition or other condition or circumstance that, in the opinion of the investigator, may make a subject unsuitable for inclusion or unlikely or unable to complete the study or comply with study procedures and requirements.
3. Previous participation in a clinical study with GLPG1690 (active or placebo).
4. 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).
5. Criterion modified per amendment.

    5.2 A current immunosuppressive condition (e.g. human immunodeficiency virus [HIV] infection, congenital, acquired, medication-induced). Subjects treated with stable doses of immunosuppressive medications for reasons other than IPF are allowed to participate in the study on a case-by-case basis based on discussion with the sponsor's medical monitor.

6. Criterion modified per amendment.

    6.1 Positive blood testing for hepatitis B surface antigen (HB_S Ag) or hepatitis C virus (antibody, confirmed by hepatitis C virus (HCV) RNA positivity). Note: Subjects with a resolved hepatitis A at least 3 months prior to screening can be screened.

7. History of malignancy within the past 5 years (except for carcinoma in situ of the uterine cervix, basal cell carcinoma of the skin that has been treated with no evidence of recurrence, prostate cancer that has been medically managed through active surveillance or watchful waiting, squamous cell carcinoma of the skin if fully resected, and Ductal Carcinoma In Situ).
8. Criterion modified per amendment.

    8.1 Clinically significant abnormalities detected on ECG of either rhythm or conduction, a QTcF >450 ms, or a known long QT syndrome. Patients with

implantable cardiovascular devices (e.g. pacemaker) affecting the QT interval time may be enrolled in the study based upon investigator judgment following cardiologist consultation if deemed necessary, and only after discussion with the medical monitor.

9. Currently taking medication known to be a substrate mainly metabolized by CYP2C8 (see Appendix 3).
10. Currently taking medication known to be strong inducers of CYP3A4 (Appendix 4), and also including St-John's Wort.
11. Currently taking medication known to be strong inhibitors of CYP3A4 (Appendix 5).
12. Currently taking medication known to be potent inducers of P-gp (Appendix 4).
13. Currently taking medication known to be potent inhibitors of P-gp (Appendix 6).
14. Criterion modified per amendment.

    14.1 Acute IPF exacerbation within 6 months prior to screening and/or during the screening period. The definition of an acute IPF exacerbation is as follows: 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 and deterioration not fully explained by cardiac failure or fluid overload (see Appendix 11).
15. Criterion modified per amendment.

    15.1 Lower respiratory tract infection requiring treatment within 4 weeks prior to screening and/or during the screening period.
16. Interstitial lung disease associated with known primary diseases (e.g. sarcoidosis and amyloidosis), exposures (e.g. radiation, silica, asbestos, and coal dust), or drugs (e.g. amiodarone).
17. History of lung volume reduction surgery or lung transplant. Note: being on a transplant list is allowed.
18. Diagnosis of severe pulmonary hypertension (investigator-determined).
19. Unstable cardiovascular, pulmonary (other than IPF), or other disease within 6 months prior to screening or during the screening period (e.g. acute coronary disease, heart failure, and stroke).
20. Criterion modified per amendment.

    20.1 Had gastric perforation within 3 months prior to screening or during screening, and/or underwent major surgery within 3 months prior to screening, during screening or have major surgery planned during the study period.
21. Criterion modified per amendment.

    21.1 A history of being admitted to an institution under an administrative or court order, if applicable by local legislation, as well as any subjects falling into any of the categories of persons listed by applicable law and regulations as protected persons for which participation in a study is prohibited or subject to restrictions.
22. Criterion modified per amendment.

    22.2 History of nintedanib-related increase in ALT and/or AST of >5xULN and increased susceptibility to elevated LFT; moderate to severe hepatic impairment (Child-Pugh B or C); and/or abnormal LFT at screening, defined as AST, and/or

ALT, and/or total bilirubin ≥1.5xULN, and/or GGT ≥3xULN. Retesting is allowed once for abnormal LFT.

23. Abnormal renal function defined as estimated creatinine clearance, calculated according to Cockcroft-Gault calculation (C_{Cr}) <30 mL/min. Retesting is allowed once.
24. Hb level <10 g/dL. Retesting is allowed once.
25. Criterion modified per amendment.

    25.1 Concurrent participation in another interventional drug, device, or biological investigational research study, or use of an investigational agent within 5 half-lives of the agent (or within 8 weeks when half-life is unknown, or within 6 months if the investigational agent is an antibody) prior to screening is not allowed.
26. Use of any of the following therapies within 4 weeks prior to screening and during the screening period, or planned during the study: warfarin, imatinib, ambrisentan, azathioprine, cyclophosphamide, cyclosporine A, bosentan, methotrexate, sildenafil (except for occasional use), prednisone at steady dose >10 mg/day or equivalent.
27. Current alcohol or substance abuse in the opinion of the investigator.
28. Pregnant, breastfeeding, or planning to become pregnant or breastfeed during the study treatment or within 30 days after the last dose of IMP.
29. Clinical laboratory test suggestive of cholestasis with total serum bile acid levels >3xULN.

4.5.3. Prohibition and Restrictions

4.5.3.1. Precautions for Sexual Intercourse

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

4.5.3.1.1. Female Subjects

In line with the Heads of Medicines Agencies (HMA)'s Clinical Trial Facilitation Group (CTFG) recommendation [3], female subjects are considered of non-childbearing potential if they meet one of the following criteria:

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

All other female subjects are considered to be of childbearing potential and are required to have a negative serum pregnancy test before treatment. They must use one of the following highly effective methods of birth control from the time of signing of the ICF, during the clinical study, and for at least 30 days after the last dose of IMP:

- Combined (estrogen- and progesterone-containing) (oral, intravaginal, transdermal) hormonal contraception associated with inhibition of ovulation plus a barrier method[1].
- Progesterone-only hormonal (oral, injectable, implantable) contraception associated with inhibition of ovulation plus a barrier method[1].
- Intrauterine device.
- Intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Sexual abstinence defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the subject.

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

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

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

Female subjects of childbearing potential will be requested to do a monthly urine pregnancy test during the study. The monthly pregnancy test outcome must be documented on the subject diary card and at the next visit in the source and case report form (CRF). In case of a positive urine pregnancy test at home, the subject should immediately contact the clinical study center and the investigator must report this immediately, and under no circumstances later than 24 hours after being made aware.

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

Pregnant women or women planning to become pregnant during the study are not allowed to take part in this study.

4.5.3.1.2. Male Subjects

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

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

Non-vasectomized male subjects with female partners of childbearing potential must be willing to use a condom from the time of the first dose of IMP, during the clinical study, and for at least 90 days after the last dose of IMP in addition to having their female partner use one of the following forms of contraception:

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

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

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

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

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

Male subjects with a pregnant or breastfeeding partner should use a condom to prevent exposure through seminal fluid.

No sperm donation is allowed from the first dose of the IMP until 90 days after the last dose.

4.5.3.2. Prior and Concomitant Medications

Prior therapy

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

Concomitant therapy

Should any treatment other than the IMP be used during the course of the study, the name of the therapy, the dosage, the route, the reason for therapy, and the start and stop dates of administration must be recorded until the last visit. For subjects receiving oxygen, the volume administered per minute will also be recorded at each visit.

Concomitant therapies taken for the long-term treatment of pre-existing conditions can continue during the study, provided they are in accordance with the in- and exclusion criteria (see Sections 4.5.1 and 4.5.2, respectively). It is required that the use of these medications should

have been stable from 4 weeks prior to screening and during the screening period (at the investigator's discretion). For nintedanib and pirfenidone, subjects need to have received a stable dose for at least two months prior to screening and during screening; stable being defined as the highest dose tolerated by the subject during those two months.

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

The following therapies are prohibited during the course of the study and within 4 weeks prior to screening, because of lack of benefit or suggestion of harm in IPF: warfarin, imatinib, ambrisentan, azathioprine, cyclophosphamide, cyclosporine A, bosentan, methotrexate, sildenafil (except occasional use), prednisone at steady dose >10 mg/day or equivalent.

If during the study, the subject's condition necessitates the use of one of the above mentioned medications (excluding high-dose steroids), the use of IMP should be interrupted until resolution or stabilization of this condition, preferably after consultation with the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available).

Precautions with concomitant medication known to prolong the QT interval

The use of medication known to prolong QT interval during the study needs to be based on a benefit-risk evaluation by the investigator, e.g. in the case of atrial fibrillation. In certain other situations (e.g. the initiation of macrolides or fluoroquinolones in case of a lower respiratory tract infection), when the benefit-risk evaluation necessitates the administration of medication known to or potentially prolonging QT, IMP can be interrupted as evaluated by the investigator after clinical assessment of the subject's profile, including the baseline QTcF and how this has changed over time for this specific subject. If the investigator elects to continue IMP, additional monitoring will be performed as per investigator's judgment. A non-exhaustive list of medication known to prolong QT interval is provided in Appendix 7.

Precautions with other concomitant medications

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

- GLPG1690 demonstrated a strong time-dependent inhibition potential against CYP2C8-mediated metabolism. Consequently, GLPG1690 should not be used concomitantly with medications primarily or solely metabolized via CYP2C8 (see Appendix 3). For other medications involving part of their metabolism pathway via CYP2C8, caution should be applied on a case-by-case basis taking into consideration the benefit/risk ratio. Statins such as fluvastatin and pitavastatin are metabolized to some degree by CYP2C8, and need to be used with caution. Other statins such as simvastatin, lovastatin, and atorvastatin are theoretically less metabolized by CYP2C8. Monitoring of LFTs and creatine kinase is implemented during the study, and guidance to the subject aligned with guidance for statins in clinical practice is therefore strongly recommended. Loperamide is also a substrate of CYP2C8, and special caution should be applied in alignment with clinical practice.

- GLPG1690 is a substrate of CYP3A4 and P-gp, and could therefore be influenced by their respective inhibitors and inducers. GLPG1690 exposure is reduced up to 90% by the strong CYP3A4/potent P-gp inducer rifampin. As a consequence, strong inducers of CYP3A4 and/or P-gp are part of the exclusion criteria and should be avoided during the study to ensure proper exposure to GLPG1690 (see Appendix 4). For inhibition, strong CYP3A4 and dual strong 3A4 and potent P-gp inhibitors have shown that GLPG1690 exposure increased by 3 to 4 fold when coadministered therefore use of known strong CYP3A4 inhibitors and potent P-gp inhibitors is prohibited during the study (see Appendix 5 and Appendix 6). Antibiotics from the macrolide therapeutic class are excluded, unless they are used for the short-term treatment of a lower respiratory tract infection with interruption of IMP, which is restarted as soon as possible after the completion of the treatment with macrolides.

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

In certain situations, when the benefit-risk evaluation necessitates the administration of medication excluded from use during the study, IMP should be interrupted and restarted as soon as possible.

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

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

Rescue medication

If the subject shows a worsening of his/her IPF disease condition (e.g. acute IPF exacerbation), all treatment options are allowed at the investigator's discretion. The decision to continue the IMP should be taken on a case-by-case basis by the investigator and in case of doubt can be discussed with the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available).

4.5.3.3. Food and Beverage Restrictions

The use of St-John's Wort, a strong CYP3A4 inducer, is prohibited during the study.

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

4.5.3.4. Other Prohibitions and Restrictions

Not applicable.

4.5.4. Treatment Discontinuation, Subject Withdrawal, and Study Termination

All subjects will continue on IMP until the last subject reaches 52 weeks into the study (Visit 12) (for details, please refer to Section 4.1 and to Section 6.1 "Specific study visits when the last subject reaches 52 weeks into the study (Visit 12)").

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.

Subjects who choose to withdraw from study participation will be asked if they are prepared to complete a last visit. In this case, either the EoST or EoSA visit should be performed. The subjects' vital status information will be collected at the time of the EoST/EoSA visit of the last subject who reaches 52 weeks in the study (Visit 12), according to national, ethical, and regulatory guidelines, and as per the subjects' confirmation in the signed main ICF. If the subject initially confirmed no vital status information to be collected, but reconsiders at the time of actual withdrawal of consent, the subject has to re-consent for this in writing.

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

Subjects who discontinue IMP early (ETD), with the exception of patients who withdraw consent and patients lost to follow-up, will be encouraged to complete all following visits and evaluations as originally planned per protocol (see below, "Procedures in case of early treatment discontinuation (ETD)").

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 subjects, investigator(s), and relevant authorities will be informed of the reason for clinical study termination.

Discontinuation of IMP

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

- Life-threatening AE or a serious adverse event (SAE) that places the subject at immediate risk.
- Confirmed pregnancy: if a subject becomes pregnant during the study (to be confirmed by local serum pregnancy test; central measurement will also be performed), the IMP has to be stopped immediately and the subject has to be followed up until birth or otherwise termination of pregnancy. The subject needs to be unblinded immediately and repeat counseling on birth defect risk must be offered in case she was on active drug.

- Arrhythmia or conduction abnormality, including but not limited to prolonged QTcF, where the severity is categorized as Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher.
- An increase for QTcF of >60 ms from baseline (Visit 3) or QTcF >500 ms at any ECG recording (any recording of triplicate ECG or single ECG) needs to be confirmed by an ECG recording as soon as possible from the original abnormal recording at the same visit. If the abnormal recording is discovered after the visit, the recording should be confirmed as soon as possible. In case of an abnormal ECG on both of these two recordings is confirmed, the investigator needs to send an immediate alert to the central reader for confirmation as well as to the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available). If the ECG abnormality is before IMP intake, IMP administration will be withheld until the central reader has reviewed the ECG registration. In case of confirmation of the ECG abnormality, IMP will be discontinued for this subject. Only in case a response of the central reader is not available within the timeframe of the visit, the investigator can proceed to discontinue the treatment of the subject.

