CLINICAL STUDY PROTOCOL

STUDY TITLE:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Pamrevlumab in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
PROTOCOL NUMBER:	FGCL-3019-091
PHASE:	Phase 3
STUDY SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
KEY SPONSOR CONTACT(S):	
IND NUMBER:	
STUDY DRUG:	Pamrevlumab (FG-3019)
Original Protocol:	17 December 2018
Amendment 1.0:	17 March 2019
Amendment 2.0:	25 September 2019
Amendment 3.0:	19 February 2020
Amendment 4.0:	26 May 2020
Amendment 5.0:	04 November 2020
Amendment 6.0:	31 October 2022

INVESTIGATOR SIGNATURE PAGE

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INVESTIGATOR STATEMENT

I have read the protocol, including all appendices, and the current Investigator's Brochure (IB), and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will conduct this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision copies of the protocol and access to all information provided by FibroGen, Inc. I will discuss this material with them to ensure that they are fully informed about the drugs and the study.

I will conduct the trial in accordance with the guidelines of Good Clinical Practice (GCP) including the archiving of essential documents, the Declaration of Helsinki, and any applicable local health authority, and Institutional Review Board (IRB)/Independent Ethics Committee (IEC) requirements.

Investigator Name (Printed)		Institution
Signature		Date

Please return a copy of this signature page to FibroGen (or designee). Please retain the original for your study files.

CONFIRMATION OF PROTOCOL APPROVAL

Original Protocol Date: 17 December 2018

Amendment 1.0: 17 March 2019

Amendment 2.0: 25 September 2019

Amendment 3.0: 19 February 2020

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This protocol is approved by FibroGen.

	*See appended final page for 21 CFR part 11 compliant approval	Date

AMENDMENT 6.0: KEY CHANGES

The protocol has been edited for clarity, consistency, and quality of content (typos, grammatical errors, flow, etc.). A redline version documenting all changes from the previous version of this document is available upon request.

Description of Key Change	Rationale for Change	Section(s) Affected
Removed outdated IB language.	To remove outdated IB language.	Section 2.5, Section 2.6.3
Updated and clarified primary, secondary and exploratory endpoints.	Endpoints clarified and updated to optimize for clinical relevance.	Synopsis, Section 3.2, Section 8.3.4
Added when early termination visits should occur.	To clarify timing of early termination visits.	Section 3.3.1, Section 4.4, Appendix 1. Appendix 6
Clarified required procedures/assessments at early termination visits.	To further clarify the required procedures/assessments for early termination visits.	Section 4.4
Added Open-label Extension language.	To further clarified the infusion rate and post-infusion observation periods for Open-label Extension visits.	Table 1
Added recommendation for COVID-19 vaccine and study drug administration.	To clarify the recommendation for COVID-19 vaccine and study drug administration timing.	Section 5.1.6
Clarified requirement for medications and supplies for Home Health Care.	To further clarify the requirement for medication and supplies for suspected hypersensitivity/analytical events for Home Health Care	Section 5.1.7
Added preliminary non-clinical study results	Preliminary results of rabbit embryo-fetal development study available to inform contraception recommendations.	Section 5.2.3
Added language regarding pregnancy testing	To align with the CTFG v1.1. embryo-fetal risk contraception recommendations regarding pregnancy testing in the event of delayed menstruation.	Section 5.2.3, Appendix 1, Appendix 2
Added PK, HAHA and, HAHA-NA, CTGF and tryptase scheduled blood draws and at the time of any suspected hypersensitivity/anaphylactic reactions.	To meet Regulatory recommendations for immunogenicity testing.	Section 6.2.4.2, Appendix 2
Clarified the order of Patient Reported Outcome questionnaire administration.	To further clarify the order in which Patient Report Outcome	Section 6.2.6

	questionnaires should be administered.	
Added visit window for EX Day 1	To clarify the visit window for EX Day 1	Appendix 6
Clarified main study procedures and AEs.	To clarify main study procedures and AEs versus OLE.	Appendix 6
In addition to the changes listed above, minor editorial changes were made throughout the document to improve consistency and clarity.	To correct typographical errors, and to improve consistency and clarity.	Throughout the document

1. PROTOCOL SYNOPSIS

PROTOCOL SYNOPSIS	
Study Title:	A Phase 3, Randomized, Double-Blind, Placebo-Controlled Efficacy and Safety Study of Pamrevlumab in Subjects with Idiopathic Pulmonary Fibrosis (IPF)
Protocol Number:	FGCL-3019-091
Investigational Product:	Pamrevlumab (FG-3019)
Study Phase:	Phase 3
Indication:	Idiopathic Pulmonary Fibrosis
Number of Subjects Planned:	Approximately 340
Number of Sites Planned:	Approximately 120
OBJECTIVES	
The overall objective of this trial is to evaluate the efficacy and safety of pamrevlumab as compared to placebo in subjects with idiopathic pulmonary fibrosis.	

ENDPOINTS

Primary Endpoint:

- Change in FVC (L) from baseline at Week 48

Secondary Endpoints:

- Time