  If a normal QTcF is reported during the visit, but the central cardiologist reports it as abnormal (any of the two criteria above), then the IMP should be discontinued as soon as possible.
- Increase in LFTs (also see Appendix 9):
  - At Visit 3 immediately after randomization: test results will only be available after the first IMP intake. If the subject meets the exclusion criteria for AST, ALT, total bilirubin, and GGT, then treatment with IMP will be discontinued.
  - Any other visit:
    - AST or ALT ≥8xULN
    - AST or ALT ≥3xULN with signs of severe liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥1.5xULN or INR >1.5)
    - AST or ALT ≥3xULN for more than 2 weeks
    - AST or ALT ≥3xULN during re-escalation
- Clinical laboratory test suggestive of cholestasis with total serum bile acid levels >3xULN on a sample taken in fasted state (at least 8 hours fasted). If the routine random or postprandial total serum bile acid sample is >3xULN, then the subject should have a fasted sample taken within 1 to 5 days. The results of this test will determine whether the subject should discontinue IMP or not.
- Chronic (defined as: anticipated to be administered for more than 3 months) use of concomitant medication not permitted during the study.
- Closing of the study by the sponsor or regulatory authorities.

Wish of the subject to stop taking IMP.

For a subject having:

- AST or ALT ≥8xULN
- AST or ALT ≥3xULN with signs of severe liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥1.5xULN or INR >1.5)

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

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

Every effort should be made to keep subjects in the study and on treatment. However, the investigator can consider stopping treatment with IMP, preferably after consultation with the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available), 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).

- At Visit 3: as the blood sample is taken before first IMP intake and the results are only available after first IMP intake, the investigator needs to justify continuation of IMP in writing for abnormal results (based on the exclusion criteria) for:
  - Creatinine clearance
  - Hb

The reason(s) for stopping the IMP will be documented in the CRF.

<u>Procedures in case of early treatment discontinuation (ETD)</u>

Subjects who discontinue IMP early will complete an ETD visit. They will be encouraged to complete all following visits and evaluations as originally planned per protocol (i.e. including an EoSA visit when the last subject reaches 52 weeks into the study [Visit 12]). The subject will be informed about this at signing of the ICF.

In particular, the subject will be requested if at all possible to attend:

- the first scheduled visit after their Early Treatment Discontinuation (ETD)
- The Week 26 visit (if not done before IMP discontinuation)

- the Week 52 visit (if not done before IMP discontinuation)
- after Week 52, visits every 24 weeks up to EoSA, as described in Section 6.11.2

An ETD visit will be scheduled as soon as possible from the day of early discontinuation of IMP. In case the subject discontinues IMP on a scheduled visit, that visit should be completed and, in addition, the assessments from the ETD visit that are not part of the scheduled visit should be performed. If the subject is not able or not willing to come back for an ETD visit, the investigator will contact the subject by phone, and if the subject has agreed to this in the ICF, may consult the subject's medical record and/or contact the subject's general practitioner or relatives, if necessary, to obtain the needed information.

4.6. MEASURES TO MINIMIZE BIAS

4.6.1. Randomization

At screening, subjects will be assigned a subject identification number. When a subject is confirmed to be eligible for the clinical study, he/she will be randomized.

A total of approximately 750 subjects will be randomized in a 1:1:1 ratio to receive GLPG1690 600 mg q.d., GLPG1690 200 mg q.d., or matching placebo for at least 52 weeks. Allocation of each subject to a given treatment will be described in a randomization list prepared by a CRO. This randomization list will be stratified in a balanced manner for background local standard of care for treatment of IPF (nintedanib, pirfenidone, or neither). Recruitment may stop earlier in one or more strata to maintain the balance as indicated, while the other strata(s) continue to recruit. Upon qualification for the study, allocation of each subject to a given treatment will be done using a centralized electronic system (interactive web response system [IWRS]) with permuted blocks.

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

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

4.6.2. Blinding and Unblinding

This is a randomized, double-blind clinical study. The subject and the entire clinical study team, including the investigators, clinical study coordinators, and sponsor personnel are blinded to treatment assignment, except for situations described in the last paragraph of this section.

Blinded and packaged medication will be provided to the clinical study center. All IMP formulations will be packaged in the proper proportion to assure desired dosages and maintenance of the blinding. In case of down-titration, interruption, or re-escalation, a sham dose level is available for the treatment allocation arm of GLPG1690 200 mg in order to ensure the same number of steps as the other treatment allocation arms and to ensure blinding (for details, refer to Sections 4.1 and 5.2). The different steps are blinded for treatment allocation but not for dose level.

The blind can be broken only if the investigator deems it necessary for the safety of a subject. The investigator is encouraged to discuss considerations to break the blind with the CRO

medical monitor (as per study contact list) or the sponsor's study physician (in case the former is not available), whenever possible and where the situation allows. However, the responsibility to break the treatment code in emergency situations resides solely with the investigator. The investigator is not required to discuss unblinding beforehand if he/she feels rapid emergency unblinding is necessary, but is required to inform the CRO medical monitor and sponsor in a timely fashion after unblinding has occurred.

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

Code-break information (via IWRS vendor/randomization list) will be provided to the bioanalytical laboratory responsible for plasma drug determination sample analysis and to the sponsor pharmacovigilance lead for SAE reporting purposes. The IDMC will have access to unblinded data (for details, refer to Section 8.1).

5. INVESTIGATIONAL MEDICINAL PRODUCT

5.1. IDENTITY OF THE INVESTIGATIONAL MEDICINAL PRODUCT

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

GLPG1690 will be provided as film-coated tablets for oral use, containing 100 mg or 200 mg G451990 each (G451990 is the compound code for GLPG1690). The placebo will be provided as matching film-coated tablets for oral use. The GLPG1690 100-mg tablets and the placebo tablets matching the GLPG1690 100-mg tablets will be smaller than the GLPG1690 200-mg tablets and the placebo tablets matching the GLPG1690 200-mg tablets.

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

5.2. DOSAGE AND ADMINISTRATION

The following doses will be tested; three tablets will be provided per dose (high [original] dose level):

- GLPG1690 600 mg q.d. (as three GLPG1690 200-mg tablets)
- GLPG1690 200 mg q.d. (as one GLPG1690 200-mg tablet and two placebo tablets, matching the GLPG1690 200-mg tablet)
- placebo q.d. (as three placebo tablets, matching the GLPG1690 200-mg tablet)

The following doses will be provided for down-titration and re-escalation; two tablets will be provided per dose:

Low (reduced) dose level:

- GLPG1690 200 mg q.d. (as one GLPG1690 200-mg tablet and one placebo tablet, matching the GLPG1690 100-mg tablet)
- GLPG1690 100 mg q.d. (as one GLPG1690 100-mg tablet and one placebo tablet, matching the GLPG1690 200-mg tablet)
- placebo q.d. (as one placebo tablet, matching the GLPG1690 200-mg tablet and one placebo tablet, matching the GLPG1690 100-mg tablet)

Intermediate (reduced) dose level:

- GLPG1690 400 mg q.d. (as two GLPG1690 200-mg tablets)
- GLPG1690 200 mg q.d. (as one GLPG1690 200-mg tablet and one placebo tablet, matching the GLPG1690 200-mg tablet)
- placebo q.d. (as two placebo tablets, matching the GLPG1690 200-mg tablet)

Refer to Figure 2 in Section 4.1.2 for an overview of number of tablets to be taken per dose level.

Subjects will be instructed to swallow the tablets as a whole with a glass of water and to not chew the drug prior to swallowing. On visit days, subjects will be instructed to take their IMP at the clinical study center, to allow for predose (i.e. before IMP intake) assessments to be completed.

At Visits 3, 9, and 12, the subject will be asked to take pirfenidone or nintedanib (if applicable) at the clinical study center.

If a subject misses a dose (e.g. because he/she forgot to take the medication), he/she should take the missed dose within 12 hours after the planned intake time and within 2 hours of food intake. If the IMP is not taken within 12 hours after the planned time, the missed dose should be skipped.

The IMP is to be taken q.d. at the same time every day with food (e.g. breakfast, small meal, or a snack) or after food intake, taking into account the timing of the planned visits, with a maximum of 2 hours between the food intake and IMP intake.

For subjects who are taking nintedanib as standard of care medication at screening or randomization or who start nintedanib during the study, it is recommended to take the IMP at or after lunch (approximately 4 hours after nintedanib morning intake).

5.3. PACKAGING, LABELING, AND DISTRIBUTION

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

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

Each medication kit will be identified with a unique kit number. A multiple of kits will be provided to the subject at each visit, providing the subject with sufficient tablets to cover the period until the next scheduled visit.

The distribution to the clinical study center will only occur after all required documentation is obtained including clinical study approval by Competent Authorities and the IECs/IRBs,

documentation on which the assessment of the investigator's qualifications was based (e.g. curriculum vitae), and the signed and dated study agreement and financial agreement. The IMP is to be dispensed according to the protocol.

In case study subjects cannot attend site visits, due to any COVID-19-related reason, direct-to-patient (DTP) shipment of IMP has been implemented and can be used to ensure the dosing regimen per protocol requirement can be maintained. DTP should only be used in case of emergency where on-site IMP dispensing is not possible, and if allowed per local regulations. Local guidelines must be followed and regulatory approval or notification of authorities may be required. The DTP process used will be reviewed and approved by the sponsor. If the DTP shipments originate from the investigational site(s), their coordination will be ensured by the investigational site(s) in collaboration with the CRO to ensure clinical integrity without the involvement of the sponsor. Detailed guidance on the shipment has been provided to the sites in COVID-19 guidance documents. Consent of the subjects to receive IMP at home is required prior to the shipment of IMP, and should be documented in the source data. Return shipment of unused IMP from the subjects to the site may be implemented if allowed per local regulations.

5.4. STORAGE

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

5.5. TREATMENT COMPLIANCE AND DRUG ACCOUNTABILITY

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

The investigator or designated clinical study personnel will maintain a log of the total amount of IMP received at the clinical study center, amount dispensed to the subject, and the amount of IMP returned by the subject to the clinical study center. IMP supplies for each subject will be inventoried and accounted for throughout the clinical study. These records will be checked against the inventory by the study monitor on a regular basis. All clinical supplies will be stored in locked facilities.

Subjects will return any unused IMP and empty IMP packages at each study visit. Missed doses should be discussed to try to ascertain the reason(s). Every effort should be made to ensure proper subject dosing. Subjects with poor compliance will be re-trained by the clinical study center.

Treatment compliance will be assessed by the investigator or designee. At each visit, clinical study center staff will review treatment compliance by assessing the number of returned IMP.

6. CLINICAL STUDY ASSESSMENTS

Every effort should be made to ensure that protocol-required tests and procedures are completed as described in the Schedule of Activities (see Section 6.11). To avoid inter-observer variability, a reasonable effort should be made to ensure that all safety and efficacy evaluations are completed by the same individual who made the initial baseline determinations.

For subjects who, for any COVID-19-related reason, cannot perform study procedures, extended visit windows, the possibility to conduct phone/televisits followed by home (or other remote location) visits, and alternative assessment procedures are detailed in Section 6.1.1.

6.1. TIMING OF ASSESSMENTS

The study assessments will be undertaken at time points as specified in the Schedule of Activities in Section 6.11. A window of ±2 days is allowed for Visits 4 and 5, ±4 days for Visits 6 to 12, and ±7 days for all visits after Visit 12.

The ICF needs to be signed before any study procedure, including screening procedure, is carried out. The ICF signature is the start of the 28-day screening period and will be used as the date of Visit 1.

Please note that the both Visit 1 and Visit 2 can have a duration of more than one day to accommodate all screening assessments.

Visit 1: The preferred sequence of study assessments will be as follows (urine analysis can be done at any stage during the visit):

1. Only for subjects taking nintedanib: the time of nintedanib intake will be recorded.
2. In- and exclusion criteria, demographics, medical history, alcohol consumption, and smoking habits
3. EQ-5D, SGRQ, LCQ, K-BILD, VAS Cough and Urge to Cough questionnaires
4. ECG (triplicate)*
5. Oxygen saturation (SpO_2) test
6. Spirometry** (Spirometry should not be repeated until notification from the central reader is received)
7. DLCO
8. Assessment of (S)AE(s) and prior and concomitant medication
9. Physical examination and vital signs (supine heart rate, respiratory rate, systolic and diastolic blood pressure [SBP and DBP], and body temperature)
10. Blood sampling for safety, FSH (if applicable), serum pregnancy test, and clinical laboratory tests
11. Only for subjects taking nintedanib: blood sampling for nintedanib concentration assessment 2-4 hours after nintedanib intake
12. Blood sampling for target biomarkers/PD
13. Blood sampling for disease-specific biomarkers
14. 6MWT with Borg scale before and after 6MWT
15. Repeat spirometry** if acceptability and repeatability criteria as defined in the ATS/ERS/JRS/ALAT guidelines are not met as confirmed by the central spirometry reader

16. Only for subjects taking nintedanib: blood sampling for nintedanib concentration assessment 5-10 hours after nintedanib intake

*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 (for details, refer to Section 6.6.5).

**Subjects using inhaled bronchodilators can do this after the confirmed spirometry assessment, unless clinically indicated to administer earlier.

Note: If needed, an HRCT needs to be planned and performed during the screening period before Visit 2. This can be done during an unscheduled visit in the screening period. A repeat HRCT is only allowed to be performed once for study eligibility; if the HRCT is >12 months old; or if the available historic HRCT cannot be evaluated.

As soon as possible after signing the ICF, the investigator will transmit the HRCT images and the LB specimens (if available) for review (for details, refer to Section 6.3 and Appendix 1).

Subjects can only proceed to Visit 2 if the diagnosis of IPF is confirmed by central reading of the chest HRCT and (if available) LB, and if all other test results with the exception of ECG (if a retest is needed) allow the subject to proceed.

Visit 2:

1. Repeat abnormal ECG if the central reading of the Visit 1 ECG report confirms that QTcF does not meet eligibility criterion.
2. Spirometry* (Spirometry should not be repeated until notification from the central reader is received)
3. Oxygen saturation test
4. Oxygen titration test for the 6MWT with Borg scale
5. Assessment of (S)AE(s) and concomitant medication
6. Repeat spirometry* if acceptability and repeatability criteria as defined in the ATS/ERS/JRS/ALAT guidelines are not met as confirmed by the central spirometry reader
7. Repeat liver function tests, creatinine clearance and Hb if needed
8. Repeat total serum bile acid if needed on a sample taken in fasted state (at least 8 hours fasted)

*Subjects using inhaled bronchodilators can do this after the confirmed spirometry assessment, unless clinically indicated to administer earlier.

Subsequent visits: the preferred sequence of study assessments during the IMP intake period, will be as follows (please take note of assessments that may be only required at certain visits and refer to the Schedule of Activities for further details):

1. Randomization via IWRS (at Visit 3 only)
2. Urine pregnancy test (if applicable) with urine analysis
3. EQ-5D, SGRQ, LCQ, K-BILD, VAS Cough and Urge to Cough
4. ECG (triplicate) at Visits 3 and 4; ECG (single) for any following visit*

For subjects on nintedanib either at screening and randomization or starting nintedanib during the study, the blood sampling at Visits 3, 9, and 12 (i.e. items 10 to 14 in this list) can be performed after the ECG assessment and before the oxygen saturation test.

5. Oxygen saturation (SpO_2) test
6. Spirometry**
7. DLCO
8. Assessment of (S)AE(s) and concomitant medication, alcohol consumption, and smoking habits
9. IMP collection for IMP accountability
10. Physical examination and vital signs (supine heart rate, respiratory rate, SBP and DBP, and body temperature)
11. Blood sampling for clinical laboratory tests
12. Blood sampling for genotype analysis (only at Visit 4)
13. Blood sampling for concentration analysis of GLPG1690 and pirfenidone or nintedanib (as detailed in Section 6.7, Table 1):
    - For all subjects before pirfenidone or nintedanib intake, if applicable (Visits 3, 9, and 12) ***
    - For subjects taking nintedanib at screening and randomization, until they stop taking nintedanib:
        - after nintedanib intake (2-6 hours postdose) and before IMP intake at Visits 4, 5, 6,7, 8, 10, and 11, and every 12 weeks after Visit 12 (week 52) ****
    - For subjects not taking nintedanib at screening and randomization and those stopping nintedanib during the study:
        - after pirfenidone or nintedanib intake, if applicable, and before IMP (Visits 7 and 10), and every 24 weeks after Visit 12 (week 52) ****
14. Blood sampling for target biomarkers/PD (Visits 3, 7, 9, 10, 12, and every 24 weeks thereafter)
15. Blood sampling for disease-specific biomarkers (Visits 3, 7, 9, 12, and every 24 weeks thereafter)
16. 6MWT before IMP intake at baseline (Visit 3); under the same conditions as the final result in the oxygen titration period (Visit 2), with Borg scale before and after 6MWT

IMP INTAKE (See Section 5.2 for IMP administration instructions)

17. 6MWT after IMP for all visits after Visit 3 (Visits 9 and 12, and every 24 weeks thereafter); under the same oxygen requirements as the final result in the oxygen titration period, with Borg scale before and after 6MWT
18. ECG between 2 to 3 hours after IMP intake and at least 30 minutes after completing 6MWT
    a. Triplicate ECG at Visits 3 and 4.
    b. Single ECG at Visits 5, 7, and 10
19. Blood sampling for concentration analysis of GLPG1690 and pirfenidone or nintedanib between 2 to 3 hours after IMP intake, at approximately the same time as the ECG (only at Visits 7 and 10)****
20. Blood sampling for target biomarkers/PD between 2 to 3 hours after IMP intake at approximately the same time as the ECG (only at Visits 7 and 10)

21. Repeat spirometry** if confirmation acceptability and repeatability criteria based on the ATS/ERS/JRS/ALAT guidelines are not met
22. Dispense and review diary card

*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 (for details, refer to Section 6.6.5)

**Subjects using inhaled bronchodilators can do this after the confirmed spirometry assessment, unless clinically indicated to administer earlier.

***At these visits, the subject needs to take pirfenidone or nintedanib (as applicable) at the clinical study center.

****At these visits, the subject needs to take pirfenidone or nintedanib (as applicable) as per his or her normal routine, and, for subjects taking nintedanib at screening and randomization, until they stop taking nintedanib, record the time of intake on the diary card.

Specific study visits when the last subject reaches 52 weeks into the study (Visit 12)

The EoST visit captures the end of study treatment for subjects still taking IMP when the last subject reaches 52 weeks (Visit 12). For subjects still taking IMP and who had a scheduled visit at the clinical study center within 6 weeks before the date that the last subject reaches 52 weeks into the study (Visit 12), the last scheduled visit will be documented as the EoST visit. For subjects still taking IMP and who had their last scheduled visit more than 6 weeks before the date that the last subject reaches 52 weeks into the study (Visit 12), a scheduled visit will be planned within 2 weeks of this date. Note that these subjects will continue IMP intake until their EoST visit.

The EoSA visit captures the end of study assessments for subjects who discontinued IMP and will have had an ETD visit. The scheduling of this visit is equal to the EoST visit.

A follow up visit will be scheduled 4 weeks after EoST/EoSA visit (visit at clinical center or phone call, depending whether only vital status or also a PD blood sample needs to be collected). At this FU visit vital status will be collected from all subjects, as well as blood samples for PD from a subset of subjects who completed an EoST visit (i.e. those subjects discontinuing IMP at EoST). The purpose of these samples is to gather additional data on the LPA C18:2 levels and as needed establish an LPA time course after the last dose of IMP.

6.1.1. Alternative Timing and Assessment Procedures for Subjects who, due to any COVID-19-related Reason, Cannot Perform the Study Procedures

Screening and randomization of subjects (at Visit 3) can only be conducted on site and all assessments should be completed according to the Schedule of Activities (Section 6.11).

If it is known or anticipated that Visit 4 cannot be performed on site, the subject should not be randomized. If Visit 4 is scheduled but turns out not to be feasible despite all precautions, a

home visit or visit at another remote location, if feasible and available, is strongly recommended.

The visit windows for Visits 5, 6, 7, 8, 10, and 11 may be increased to ±7 days and the visit windows for Visit 9 and Visit 12 may be increased to ±28 days.

At each visit, the subject will continue the intake of IMP (if confirmed by the responsible investigator or delegate, as detailed below) and will be supplied with IMP to cover the extended visit windows (as described in Section 5.3). Urine pregnancy tests (if applicable) and subject diary cards may also be supplied to the subject's home.

Assessments and Activities to be performed at remote and on-site visits

For Visit 4 and all visits thereafter, if a randomized subject is not able to attend a scheduled study visit on site and a phone/televisit is conducted instead, then the study assessments should be conducted according to the Schedule of Activities (Section 6.11) as much as possible, in particular for Visits 9 and 12.

If possible and available, trained study staff or trained personnel are encouraged to carry out study assessments at the subject's home or another remote location (i.e. conduct phone call first, then conduct home/remote location visit).

Sites should assess risk to subjects' safety incurred by home (or other remote location) visits and ensure that the staff sent to the subject's home do not pose a risk of infection to the subject or vice versa.

At the phone/televisits or home (or other remote location) visits, the investigator should collect information on adverse events (changes of ongoing or new events), changes in concomitant medications or standard of care, and enquire about ongoing IMP intake (completion of subject diary cards).

At the home (or other remote location) visits, the following assessments should be performed (if appropriate as per Schedule of Activities, Section 6.11). If it is not possible to perform all assessments, every effort should be made to complete the assessments indicated with an asterisk (*)

- physical examination (including weight) *
- vital signs assessment *
- safety blood sample collection for central laboratory assessment where possible or local laboratory assessment (if sampling conditions as per laboratory manual cannot be ensured) *
- spirometry (using the study device) *
- 12-lead electrocardiogram (ECG) using the study device if possible or local assessment *
- electronic clinical outcome assessment (eCOA) collection using the tablet device provided for the study *
- arterial SpO_2
- urine pregnancy test (if applicable) *

In addition, all efforts should be made to review and collect the subject diary cards and perform drug accountability as well as retrieving the (un)used IMP blisters.

The 6MWT and DLCO can be performed if circumstances allow.

Blood samples for PK, target biomarker/PD (LPA), or disease-specific biomarker assessments should not be collected at home visits.

Additional guidance for on-site visits

If an on-site visit for randomized subjects is feasible, all assessments for the applicable visit should be performed according to the Schedule of Activities (Section 6.11). However, if it is not possible to conduct all the assessments, then the following assessments/activities should be prioritized:

- adverse events (changes of ongoing or new events) as well as information on hospitalization between visits
- changes in concomitant medications or standard of care, enquiring about ongoing IMP intake (completion of subject diary cards), as well accountability and return of (un)used IMP blisters
- vital signs
- safety blood sample collection (for central laboratory)
- spirometry and ECG (using the study devices)
- eCOA (using the tablet device provided for the study)
- 6MWT
- DLCO
- Urine pregnancy test (if applicable)

Guidance on continuation of IMP during the COVID-19 pandemic

The ultimate decision to continue or interrupt IMP remains with the investigator except when three consecutive on-site visits have been missed and could not be replaced by phone/televisits, home (or other remote location) visits, and/or local lab assessments, or if the safety assessments could not be performed within the indicated time periods. In these cases, IMP should be interrupted.

In general, the decision on IMP continuation shall depend on the investigator's assessment of the subject's clinical condition, and on the occurrence and severity of adverse events and the results of laboratory assessments.

Timely (in accordance to adjusted visit windows) local safety laboratory assessment and home/local ECG (if possible), are strongly recommended to support the decision regarding continuation of IMP. If these assessments are not feasible, then the investigator should collect minimal assessments, such as physical condition, adverse events, and concomitant medication to help decide on the subject's continuation of IMP. If only phone/televisits are possible, the decision to continue IMP may be based on this information.

The following criteria should be adhered to when making the decision on continuation of IMP and every effort should be made to capture safety assessments to ensure IMP can be continued. The recommendations are specific to the study phase:

First phase: In case of missing visits between Visit 4 to Visit 8 (Week 2 to Week 18), safety assessments must be performed within an 8-week timeframe.

Second phase: In case of missing visits between Visit 9 to Visit 12 (Week 26 to Week 52), safety assessments must be performed within a 12-week timeframe.

Third phase: After Visit 12 (Week 52 to End of Study), safety assessments must be performed within a 16-week timeframe.

If during any of these phases, safety assessments at home or at another remote location are not feasible, then at a minimum, local laboratory evaluations are needed to evaluate if the subject can continue IMP. ECG alternatives are to be discussed with the medical monitor.

If IMP was interrupted, once safety assessments as specified above have been performed, the investigator may consider the re-start of IMP.

6.2. UNSCHEDULED VISITS

Additional visits can be performed at other time points for any safety assessment if clinically indicated. If local regulations allow, home visits can be performed for safety laboratory sampling at the investigator's discretion. These unscheduled visits and outcomes of additional assessments need to be recorded in the source and, if performed before the subject's last visit per protocol, also in the CRF.

6.3. INITIAL SUBJECT AND DISEASE CHARACTERISTICS

Subjects will be asked to attend the clinical study center for two screening visits, after giving written informed consent.

The subject can only proceed to Visit 2 (screening visit 2) if the diagnosis of IPF is confirmed by central reading of the chest HRCT and by central review of the available LB, if required (according to the criteria in Appendix 1), and if all other test results of Visit 1 allow the subject to proceed.

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

- Laboratory values for LFTs, creatinine clearance, and Hb can be retested once
- Lost or invalid blood or urine samples

Rescreening: in case of screening failure, subjects are allowed to be rescreened a maximum of two times, with an interval taking into account the eligibility criteria at the investigator's discretion. When in doubt, the investigator can discuss rescreening with the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available), on a case-by-case basis. Rescreening with the purpose to repeat a HRCT scan, is not allowed.

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.

Visit 1

The subject's historical HRCT and LB (if available) will only be sent for review if the minimum requirement of HRCT slide thickness of <1.5 mm is met. Central reading will be performed by two readers for the confirmation of the IPF diagnosis through:

- Central review of chest HRCT, with adjudication by a third reader, if necessary
- Central review of LB (if available) will be performed by one reader

Note that both the chest HRCT and LB (if available) need to be sent to central review as soon as possible after signing the ICF to allow for central reading and confirmation of IPF diagnosis before Visit 2. Additional details are provided in Appendix 1. If needed, an HRCT needs to be planned and performed during the screening period before Visit 2. If an historical LB is available it can be used for the assessment of eligibility, but no new biopsy is required.

For subjects on nintedanib, the time of last nintedanib intake on the day of Visit 1 will be verified by the investigator, and subjects will have blood samples taken for PK at Visit 1 between 2-4 hours; and 5-10 hours after the intake of nintedanib.

In addition, at the first screening visit, information on demographics (age, sex, and race) and medical history (including the multidisciplinary diagnosis of IPF at the clinical study center if present, the duration of disease, disease progression prior to screening [inclusion criterion], prior [up to 12 weeks] and concomitant medications [for IPF and other co-morbidities], contraception, alcohol consumption, and smoking habits) will be collected. A full physical examination will take place (including measurement of height and weight) and vital signs, pulse oximetry (to measure SpO_2), triplicate ECG, clinical laboratory assessments (including serology, FSH [if applicable]), serum pregnancy test (if applicable), spirometry, DLCO, 6MWT with Borg scale, and EQ-5D, SGRQ, LCQ, K-BILD, VAS Cough and Urge to Cough questionnaires will be conducted to determine the subject's eligibility for study participation. In addition, samples for target biomarker/PD and disease-specific biomarkers will be taken.

Visit 2

At Visit 2, a second spirometry will be performed, as well as an oxygen saturation test and the oxygen titration test for the 6MWT test with Borg scale. For the oxygen titration test, resting SpO_2 should be ≥88% with maximum 6 L O_2/minute. During the walk, SpO_2 should be ≥83% with maximum 6 L O_2/minute or ≥88% with 0, 2, or 4 L O_2/minute.

During the screening period, two spirometry measurements will be performed on different visits (Visit 1 and Visit 2). Both measurements need to meet acceptability and repeatability criteria as specified by the most recent ATS/ERS/JRS/ALAT guidelines [19]. If repeat values are within the acceptability criteria and completed within the screening window for the two screening visits, the subject is eligible for the study.

At the screening visits, central review of the spirometry will be performed as much as possible during the visit. In case the acceptability and repeatability criteria as specified by ATS/ERS/JRS/ALAT guidelines are not met, a repeat spirometry should be performed during the same visit, ideally within 1 hour time.

The in- and exclusion criteria will be checked to assess eligibility for the study. All screening tests will be reviewed to confirm eligibility before randomization and first IMP intake. After the subject's eligibility for the study has been confirmed, the subject will be randomized into

the study at Visit 3 before IMP intake to receive treatment with GLPG1690 600 mg q.d., GLPG1690 200 mg q.d., or matching placebo.

A history of progression of disease, as defined by a relative decline in the FVC of at least 10% of the predicted value, during the 1 year prior to screening will be recorded, if available.

6.4. SUBJECT DIARY CARD

Subjects will be given a diary card at Visit 3 to record the following:

- from Day 1 until EoST/EoSA visit, subjects will be asked to record the date of IMP intake and the number of tablets taken for each administration
- All subjects taking nintedanib (i.e. subjects taking nintedanib at screening and randomization or starting nintedanib during the study) until they stop taking nintedanib, will be asked to indicate via tick box whether each IMP administration was approximately 4 hours after the nintedanib morning dose
- only for subjects taking nintedanib at screening and randomization until they stop taking nintedanib, subjects will be asked to record the time they take nintedanib at home in the morning on the day of Visits 4, 5, 6, 7, 8, 10, and 11, and after Visit 12 (Week 52), in the morning on the day of the Visits every 12 weeks until the EoST/EoSA visit
- from Day 1 until EoST/EoSA visit, subjects will be asked to record changes in concomitant medication regimen, including new medicines not captured in medication history, use of bronchodilators, monthly urine pregnancy test outcome (only for WOCBP), and any other concomitant medication used as well as any emerging AE

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

If subjects, due to any COVID-19-related reason, cannot attend visits on site, subject diary cards may be sent and should be completed as has been done prior to the COVID-19 outbreak. All efforts should be made to review and collect the diary cards at home or other remote location visits (where feasible), but certainly at the next on-site visit.

6.5. EFFICACY ASSESSMENTS

6.5.1. Pulmonary Function

6.5.1.1. Spirometry

Spirometry will be performed at the clinical study center before IMP intake and repeated after IMP intake if indicated (see below) to assess pulmonary function at the time points specified in the Schedule of Activities (Section 6.11) and according to the sequence of study assessments described in Section 6.1.

Clinical study centers will be provided with spirometers to be used for all study spirometry assessments. Spirometry devices will not be used for other purposes than this study.

The clinical study center-based spirometry must meet the criteria for acceptability and repeatability as defined in the ATS/ERS/JRS/ALAT guidelines [19] for screening, and will be based on ATS/ERS/JRS/ALAT guidelines after randomization.

Pulmonary function will be measured in a standardized manner and results should be transmitted electronically during the visit immediately after performing the spirometry and evaluated by a central reader. In case the acceptability and repeatability criteria as specified by ATS/ERS/JRS/ALAT guidelines are not met, a repeat spirometry should be performed during the same visit of the screening period. After randomization, a repeat spirometry should be performed during the same visit, based on the ATS/ERS/JRS/ALAT guidelines [19].

Timing of spirometry

The spirometry test is to be performed preferably at approximately the same time every visit.

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

- withheld their short-acting β-agonist (e.g. albuterol) or anticholinergic (e.g. ipratropium bromide) for >6 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 at the end of the visit, after acceptability and repeatability as specified by or based on ATS/ERS/JRS/ALAT guidelines [19] has been confirmed by the central reader for the spirometry test. In case the subject has taken a bronchodilator before spirometry, the visit should be re-scheduled within the foreseen timeframe to allow spirometry assessment without bronchodilator.

Spirometry parameters and calculation of predicted values

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

- FVC (mL) and %FVC
- FEV_1 (mL) and percent predicted forced expiratory volume in 1 second (%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 [27].

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.5.1.2. DLCO

The DLCO test, corrected for Hb, will be performed according to local practice at the time points specified in the Schedule of Activities (Section 6.11). Each DLCO test should be performed using the same equipment.

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.5.1.3. Arterial Oxygen Saturation

Arterial SpO_2 will be measured by pulse oximetry before IMP intake at the time points specified in the Schedule of Activities (Section 6.11). SpO_2 will be collected after the subject has been at rest (seated or supine) for at least 5 minutes and will be measured at the same location of the extremity using the same device as much as possible.

If applicable, the flow of additional oxygen needs to be recorded in L/min.

Normal ranges for SpO_2 are presented in Appendix 8.

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.5.2. Clinical Endpoints

A time to (first) event analysis will be conducted for each of the following secondary endpoints:

- Mortality: all-cause and respiratory-related
- Hospitalization: all-cause and respiratory-related
- Lung transplant
- Acute IPF exacerbation
- All-cause mortality or lung transplant
- All-cause mortality, or lung transplant, or qualifying for lung transplant
- All-cause mortality, ≥10% absolute decline in %FVC, or respiratory-related hospitalizations
- All-cause mortality or respiratory-related hospitalizations

These endpoints will be adjudicated by the CEAC (for details, refer to Section 8.2).

6.5.3. Quality of Life

Patient-reported outcome instrument

The following instruments will be used at the time points indicated in the Schedule of Activities (Section 6.11):

- EQ-5D
- SGRQ
- K-BILD
- LCQ
- VAS Cough and Urge to Cough

The 3-level version of EuroQOL 5-Dimensions Questionnaire (EQ-5D-3L) consists of two pages: the EQ-5D descriptive system and the EuroQOL visual analogue scale (EQ VAS). The EQ-5D descriptive system is split into five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has three levels, which results in a 1-digit number that expresses the level selected for that dimension. The digits for the five dimensions can be combined into a 5-digit number that describes the subject's health state. The

EQ VAS records the subject's self-rated health on a vertical VAS and can be used as a quantitative measure of health outcome that reflects the subject's own judgment.

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

The K-BILD health status questionnaire is a 15-item questionnaire split into three domains: psychological, breathlessness and activities, and chest symptoms. Scores are weighted such that every domain score and the total score range from 0 to 100, with higher scores indicating a better health status.

Subjects with IPF commonly present with a (severe) non-productive cough. Cough will be evaluated using the LCQ. The LCQ is a 19-item questionnaire split into three domains: physical, psychological, and social. Scores are calculated by domain (range from 1 to 7) and then added to obtain the total score (range from 3 to 21, with higher scores indicating a better health status).

VAS Cough and Urge to Cough will use a VAS of 100 mm with extremes "no cough" to "worst possible cough", and "no urge" to "highest urge to cough".

These questionnaires will be completed electronically, using a tablet device at the clinical study center. Subjects must be able to read and complete the EQ-5D, SGRQ, K-BILD questionnaire, LCQ, and VAS Cough and Urge to Cough by themselves. They should not receive any help from anyone (such as family and friends or study staff) in interpreting or responding to the questions and need to complete the questionnaires in a quiet environment at the clinical study center.

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.5.4. Functional Exercise Capacity Testing: 6MWT

A 6MWT will be performed at the clinical study center to assess pulmonary function at the time points specified in the Schedule of Activities (Section 6.11), and according to the manual provided.

The 6MWT measures the distance that a subject can walk at his/her pace on measured, flat hard surface in a period of 6 minutes. The 6MWT has been established as the walk test of choice in cardiorespiratory diseases. The change in 6-Minute Walk Distance has been found to be highly predictive of mortality [6]. Also, the Minimal Clinical Important Difference (MCID) has been validated [21].

The 6MWT will be performed based on the ATS recommendations [1] and will be accompanied by the Borg scale for dyspnea. The subject should not have a contraindication to perform the 6MWT at any visit during screening and during the treatment period. Contraindications for performing the 6MWT are provided in Appendix 10.

At Visit 1, the 6MWT distance of 150 meters will have to be met to be eligible to proceed to Visit 2. The subject should not have a contraindication to perform the 6MWT (Appendix 10) or should not have a condition putting the subject at risk of falling during the test (investigator's discretion). The use of a cane is allowed, the use of a stroller is not allowed at all for any condition. The test is performed under the usual conditions for the patient, with or without oxygen as applicable.

At Visit 2, an oxygen titration test will be performed, according to the manual description. The subject should not have a contraindication to perform the 6MWT. For the oxygen titration test, resting SpO_2 should be ≥88% with maximum 6 L O_2/min. During the walk, SpO_2 should be ≥83% with maximum 6 L O_2/minute or ≥88% with 0, 2 or 4 L O_2/minute. A subject will not be eligible if these criteria are not met.

For each following visit, the subject should not have a contraindication to perform the 6MWT. At Visit 3, 6MWT will be performed before IMP intake. For all visits after Visit 3 (Visits 9 and 12, and every 24 weeks thereafter), 6MWT will be performed after IMP intake. The 6MWT will be done under the same oxygen requirements as the final result in the oxygen titration period (Visit 2).

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.5.5. Health Resource Utilization

Health resource utilization parameters will be collected throughout the treatment period,

- Types of hospitalizations, (e.g. intensive care unit stay, stay in a hospital room)
- Changes in type of hospitalization
- Length of hospital stay
- Requiring ventilation
- Days on ventilation
- Healthcare encounters

6.6. SAFETY ASSESSMENTS

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

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.6.1. Adverse Events

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

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

6.6.2. Clinical Laboratory Evaluations

Blood samples will be collected before IMP intake by venipuncture (or indwelling catheter) at the time points indicated in the Schedule of Activities provided in Section 6.11 (see also Section 6.1). In addition, urine samples for the clinical laboratory evaluations will be collected. Subjects do not need to be fasted at the time of sampling, unless specifically indicated. Clinical laboratory evaluations will be performed by the central laboratory.

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

- Hematology: hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), Hb, red blood cell count, white blood cell (WBC) count, WBC differential count (absolute and relative), and platelets.
- Coagulation: activated partial thromboplastin time and prothrombin time, INR.
- Clinical chemistry: random glucose, urea, creatinine, uric acid, sodium, potassium, calcium, chloride, phosphorus, AST, ALT, GGT, total bilirubin, alkaline phosphatase, lactate dehydrogenase, total serum bile acid, albumin, total proteins, triglycerides, cholesterol, high density lipoprotein, low density lipoprotein, amylase, lipase, and creatine kinase (CK) (CK- muscle/brain [CK-MB] to be performed if CK is elevated).
- Urinalysis:
  - Dipstick: pH, glucose, proteins, blood, leucocytes;
  - Microscopic examination of the sediment (cylinders, erythrocytes, leucocytes), if indicated.
- Serology: hepatitis B surface antigen and hepatitis C antibody, and HIV 1 and HIV 2 antibodies only at screening. Positive hepatitis and HIV results should be reported by the investigator as required by local law. To assess eligibility, a positive hepatitis C antibody test should be confirmed by hepatitis C virus (HCV) RNA test.
- FSH test for females at screening to confirm menopause, if applicable.
- Urine pregnancy tests will be performed (only for WOCBP) on a monthly basis at home or at the clinical study center, with one additional test at the clinical study center at Visit 4. At screening, a serum pregnancy test (beta-human chorionic gonadotropin) will be performed. A positive urine pregnancy test needs to be confirmed as soon as possible by a serum pregnancy test (local sample; central sample to be sent as well).

Reference ranges will be supplied by the central laboratory. Clinical laboratory values outside the normal range will be flagged and clinical relevance will be assessed by the investigator. Clinically significant laboratory test abnormalities as judged by the investigator should be recorded as AEs. More frequent sampling as well as additional tests may be performed as deemed necessary by the investigator to follow up and resolve any safety concerns. In some circumstances, local laboratory results are allowed to be used (e.g. positive urine pregnancy test, abnormal liver function tests) for diagnosis of decision, but a central sample should also be collected and analyzed.

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

6.6.3. Physical Examination

Physical examinations (including weight) will be conducted by a physician, trained physician's assistant, or nurse practitioner (as acceptable according to local regulations) before IMP intake at visits specified in the Schedule of Activities in Section 6.11 (see also Section 6.1). At screening, height will be measured as well. The person conducting the physical examinations will document this in the subject's medical records. Clinically significant abnormal findings should be recorded as AEs.

6.6.4. Vital Signs

Vital signs (heart rate, respiratory rate, SBP and DBP, and body temperature) will be recorded before IMP intake in a standardized manner (i.e. after the subject has rested in a supine position for 5 minutes) at visits specified in the Schedule of Activities in Section 6.11 (see also Section 6.1). Vital sign parameter normal ranges are presented in Appendix 8. Clinically significant abnormal values should be recorded as AEs.

6.6.5. Electrocardiogram

At the time points specified in the Schedule of Activities (see Section 6.11 and also Section 6.1), an ECG will be recorded. Triplicate ECGs will be performed at Visit 1 and at Visits 3 and 4 (before and 2-3 hours after IMP intake). At all other time points, a single ECG will be performed before IMP intake (or irrespective of IMP intake at the ETD [if applicable] and EoST/EoSA visits). In addition, a single ECG will also be performed between 2 to 3 hours after IMP intake at Visits 5, 7, and 10. Central reading will be performed for all ECGs at all time points. The ECG must be taken after subjects rested for at least 5 minutes in the supine position. Triplicate ECGs will be taken within preferably 6 minutes, with an approximate 2-minute interval between ECGs. Each ECG will be interpreted by the investigator for clinical significance at the moment of the measurement. In case of abnormal findings, even if not clinically significant, a repeat ECG will be performed as soon as possible after the original abnormal recording within the same visit (if possible) and interpreted by the investigator. If the abnormal recording is discovered after the visit, the recording should be confirmed as soon as possible.

For Visit 3, triplicate abnormal QTcF >450 msec (as described in exclusion criterion 8) predose readings (and confirmatory repeat as soon as possible after the abnormal recording within the same visit if possible) need to be transmitted immediately to the central reader for review before IMP intake by the subject. The result of the review will be transmitted to the investigator and preferably the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available). The decision to dose the subject will be taken by the investigator, after consultation with the CRO medical monitor (as per study contact list) or sponsor's study physician (if the former is not available). In case a timely response from the central reader is not available, the investigator will decide whether to dose the subject or not. If the QTcF at Visit 3 predose is reported during the visit as normal, but the overread by the cardiologist reports a QTcF >450 ms, then the recording should be confirmed as soon as possible and the investigator needs to justify the continuation of IMP documenting this in the source and continue to monitor the patient.

At Visit 3 (after IMP intake) and Visit 4 (before and after IMP intake), abnormal triplicate ECGs and their confirmatory repeat reading will be transmitted to the central reader for expedited review. Refer to Section 4.5.4 for details on abnormal ECG readings.

For other time points with abnormal ECG reading, the investigator should alert the central reader. In that case, the ECG will be reviewed as soon as possible on the same day. The conclusion/evaluation of the central cardiologist reader will overrule the reading of the ECG device.

At other time points with normal ECG reading, the standard review times will be adhered to.

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 ECG needs to be taken before the venipuncture and at least 30 minutes after the failed attempt.

ECG parameters to be recorded include the following: heart rate, PR interval, QRS interval, uncorrected QT interval, QTc, morphology, and rhythm. QTcF will be considered as normal if ≤450 ms. A prolongation of QTcF to >500 ms or an increase from baseline of >60 ms will be considered a threshold of concern and the subject should be discontinued (for details, refer to Section 4.5.4). Normal ranges for ECG are provided in Appendix 8.

ECG abnormalities will be interpreted by the investigator for clinical significance. Clinically significant abnormal values should be recorded as AEs.

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.7. PHARMACOKINETIC ASSESSMENTS

PK assessments will include concentration analysis of GLPG1690, pirfenidone and nintedanib.

Plasma concentrations of GLPG1690, pirfenidone or nintedanib will be measured using a validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method and will be performed by the bioanalytical laboratory in charge of these analyses (ARDENA Biochemical Laboratory).

To be able to investigate the potential interactions between GLPG1690 and pirfenidone or nintedanib, the following samples will be collected to measure levels of GLPG1690 and pirfenidone or nintedanib (also see Table 1, and Schedule of Activities in Section 6.11). For subjects taking neither pirfenidone nor nintedanib, the samples need to be collected in relation to the specified IMP intake.

- At Visit 1 (screening), for patients on nintedanib, the time of morning nintedanib intake will be verified by the investigator. Blood samples will be taken between 2-4 hours; and 5-10 hours after the morning intake of nintedanib.
- At Visits 3, 9, and 12, samples will be collected before IMP and pirfenidone or nintedanib morning intake. At these visits, the subject needs to take pirfenidone or nintedanib (as applicable) at the clinical study center.
- For subjects taking nintedanib at screening and randomization, until they stop taking nintedanib:
  - At Visit 4, 5, 6, 7, 8, 10, and 11, samples will be collected 2-6 hours after the morning nintedanib intake and before IMP intake. At these visits, the subject needs to take nintedanib (as applicable) as per his or her regular routine, and record the

time of intake on the diary card. In addition, at Visits 7 and 10, samples will be collected 2-3 hours after IMP intake.

- After Week 52 (Visit 12), samples will be collected 2-6 hours after the morning nintedanib intake and before IMP intake with a 12-week interval (until EoST/EoSA). At these visits, the subject needs to take nintedanib as per their regular routine, and record the time of intake on the diary card.

– For subjects not taking nintedanib at screening and randomization and those stopping nintedanib during the study:
  - At Visits 7 and 10, samples will be collected after the pirfenidone or nintedanib morning intake and before IMP intake. At these visits, the subject needs to take pirfenidone or nintedanib (as applicable) as per his or her regular routine.
    In addition, samples will be collected 2 to 3 hours after IMP intake during these two visits.
  - After Week 52 (Visit 12), samples will be collected after the pirfenidone or nintedanib morning intake if applicable, but before IMP intake, with a 24-week interval (until EoST/EoSA). At these visits, the subject needs to take pirfenidone or nintedanib (as applicable) as per their regular routine.
– At the ETD (if applicable) and EoST/EoSA visits, samples will be collected irrespective of IMP, pirfenidone, or nintedanib intake.

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

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

Table 1 PK samples to be collected per subjects' Standard of Care treatment

Subjects' Standard of Care	Visits	PK Sampling
Subjects on nintedanib at screening and randomization until they stop taking nintedanib	Visit 1	1 sample 2 to 4 h, and 1 sample 5-10 h after the morning intake of nintedanib
	Visits 3, 9,and 12	before nintedanib intake
	Visits 4, 5, 6, 7, 8, 10, and 11	2-6 h after nintedanib intake but before IMP intake
	Visits 7 and 10	2-3 h after IMP intake
	every 12 weeks after Week 52 (Visit 12)	2-6 h after nintedanib intake but before IMP intake
	ETD, EoST, or EoSA Visit	irrespective of nintedanib or IMP intake time
All other subjects	Visits 3, 9,and 12	before nintedanib, pirfenidone or IMP intake
	Visits 7 and 10	after nintedanib or pirfenidone intake (if applicable) but before IMP intake
	Visits 7 and 10	2-3 h after IMP intake
	every 24 weeks after Week 52 (Visit 12)	after nintedanib or pirfenidone intake (if applicable) but before IMP intake
	ETD, EoST, or EoSA Visit	irrespective of nintedanib or pirfenidone (if applicable) or IMP intake time

Note that subjects can change Standard of Care treatment during the study and the applicable PK sampling schedule should be followed

6.8. PHARMACODYNAMIC ASSESSMENTS

Target engagement will be measured by determination of LPA species (LPA C18:2) in plasma. Other LPA species might be analyzed if deemed appropriate.

Blood samples for the target engagement biomarker (PD) assessments will be collected at Visit 1 and before IMP intake at Visits 3, 7, 9, 10, and 12, and every 24 weeks thereafter until EoST/EoSA, as specified in the Schedule of Activities in Section 6.11 (see also Section 6.1). At Visits 7 and 10, blood samples for the target engagement biomarker (PD) assessments will also be collected after IMP intake. At the ETD (if applicable) and EoST/EoSA visits, samples will be collected irrespective of IMP intake.

An additional blood sample will be collected at the FU visit from a subset of subjects who completed an EoST visit (i.e. those subjects discontinuing IMP at EoST). The applicable subset of subjects will be determined at the time depending on the date of randomization to take the duration of LPA blood sample stability into account from baseline collection till FU visit. The purpose of these samples is to gather additional data on the LPA C18:2 levels and as needed to establish an LPA time course after the last dose of IMP.

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

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.9. OTHER ASSESSMENTS

6.9.1. Disease-specific Biomarker Evaluations

Disease and/or drug-related biomarkers including, but not limited to, extracellular matrix synthesis and turnover (i.e. neo-epitopes), inflammatory cells, alveolar epithelial and oxidative stress markers, and analytes may be assessed in plasma and/or serum, if deemed appropriate.

In addition, other analytes such as metabolites or endogenous biomarkers might be assessed in plasma and/or serum, if deemed appropriate.

Blood samples for potential serum disease-specific biomarker analysis and for potential plasma disease-specific biomarker analysis will be collected at Visit 1 and before IMP intake at Visits 3, 7, 9, and 12, and every 24 weeks thereafter until EoST/EoSA, as specified in the Schedule of Activities in Section 6.11 (see also Section 6.1). At the ETD (if applicable) and EoST/EoSA visits, samples will be collected irrespective of IMP intake.

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

If subjects, due to any COVID-19-related reason, cannot attend visits on site, see Section 6.1.1.

6.9.2. Genotype Evaluation

Genetic studies showed that rare mutations are associated with IPF. An optional blood sample will be collected by venipuncture if compliant with local IEC/IRB requirements and if the subject has provided consent and signed the genetic sample ICF. The sample can be collected during the indicated visit in the Schedule of Activities in Section 6.11 (see also Section 6.1), or during any following visit in case it was not collected. Genomic analysis of IPF genomic risk factors will be performed at a later stage on stored samples if deemed appropriate.

Samples will be obtained by venipuncture (or indwelling catheter) preferably in the forearm.

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

6.10. SAMPLE MANAGEMENT

After the end of the study (i.e. the last visit of the last subject), 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/IEC-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 protocol 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 protocol (e.g. biomarker analysis) and the data obtained may in no case be used for the purpose of identification or re-identification of subjects.

6.11. SCHEDULE OF ACTIVITIES

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

6.11.1. Schedule of Activities: Screening and First 52 Weeks of Study Treatment

For subjects who, for any COVID-19-related reason, cannot perform study procedures, extended visit windows, the possibility to conduct phone/televisits and home (or other remote location) visits, and alternative assessment procedures are detailed in Section 6.1.1.

EVENT	**SCREENING PERIOD**		**FIRST 52 WEEKS OF STUDY TREATMENT**										
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ETD**
Study days (D) or weeks (W) ± visit window	**D-28 to D-1**		**D1**	**W2 (D15) ±2 d**	**W4 (D29) ±2 d**	**W8 (D57) ±4 d**	**W12 (D85) ±4 d**	**W18 (D127) ±4 d**	**W26 (D183) ±4 d**	**W34 (D237) ±4 d**	**W42 (D295) ±4 d**	**W52 (D365) ±4 d**	
Informed consent (Section 6.3)	✓[1]												
FSH (if applicable) and serology (Section 6.6.2)	✓												
HRCT sent for central review (Section 6.3)	✓												
LB (if available) sent for central review (Section 6.3)	✓												
Inclusion/exclusion criteria (Sections 4.5.1, 4.5.2, 6.3)	✓	✓											
Demographics (Section 6.3)	✓												
Medical history (Section 6.3)	✓												

EVENT	SCREENING PERIOD		FIRST 52 WEEKS OF STUDY TREATMENT										
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ETD**
Study days (D) or weeks (W) ± visit window	**D-28 to D-1**		**D1**	**W2 (D15) ±2 d**	**W4 (D29) ±2 d**	**W8 (D57) ±4 d**	**W12 (D85) ±4 d**	**W18 (D127) ±4 d**	**W26 (D183) ±4 d**	**W34 (D237) ±4 d**	**W42 (D295) ±4 d**	**W52 (D365) ±4 d**	
Alcohol consumption and smoking habits (Section 6.3)	✓		✓						✓			✓	✓
Physical examination (Section 6.6.3)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Vital signs (Section 6.6.4)	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
ECG triplicate recording (Section 6.6.5)	✓												
ECG triplicate recording before IMP intake (Section 6.6.5)			✓	✓									
ECG triplicate recording 2-3 hours after IMP intake (Section 6.6.5)			✓	✓									
ECG single recording before IMP intake (Section 6.6.5)					✓	✓	✓	✓	✓	✓	✓	✓	
ECG single recording 2-3 hours after IMP intake (Section 6.6.5)					✓		✓			✓			
ECG single recording (Section 6.6.5)													✓

EVENT	SCREENING PERIOD		FIRST 52 WEEKS OF STUDY TREATMENT										
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ETD**
Study days (D) or weeks (W) ± visit window	**D-28 to D-1**		**D1**	**W2 (D15) ±2 d**	**W4 (D29) ±2 d**	**W8 (D57) ±4 d**	**W12 (D85) ±4 d**	**W18 (D127) ±4 d**	**W26 (D183) ±4 d**	**W34 (D237) ±4 d**	**W42 (D295) ±4 d**	**W52 (D365) ±4 d**	
Pregnancy test (serum) (Sections 6.6.2 and 4.5.3.1.1)	✓												
Pregnancy test (urine) (Sections 6.6.2 and 4.5.3.1.1)			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical laboratory tests (Section 6.6.2) [2]	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Spirometry (Section 6.5.1.1)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DLCO (Section 6.5.1.2)	✓		✓						✓			✓	
Oxygen saturation test (Section 6.5.1.3)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
6MWT and Borg scale (Section 6.5.4)	✓	✓	✓						✓			✓	
Randomization by IWRS (Section 4.6.1)			✓										
Dispense IMP (Section 5.2)			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Collect IMP/perform drug accountability (Section 5.5)				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

EVENT	SCREENING PERIOD		FIRST 52 WEEKS OF STUDY TREATMENT										
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ETD**
Study days (D) or weeks (W) ± visit window	**D-28 to D-1**		**D1**	**W2 (D15) ±2 d**	**W4 (D29) ±2 d**	**W8 (D57) ±4 d**	**W12 (D85) ±4 d**	**W18 (D127) ±4 d**	**W26 (D183) ±4 d**	**W34 (D237) ±4 d**	**W42 (D295) ±4 d**	**W52 (D365) ±4 d**	
Diary card dispensing and collection (as applicable per visit) for drug accountability (Sections 5.5 and 6.4)			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EQ-5D and SGRQ (ePRO) (Section 6.5.3)	✓		✓						✓			✓	✓
LCQ and K-BILD questionnaire (ePRO) (Section 6.5.3)	✓		✓						✓			✓	✓
VAS Cough and Urge to Cough (Section 6.5.3)	✓		✓						✓			✓	✓
Intake P and N at clinical study center (Section 5.2)			✓						✓			✓	
PK blood samples 2-4 hours after N morning intake (Section 6.7) [3]	✓												
PK blood samples 5-10 hours after N morning intake (Section 6.7) [3]	✓												
PK blood samples before IMP and P or N intake (Section 6.7)			✓						✓			✓	

EVENT	SCREENING PERIOD		FIRST 52 WEEKS OF STUDY TREATMENT										
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ETD**
Study days (D) or weeks (W) ± visit window	**D-28 to D-1**		**D1**	**W2 (D15) ±2 d**	**W4 (D29) ±2 d**	**W8 (D57) ±4 d**	**W12 (D85) ±4 d**	**W18 (D127) ±4 d**	**W26 (D183) ±4 d**	**W34 (D237) ±4 d**	**W42 (D295) ±4 d**	**W52 (D365) ±4 d**	
PK blood samples before IMP, but after P or N intake (Section 6.7) [4]							✓			✓			
PK blood samples 2-6 hours after N intake and before IMP (Section 6.7) [3]				✓	✓	✓	✓	✓		✓	✓		
PK blood samples 2 to 3 hours after IMP intake (Section 6.7)							✓			✓			
PK blood samples (Section 6.7)													✓
Target biomarker/PD blood samples (LPA) (Section 6.8)	✓												✓
Target biomarker/PD blood samples (LPA) before IMP intake (Section 6.8)			✓				✓		✓	✓		✓	
Target biomarker/PD blood samples 2-3 hours after IMP intake (Section 6.8)							✓			✓			
Disease-specific biomarker blood samples (Section 6.9.1)	✓												✓

EVENT	SCREENING PERIOD		FIRST 52 WEEKS OF STUDY TREATMENT										
Study visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**ETD**
Study days (D) or weeks (W) ± visit window	**D-28 to D-1**		**D1**	**W2 (D15) ±2 d**	**W4 (D29) ±2 d**	**W8 (D57) ±4 d**	**W12 (D85) ±4 d**	**W18 (D127) ±4 d**	**W26 (D183) ±4 d**	**W34 (D237) ±4 d**	**W42 (D295) ±4 d**	**W52 (D365) ±4 d**	
Disease-specific biomarker blood samples before IMP intake (Section 6.9.1)			✓				✓		✓			✓	
Blood sample for genotype analysis (Section 6.9.2)				✓									
Vital status (Section 4.5.4)												✓	
Study medication intake (Section 5.2)			Throughout the treatment period										
AE assessment (Section 6.6.1)	Throughout the study												
Concomitant medication assessment and documentation (Section 4.5.3.2)	Throughout the study												

[1] The ICF signature is the start of the 28-day screening period and will be used as the date of Visit 1
[2] CK-MB to be measured if CK is elevated
[3] Only for subjects taking nintedanib at screening and randomization, until they stop taking nintedanib
[4] For subjects not taking nintedanib at screening and randomization and those stopping nintedanib during the study
d=days, ePRO=electronical patient-reported outcome, ETD=early treatment discontinuation, N=nintedanib, P=pirfenidone.
The preferred sequence of study assessments is described in Section 6.1.

6.11.2. Schedule of Activities: After 52 Weeks of Study Treatment

For subjects who, for any COVID-19-related reason, cannot perform study procedures, the possibility to conduct phone/televisits and home (or other remote location) visits, and alternative assessment procedures are detailed in Section 6.1.1.

EVENT	**AFTER 52 WEEKS OF STUDY TREATMENT**				
Study visit	**Every 12 weeks up to EoST/EoSA ±7 d**	**Every 24 weeks up to EoST/EoSA[3] ±7 d**	**ETD**	**EoST/EoSA***	**FU***
Study weeks ± visit window					**(4 weeks after EoST/EoSA) ±7 d**
Alcohol consumption and smoking habits (Section 6.3)	✓		✓	✓	
Physical examination (Section 6.6.3)	✓		✓	✓	
Vital signs (Section 6.6.4)	✓		✓	✓	
ECG single recording (Section 6.6.5)			✓	✓	
ECG single recording before IMP intake (Section 6.6.5)	✓				
Pregnancy test (urine) (Sections 6.6.2 and 4.5.3.1.1)	✓		✓	✓	
Clinical laboratory tests (Section 6.6.2)	✓		✓	✓	
Spirometry (Section 6.5.1.1)	✓		✓	✓	
DLCO (Section 6.5.1.2)		✓			
Oxygen saturation test (Section 6.5.1.3)	✓		✓	✓	
6MWT and Borg scale (Section 6.5.4)		✓			
Dispense IMP (Section 5.2)	✓				
Collect IMP/perform drug accountability (Section 5.5)	✓		✓	✓	

EVENT	AFTER 52 WEEKS OF STUDY TREATMENT				
Study visit	**Every 12 weeks up to EoST/EoSA**	**Every 24 weeks up to EoST/EoSA[3]**	**ETD**	**EoST/EoSA***	**FU***
Study weeks ± visit window	**±7 d**	**±7 d**			**(4 weeks after EoST/EoSA) ±7 d**
Diary card dispensing and collection (as applicable per visit) for drug accountability (Sections 5.5 and 6.4)	✓		✓	✓	
EQ-5D and SGRQ (ePRO) (Section 6.5.3)		✓	✓	✓	
LCQ and K-BILD questionnaire (ePRO) (Section 6.5.3)		✓	✓	✓	
VAS Cough and Urge to Cough (Section 6.5.3)		✓	✓	✓	
PK blood samples (Section 6.7)			✓	✓	
PK blood samples before IMP, but 2-6 hours after N intake (Section 6.7)[1]	✓				
PK blood samples before IMP, but after P or N intake (Section 6.7) [2]		✓			
Target biomarker/PD blood samples (LPA) (Section 6.8)			✓	✓	✓
Target biomarker/PD blood samples (LPA) before IMP intake (Section 6.8)		✓			
Disease-specific biomarker blood samples (Section 6.9.1)			✓	✓	
Disease-specific biomarker blood samples (Section 6.9.1) before IMP intake		✓			
Vital status (Section 4.5.4)				✓	✓
Study medication intake (Section 5.2)	Throughout the treatment period				
AE assessment (Section 6.6.1)	Throughout the study				

EVENT	AFTER 52 WEEKS OF STUDY TREATMENT				
Study visit	**Every 12 weeks up to EoST/EoSA**	**Every 24 weeks up to EoST/EoSA[3]**	**ETD**	**EoST/EoSA***	**FU***
Study weeks ± visit window	**±7 d**	**±7 d**			**(4 weeks after EoST/EoSA) ±7 d**
Concomitant medication assessment and documentation (Section 4.5.3.2)	Throughout the study				

d=days, ETD=early treatment discontinuation (i.e. before the EoST/EoSA visit), ePRO=electronical patient-reported outcome, EoST/EoSA=end of study treatment/end of study assessments, N=nintedanib, P=pirfenidone.

The preferred sequence of study assessments is described in Section 6.1.

[1] Only for subjects taking nintedanib at screening and randomization, until they stop taking nintedanib

[2] For subjects not taking nintedanib at screening and randomization and those stopping nintedanib during the study

[3] At these visits, the assessments from both the Every 12 weeks up to EoST/EoSA and the Every 24 weeks up to EoST/EoSA columns are included

* This can be a scheduled clinical study center visit or a phone call.

7. STATISTICAL METHODS

All statistical methods shall be detailed in the statistical analysis plan (SAP) that will be finalized prior to the database lock and unblinding. Data collected in this clinical study will be documented using summary tables, figures, and subject data listings, as appropriate.

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

Any deviations from the statistical analyses planned in this protocol will be documented in the SAP.

A protocol deviations plan will include the definition of major and minor protocol deviations and the identification of major protocol deviations which will be excluded from the per-protocol analysis. The assessments of protocol deviations (major/minor) will be done prior to database lock and unblinding.

7.1. DETERMINATION OF SAMPLE SIZE

To account for multiple testing due to multiple doses, a Bonferroni approach [9] will be applied to the alpha level with higher priority given to the high-dose group. The primary endpoint will be tested at a 4% level when comparing GLPG1690 600 mg to placebo and a 1% level for GLPG1690 200 mg group versus placebo.

Denoting Δ_{600} and Δ_{200}, the true treatment differences of the two GLPG1690 treatment groups with placebo, and assuming a common standard deviation (SD) on the 52 weeks decline in FVC of 275 mL, the probabilities that 0, 1, or 2 treatment comparisons with placebo are statistically significant, are presented in Table 2. The family-wise error rate is protected at 5% using the Bonferroni procedure. The so-called disjuncture power of the study is the probability that 1 or 2 hypotheses are rejected and is displayed in the right-most column of Table 2.

A meta-analysis of the seven placebo-controlled studies that have been conducted on nintedanib, pirfenidone, and pamrevlumab has revealed that the treatment effect at 52 weeks is estimated to be approximately 119 mL in a treatment-naïve population, the effect observed with nintedanib alone is similar (112 mL) [32]. Little information is available on the expected treatment effect of GLPG1690 in addition to pirfenidone or nintedanib. Table 2 gives an overview of the power for different scenarios for the overall treatment effect in the population of subjects on standard of care (either pirfenidone or nintedanib, or neither pirfenidone nor nintedanib).

Since the linear-slope model on the annual rate of decline in FVC accounts for missing data, the number of subjects randomized and the number of subjects included in the model is expected to be equal. An equal number of 250 subjects will be randomized to each treatment group to have at least 80% power to show a significant effect assuming the 600-mg group has a treatment effect of at least 80 mL in the overall population of treatment-naïve and patients on standard of care.

Table 2: Probability of Statistical Significance of 0, 1, or 2 Treatment Comparisons With Placebo

mL		0 Successful	1 Successful	2 Successful	Power
Δ_{600}=80	Δ_{200}=80	6.8%	23.4%	69.9%	93.2%
Δ_{600}=80	Δ_{200}=60	10.1%	46.9%	43.0%	89.9%
Δ_{600}=80	Δ_{200}=20	11.5%	84.4%	4.1%	88.5%
Δ_{600}=80	Δ_{200}=0	11.2%	88.0%	0.7%	88.8%
Δ_{600}=90	Δ_{200}=60	5.1%	51.1%	43.8%	94.9%
Δ_{600}=50	Δ_{200}=50	43.9%	34.3%	21.9%	56.1%
Δ_{600}=50	Δ_{200}=0	50.6%	48.9%	0.5%	49.4%
Δ_{600}=0	Δ_{200}=0	95.2%	4.5%	0.3%	4.8%

Based on a review of the blinded data, the SD may be reassessed.

7.2. POPULATIONS FOR ANALYSES

7.2.1. All Screened Subjects

All enrolled subjects who underwent screening assessments to check whether or not they are eligible to participate in the clinical study.

7.2.2. All Randomized Subjects

All enrolled subjects who underwent all screening assessments and were found to be eligible for the clinical study and who were randomized into the clinical study.

7.2.3. Full Analysis Set

All randomized subjects who received at least one dose of IMP.

7.2.4. Per-Protocol Set

All randomized subjects who received at least one dose of IMP, excluding subjects/data points with a major protocol violation which impacts the efficacy results.

7.2.5. Pharmacokinetic Analysis Set

All randomized subjects who received at least one dose of IMP and for whom evaluable PK data were available (e.g. excluding all protocol violations/deviations or AEs that may have an impact on the PK analysis).

7.2.6. Biomarker/PD Analysis Set

All randomized subjects who received at least one dose of IMP and have at least one post-baseline assessment with biomarkers/PD data, excluding subjects with protocol deviations that may have an impact on biomarker/PD analysis.

7.3. STATISTICAL ANALYSES

7.3.1. General Statistical Considerations

Summary tabulations will be presented and will display the number of observations, mean, SD 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 two-sided 5% level.

7.3.2. Interim Analysis

An IDMC will review the data of this study and the identically designed GLPG1690-CL-304 study on a regular basis. An interim analysis to assess futility will be performed when a reasonable number of subjects have completed 52 weeks of treatment (e.g. at least 25% subjects from the two studies combined). No interim analysis for early termination for efficacy will be performed and therefore no adjustment of the alpha level is necessary. Details on the IDMC are given in Section 8.1 and in the charter.

7.3.3. Analyses of Demographics and Baseline Characteristics

Summary statistics (mean, median, SD, minimum, maximum, number of available observations) will be provided by treatment group for continuous demographic variables (e.g. age, height, weight). Categorical endpoints will be presented by number and percentage of subjects per category. Results will be presented for the full analysis set (FAS).

Subject disposition (including reasons for early discontinuation), protocol deviations, demographics, baseline characteristics, medical history, prior and concomitant therapies, and use of IMP will be analyzed descriptively by treatment group and/or listed. No statistical inference will be performed.

Medical history terms will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and presented by the number of subjects with at least one event by System Organ Class, Preferred Term, and treatment group.

Prior and concomitant medications will be coded by the sponsor according to the World Health Organization (WHO) drug code and the Anatomical Therapeutic Classification (ATC) class code and tabulated by the number and percentages of subjects with a medication per ATC code and treatment group.

7.3.4. Analyses of Efficacy Parameters

Multiplicity Adjustment

To account for the multiple testing due to two doses being compared to placebo, a Bonferroni approach [9] will be used with higher priority given to the high-dose group. The primary endpoint will be tested at a 4% level when comparing GLPG1690 600 mg to placebo and a 1% level for GLPG1690 200 mg group versus placebo.

With respect to the multiplicity adjustment for the key secondary endpoints an additional approach was requested by the United States Food and Drug Administration (FDA) compared to EU countries. For countries outside US and EU, the EU approach will be applied.

For FDA:

FDA requested a multiplicity adjustment for the key secondary endpoints within each study. A closed-testing hierarchical approach will therefore be used for each dose group separately. The key secondary endpoints will be ordered as listed in Section 4.3.2.1 and they will be tested at a 4% level when comparing GLPG1690 600 mg to placebo and a 1% level for GLPG1690 200 mg group versus placebo. In this approach, the first key secondary endpoint in a dose group will only be tested if the primary endpoint for that dose group showed significance. The next one will only be tested if the previous one showed significance. Figure 3 details the testing order within each of the identically-designed studies.

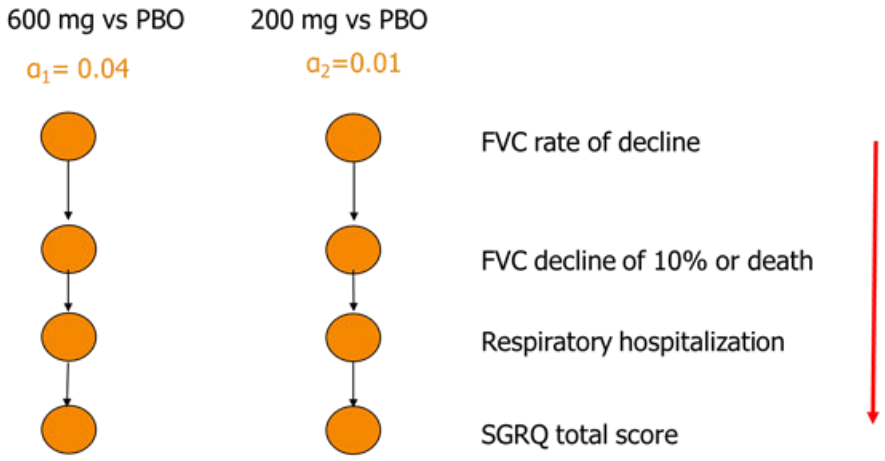

Figure 3 Multiplicity adjustment within study for FDA approach

For Countries outside the US:

To increase the probability to detect a potential treatment effect on the key secondary endpoints, some of which are rare but clinically important events, they will be analyzed using the pooled data from the two studies (GLPG1690-CL-303 and GLPG1690-CL-304). The confirmatory testing on these secondary endpoints will be done only if the primary endpoints in both studies show significance and a step-down closed-testing multiplicity adjustment will be applied, as shown in Figure 4. A key secondary endpoint in the pooled analysis will only be tested for a dose if the higher order endpoint also showed significant for that dose. Details of the pooled analyses will be provided in the pooled-analysis SAP.

Results for the key secondary endpoints for each individual study will enable the evaluation of consistency of the results between the studies. An overview of the multiplicity adjustment for the primary and key secondary endpoints is provided in Figure 4.

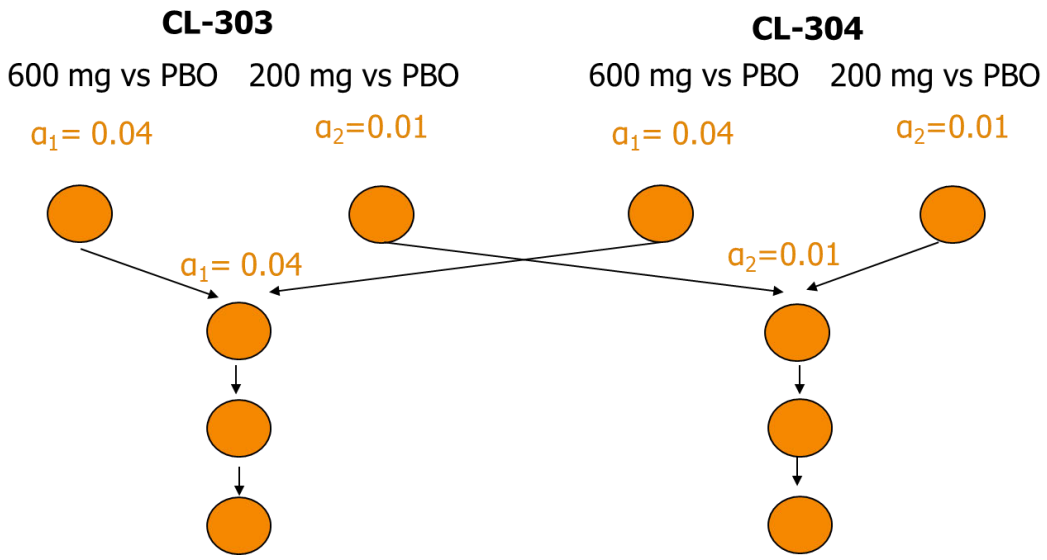

Figure 4 Multiplicity adjustment within study approach

No interim analysis for early termination for efficacy will be performed and therefore, no adjustment of the alpha level is needed.

Efficacy Analyses

All efficacy parameters (e.g. spirometry, clinical endpoints, quality of life) will be analyzed descriptively and FVC and %FVC will also be analyzed for a series of subgroups (such as baseline characteristics, background treatment, and stratum). The primary analyses will be conducted on the FAS population.

Spirometry Data

- The primary time point will be Week 52. Analyses at the end of the study are secondary.
- The rate of decline in FVC will be analyzed using a random coefficient regression model (linear slope model) including sex, age, height, and stratification factor as covariates and a random intercept and slope. The treatment effect is determined by using estimated average slopes for each treatment group on the basis of the treatment*time interaction term from the above mixed model, with time as a continuous factor and treatment as a categorical factor. All available FVC values from baseline to Week 52 will primarily be used, including those from the ETD visit for subjects who discontinued early and do not complete their study visits up to Week 52.
- As a secondary analysis, the same model will be fit using all data until the end of the study.
- The proportion of subjects who have an absolute decline ≥10% in %FVC at least once during the study or who die will be analyzed using logistic regression including sex, age, height, and stratum as factors using data up to Week 52.
- In addition, the same will be presented using all data up to the end of the study. A time-to-event analysis may also be used to analyze the composite endpoint of %FVC decline and mortality up to the end of the study.
- The %FVC change from baseline will be analyzed using a similar random coefficient regression model (linear slope model) as FVC in mL.
- Other spirometry endpoints will be summarized descriptively, similar to FVC.

Sensitivity analyses including multiple imputation methods and a per-protocol analysis will be performed to assess the impact of missing data, noncompliance, and protocol violations on the primary efficacy analyses. Additional exploratory analyses and graphical presentations may be performed when deemed useful to better understand the data. Details will be described in the SAP.

Time-to-event Data (Including Hospitalization, First Acute IPF Exacerbation, Mortality, and [Qualifying for] Lung Transplant), Using All Data up to the End of the Study

- Time-to-event endpoints will be graphically presented by Kaplan-Meier estimates. In addition, a Cox proportional-hazards model with terms for age, sex, height, and stratum will be used to analyze the hazard ratios for each dose compared to placebo.

Other Efficacy Endpoints

- A mixed-effects model with treatment, time (as a categorical factor), treatment*time, and baseline total score as factors in the model will be applied to the change from baseline in SGRQ total score.
- The change from baseline in DLCO will be analyzed similarly as change in SGRQ.
- EQ-5D, SGRQ total score and domains, LCQ total score and domains, K-BILD total score and domains, and VAS Cough and Urge to Cough will be presented using descriptive statistics by treatment group 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 by treatment group.
- The proportion of SGRQ responders and the proportion of subjects with hospitalization will be analyzed using a logistic regression model similarly as described above and presented by treatment group.
- The actual values and changes from baseline of 6MWT and Borg scale will be presented descriptively for each time point by treatment group.
- A summary by treatment group will be provided for each health resource utilization parameter: the number (%) of subjects with a hospitalization per type, the number (%) of subjects requiring ventilation, and the number (%) of subjects by type of healthcare encounter.
  For those with a hospitalization, the number (%) of subjects with a change in hospital type and the number (%) of patients with a referral by type will be presented.
  Length of hospital stay and duration on ventilation will also be summarized for those in hospital and on ventilation, respectively.

More details will be described in the SAP.

7.3.5. Analyses of Safety Data

The safety analysis will be conducted on the FAS population.

All safety data collected on or after the first dose of IMP intake up to the last follow-up visit after the last dose will be summarized by treatment group. Clinical safety will be addressed by assessing AEs, laboratory assessments, physical examinations, vital signs, and 12-lead ECGs. More details will be described in the SAP.

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. Results will be presented for the 52-week and for the complete study period, separately.

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 TEAEs:

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

Selected tables will also be presented including all AEs which occurred after the start of IMP intake up to the end of the study.

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

7.3.5.3. Clinical Laboratory Evaluations

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

7.3.5.4. Physical Examinations

Physical examination results will be summarized by body system and treatment group.

7.3.5.5. Vital Signs

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

7.3.5.6. Electrocardiogram

ECG will be analyzed descriptively. Changes from baseline (Day 1 before IMP intake) and shifts according to normal ranges will be presented as well. Frequency analyses of subjects with a QTc or QTcF prolongation of >500 ms and with a QTc or QTcF increase >60 ms change from baseline will be presented as well. Analyses will be done per treatment group.

7.3.6. Pharmacokinetics and Pharmacodynamics

The PK analysis will be conducted on the PK analysis set.

Observed GLPG1690 plasma concentrations will be analyzed using a population PK approach to characterize the PK profile of GLPG1690, and determine the covariates which might influence the PK in this population.

The existing GLPG1690 population PK/PKPD model for LPA C18:2 will be updated with these data. Visual exploratory assessment of the relationship between exposure and response (as PD, biomarkers endpoint, safety, and efficacy) will be performed to evaluate putative correlations. The time course of the FVC and the effects of treatment thereupon will be described using a longitudinal model of disease progression, if applicable.

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

The aforementioned analyses will be described in detail in a separate pharmacometric analysis plan and will be reported separately from the clinical study report.

7.3.7. Exploratory Analyses

The exploratory analyses will be performed if deemed appropriate.

All biomarker endpoints will be analyzed descriptively and will also be analyzed for a series of subgroups (such as baseline characteristics and background treatment).

Actual values, changes from baseline, and percent changes from baseline of all disease-specific biomarkers at all time points will be generated.

Actual values, changes from baseline, and percentage reduction from baseline of LPA C18:2 species peak area ratio (and other species, if deemed appropriate) at all time points will be generated. Over-time plots will be generated.

Additional exploratory analyses and graphical presentations may be performed when deemed useful to better understand the data.

8. DATA MONITORING

To protect the safety and integrity of the study data, an IDMC and CEAC will be implemented. Charters will be put in place with all committees.

8.1. INDEPENDENT DATA MONITORING COMMITTEE

In parallel to assessing potential safety risks on a regular basis, the IDMC will also examine the effect of treatment with GLPG1690 on lung function as assessed by rate of decline in FVC using the data from the identically designed studies GLPG1690-CL-303 and GLPG1690-CL-304. An interim analysis to assess futility will therefore be performed when a reasonable number of subjects have completed 52 weeks of treatment (e.g. at least 25% subjects from the two studies combined) (see Section 7.3.2). The results will be reviewed by the IDMC,

who will then make a recommendation to the sponsor on the progress of the study. Specific details on timing of the analyses, futility criteria, and statistical analyses to be performed will be detailed in the IDMC charter or SAP, as appropriate. To allow collection of as much safety information as possible on a potential down-titration dose, a futile dose will continue if the other dose does not show futility. Either the study will continue as planned or both doses (and the study) will be terminated. Sponsor personnel will remain blinded and the study will not be stopped for a beneficial effect.

8.2. CLINICAL ENDPOINT ADJUDICATION COMMITTEE

The CEAC will consist of an independent group of experts that reviews and adjudicates clinical endpoints (see Section 6.5.2), as defined by the charter, in a blinded manner. This objective data adjudication will reduce variation in outcome reporting and observer bias.

8.3. ADDITIONAL OPTIONAL INDEPENDENT REVIEW OF SAFETY DATA

Selected safety data associated with liver function test (with or without symptoms) may be subjected to review in blinded manner by an independent expert panel as needed.

9. SAFETY REPORTING

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

9.1.1. Adverse Events

An AE is any untoward medical occurrence, new or worsening of any preexisting condition, in a clinical study subject administered a medicinal product and which does not necessarily has 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 protocol-specified procedures, worsening of the targeted disease, overdose, drug abuse/misuse reports, or occupational exposure. Preexisting conditions that increase in severity or change in nature during or as a consequence of participation in the clinical study will also be considered AEs.

9.1.2. Serious Adverse Events

An SAE is defined as an AE that results in 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 (Edition 6, 28-Jun-2019) and any relevant updates/addenda.

9.1.4. Adverse Events of Special Interest

Not applicable.

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

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

The following liver enzyme elevations should be reported as SAEs:

- AST or ALT ≥8xULN
- AST or ALT ≥3xULN with signs of severe liver damage (i.e. with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia [>5%], and/or total bilirubin ≥1.5xULN or INR >1.5)

9.1.6. Special Situations

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

The investigator must report the following special situations within 24 hours of becoming aware, as indicated on Page 2 under "Emergency Contact Information":

- Pregnancy
- Abuse or misuse of study drug
    - Abuse of study drug is defined as the persistent or sporadic, intentional excessive use of the study drug, which is accompanied by harmful physical or psychological effects.
    - Misuse of study drug is defined as a situation where the study drug is intentionally and inappropriately used not in accordance with the product information.

- Drug interaction or food interaction with study drug
  - A drug interaction with study drug is defined as a situation in which there is evidence or a suspicion that the study drug interacts with another drug when both are administered together.
  - A food interaction with study drug is defined as a situation in which there is evidence or a suspicion that the study drug interacts with a food when taken together.
- Medication error with study drug
  - A medication error with study drug is defined as an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient.
- Occupational exposure to study drug
  - Occupational exposure with study drug is defined as an exposure to the study drug as a result of one's professional or non-professional occupation.
- Overdose with study drug
  - An overdose of study drug is defined as the administration of a quantity of the study drug given per administration or cumulatively, which is the intake of more than three tablets/day.
- Product complaint or quality defect of study drug
  - Product complaint or quality defect of study drug is defined as complaints or defects of the study drug arising from potential deviations in the manufacture, packaging, or distribution of the study drug.

9.2. ASSESSMENT OF ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

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

9.2.1. Assessment of Causality

The investigator is responsible for assessing the causal relationship to IMP 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**:
  - Relationship in time to IMP intake is improbable. Related to other etiologies such as concomitant medications or subject's clinical state.
- **Unlikely**:
  - Relationship in time to IMP intake is improbable (but not impossible). Concomitant disease or other drugs provide plausible explanations.
- **Possible**:
  - Relationship in time to IMP intake is reasonable. Event or laboratory test abnormality, could also be explained by disease or other drugs. Information on IMP withdrawal may be lacking or unclear.

- **Probable**:
– Relationship in time to IMP intake is reasonable. Unlikely to be attributed to concurrent disease or other drugs. Response to withdrawal is clinically reasonable and rechallenge not required.
- **Certain**:
– Relationship in time to IMP intake is plausible. Cannot be explained by concomitant disease or other drugs. Response to withdrawal is plausible (pharmacologically, pathologically). Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactory, if ethical and necessary.

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

9.2.2. Assessment of Severity

The severity of AEs should be graded using the CTCAE version 5.0. If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening) or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 3.

Table 3: Grading of AE Severity

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

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

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

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

9.2.3. Outcome

Each AE must be rated by choosing among:
– Recovered/resolved;
– Recovered/resolved with sequelae;
– Recovering/resolving;
– Not recovered/not resolved;

- Fatal;
- Unknown.

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

9.3.1. Adverse Events

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

In case an AE is ongoing at the time of the last follow-up visit, the investigator needs to follow 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 or unknown outcome AEs will not be followed up.

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

9.3.2. Serious Adverse Events

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

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

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

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

Copies of additional laboratory tests, consultation reports, post-mortem reports, hospital case reports, autopsy reports, and other documents should be sent when requested and available.

Only subject identifiers (subject number) should appear on the copies, and all names and initials should be blackened and rendered illegible. Follow-up reports relative to the subject's subsequent course must be submitted until the event has subsided or, in case of permanent impairment, until the condition stabilizes.

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

9.3.3. Pregnancy

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

All pregnancies should be followed up until delivery or pregnancy interruption. The investigator will contact the subject/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 abnormal newborn outcomes are considered SAEs and must be reported using the SAE form.

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

In case a special situation is not associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form.

In case a special situation is associated with an AE, the special situation should be reported within 24 hours by using the Special Situations form and the associated AE should be reported as specified in Section 9.3.1.

In case a special situation is associated with an SAE, the special situation should be reported within 24 hours by using the SAE form (and not the Special Situations form) and the associated SAE should be reported as specified in Section 9.3.2.

9.4. SPONSOR REPORTING REQUIREMENTS

Depending on relevant local legislation or regulations, including the applicable United States Federal Drug Administration Code of Federal Regulations, the European Union 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 (Edition 6, 28-Jun-2019) and any relevant updates/addenda or relevant local label, as applicable.

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

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

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

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

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

10.1. SPONSOR'S RESPONSIBILITIES

10.1.1. Regulatory Approval / Notification

Prior to clinical study start, this protocol 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 clinical study center 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 clinical study 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 a clinical study center include, but are not limited to:

- Successful completion of the clinical study at the clinical study center.
- The overall required number of subjects for the clinical study has been recruited.
- Failure of the investigator to comply with the protocol, 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, clinical study center, 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 protocol, 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 protocol 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). At 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 1 year, or 6 months for pediatric studies, after the end of the clinical study.

10.1.6. Publication

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

The investigator shall not be authorized to submit the results of this clinical study and any data for 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

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

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

10.2.2. Source Data and Data Capture

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

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

It is recommended that the author of an entry in the source documents should be identifiable. Following ICH-GCP Guidelines, direct access to source documents must be granted for the purpose of verifying that the data recorded in 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 ICF.

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

10.2.4. Participation Cards

If the subjects are not under 24-hour supervision of the investigator or 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

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 clinical study center and no copy will be made.

The subject will receive all information as required by the EU General Data Protection Regulation, including the identity of the controller, the clinical research purposes, the fair processing of his/her data, and all his/her data subject rights. All details are listed in the ICF.

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 protocol, ICF, any other written information given to subjects, and subject recruitment materials has been obtained from the IEC/IRB. This approval document must be dated and clearly identify the clinical study and the related clinical study documents being approved, including the subject compensation programs, if applicable.

During the course of the clinical study, at least the following documents will be 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)

- Protocol amendments
- Informed consent revision(s)

Protocol 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/or write, oral consent in the presence of at least one impartial witness who was also included when the affected person was being informed may be given. The witness may not be anyone working at the trial site nor a member of the investigating team. The orally given consent shall be documented in writing, dated and signed by the witness.

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 ICF 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.

Additional consent needs to be obtained from the subjects to allow collection of the optional blood sample for genotype evaluation if approved by the local IEC/IRB (see also Section 6.9.2).

A pregnant partner, who agrees that information will be gathered about her pregnancy, will sign a specific ICF to participate in the data collection.

Data about the health of the baby will be collected if the parents agree with the data collection and sign the specific ICF.

10.5. DATA QUALITY CONTROL / ASSURANCE

10.5.1. Monitoring

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

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

To ensure subjects' safety, protocol compliance, and the quality of the data at all times, remote data monitoring may be utilized for this study. If allowed by local regulations, study monitors may perform remote source data verification, as per monitoring plan, to confirm that source data entered into the eCRFs by authorized site personnel are accurate and complete.

10.5.2. Audit and Inspection

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

REFERENCES

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APPENDICES

APPENDIX 1: HRCT/BIOPSY CENTRAL REVIEW CRITERIA

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

The diagnostic criteria for idiopathic pulmonary fibrosis, published as the Fleischner Society White Paper [15], will be used to determine eligibility of the subject for the trial.

In case a historical LB 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.

After central review of the HRCT, subjects will be considered eligible if:

- The majority of the central readers evaluate the HRCT as showing a typical and/or probable IPF pattern, unless a historical LB, if available, is not in accordance with this diagnosis (i.e. is most consistent with an alternative diagnosis)
- The majority of the central readers evaluate the HRCT as showing a pattern indetermined for IPF and/or a pattern most consistent with non-IPF diagnosis, but an available historical LB, shows a definite UIP-IPF pattern.

The LB will not be evaluated if both 2 initial central reviewers evaluate the HRCT as showing the following pattern:

- Typical UIP-IPF pattern + Typical UIP-IPF pattern
- IPF pattern most consistent with Non-IPF diagnosis + IPF pattern most consistent with Non-IPF diagnosis

	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: DLCO

At Visit 1 (screening visit 1), DLCO must meet the following criteria [16]:

- DLCO corrected for Hb ≥30% predicted of normal

For predicted normal values, different clinical study centers may use different prediction formulas, based on the method used to measure DLCO. In any case, the method used must be in compliance with the ATS/ERS task force guideline on DLCO measurements [16] and the prediction formula appropriate for that method.

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

DLCO corrected for Hb:

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

Hb is expressed in g/dL.

APPENDIX 3: KNOWN CYP2C8 SUBSTRATES

Excluded and prohibited medication:

Amiodarone
Buprenorphine
Amodiaquine; Chloroquine
Repaglinide
Rosiglitazone, pioglitazone
Verapamil
Zopiclone

This list is intended as a guidance for the investigator.

APPENDIX 4: KNOWN STRONG CYP3A4 INDUCERS AND POTENT P-GP INDUCERS

Excluded and prohibited medication:

Barbiturates
Carbamazepine
Glucocorticoids: prednisone or equivalent > 10 mg/day
Modafinil
Oxcarbazepine
Phenytoin
Pioglitazone
Rifabutin
Rifamp(ic)in
St. John's Wort

This list is intended as a guidance for the investigator.

APPENDIX 5: KNOWN STRONG CYP3A4 INHIBITORS

Excluded and prohibited medication:

Clarithromycin
Itraconazole
Ketoconazole
Nefazodone
Telithromycin
Voriconazole

This list is intended as a guidance for the investigator.

APPENDIX 6: KNOWN POTENT P-GP INHIBITORS

Excluded and prohibited medication:

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

This list is intended as a guidance for the investigator.

APPENDIX 7: MEDICATION KNOWN TO PROLONG QT INTERVAL

Medication to be used with caution:

Disopyramide
Dofetilide
Flecainide
Ibutilide
Quinidine
Sotalol

This list is intended as a guidance for the investigator.

APPENDIX 8: NORMAL RANGES FOR VITAL SIGNS, PULSE OXIMETRY, AND ECG PARAMETERS

NORMAL RANGES FOR VITAL SIGNS

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

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

bpm = beats per minute

NORMAL RANGES FOR PULSE OXIMETRY

Normal arterial oxygen saturation (SpO_2) level: 95% to 100% in ambient air (sea level)

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	50≤ HR ≤100

APPENDIX 9: ALGORITHM FOR ELEVATED LIVER FUNCTION TESTS

<table>
<tr><td></td><td colspan="5">AST or ALT increase to</td></tr>
<tr><td></td><td>≥1.5x to 3xULN</td><td>≥3x to 5xULN</td><td>≥5x to 8xULN</td><td>≥3xULN with signs of severe liver damage[1]</td><td>≥8xULN</td></tr>
<tr><td>Visit 1 (screening)</td><td>Not eligible</td><td>Not eligible</td><td>Not eligible</td><td>Not eligible</td><td>Not eligible</td></tr>
<tr><td>Visit 3 (randomization)</td><td>Discontinue IMP[2]</td><td>Discontinue IMP[2]</td><td>Discontinue IMP[2]</td><td>Discontinue IMP[2]</td><td>Discontinue IMP[2]</td></tr>
<tr><td rowspan="2">From Visit 4 onwards</td><td>Continue as planned</td><td rowspan="2">Down-titration: reduce or interrupt IMP for at least 2 weeks
Close observation[2]</td><td rowspan="2">Down-titration: interrupt IMP for at least 2 weeks
Close observation[2]</td><td>Discontinue IMP[2]</td><td>Discontinue IMP[2]</td></tr>
<tr><td colspan="3">↙ ↘</td></tr>
<tr><td>After at least 2 weeks</td><td colspan="2">AST and ALT <3xULN</td><td colspan="3">AST or ALT ≥3xULN</td></tr>
<tr><td></td><td colspan="2">Re-escalate to next dose level for at least 2 weeks
Weekly LFTs for the first 2 weeks (biweekly for the following weeks, or more frequently at investigator’s discretion)
Repeat re-escalation to next higher dose level every 2 weeks (or longer at investigator’s discretion) if AST and ALT <3xULN</td><td colspan="3">Discontinue IMP
Report SAE and complete liver event page for any of abnormalities listed below[3]:
- AST/ALT increase ≥8xULN
- AST/ALT increase ≥3xULN with signs of severe liver damage[1]</td></tr>
</table>

[1] Signs of severe liver damage:

– total bilirubin ≥1.5xULN OR international normalized ratio >1.5, and/or

– symptoms: appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash and/or eosinophilia (>5%)

[2] Close observation recommendations:

– Monitor two to three times per week all of the following parameters: ALT, AST, alkaline phosphatase, total bilirubin, eosinophils, INR. If local regulations allow, home visits can be performed if subjects cannot come to the clinical study center.

– Frequency of retesting can be reduced to once a week or less if abnormalities stabilize or the IMP has been discontinued; however, monitoring might still be needed more frequently taking into consideration the standard of care and/or changes to this.

– Based upon Investigator’s discretion gastroenterology or hepatology consultations, additional serology testing, imaging and pathology assessments may be required

– Re-query history of symptoms, prior and concurrent diseases, concomitant medication and non-prescription medicines, herbal, dietary supplements, alcohol use, recreational drug use, special diets.

– Rule out all of the following: acute viral hepatitis, auto-immune hepatitis, alcoholic hepatitis, non-alcoholic fatty hepatitis, hypoxic/ischemic hepatitis, biliary tract disease, and cholestasis.
Re-query exposure to environmental chemical agents

[3] The following steps (as defined in Section 4.5.4 should be followed:

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

APPENDIX 10: CONTRAINDICATIONS FOR 6MWT

Absolute contraindications:

- Unstable angina during the previous month [1]
- Myocardial infarction during the previous month [1]
- SpO_2 measured by pulse oximetry <88% after 10 minutes of rest of breathing room air or at baseline oxygen flow rate [6]

Relative contraindications [1]:

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

APPENDIX 11: DEFINITION OF ACUTE IPF EXACERBATION

Definition and diagnostic criteria are defined as follows [4]:

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

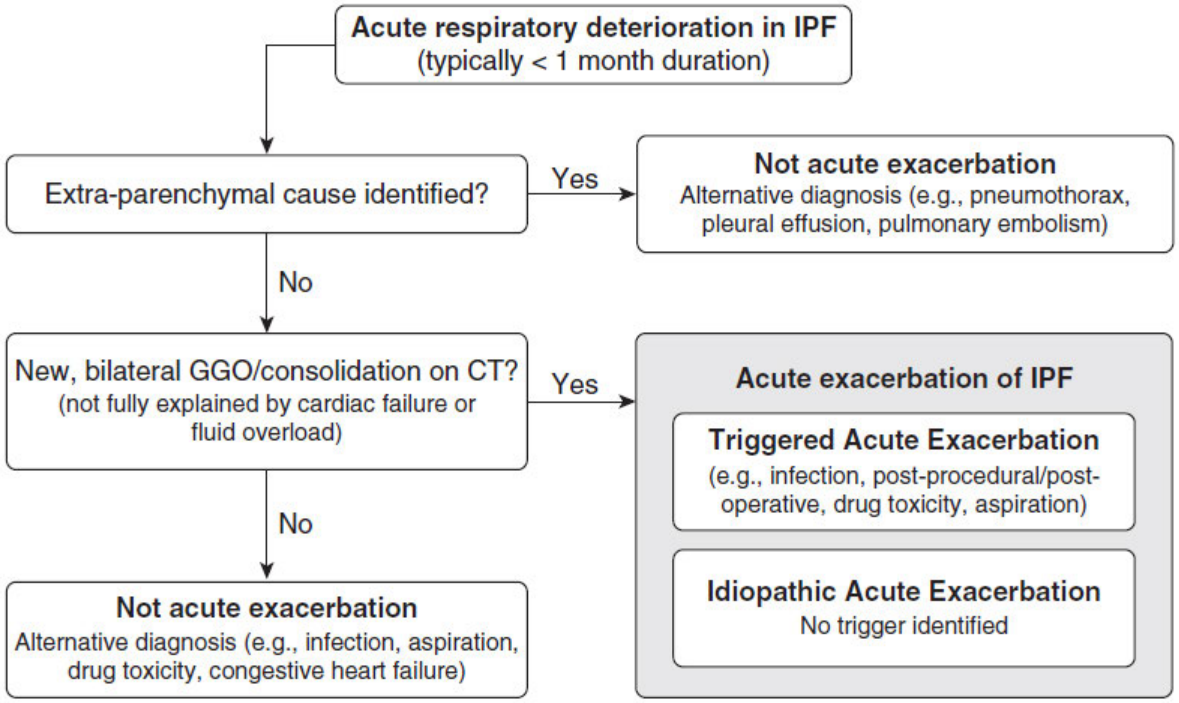

Figure 3. Proposed conceptual framework for evaluation of acute respiratory deterioration in idiopathic pulmonary fibrosis (IPF). Acute respiratory deterioration of IPF (defined as "typically <1 month in duration") can be categorized as extraparenchymal (e.g., pulmonary embolism, pneumothorax, pleural 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.

SIGNATURE PAGE – SPONSOR

Study Title: A Phase 3, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of GLPG1690 in addition to local standard of care for minimum 52 weeks 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 3, randomized, double-blind, parallel-group, placebo-controlled multicenter study to evaluate the efficacy and safety of two doses of GLPG1690 in addition to local standard of care for minimum 52 weeks 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 glpg1690-cl-303-protocol 11171

Approval	[redacted]4 GMT+0000

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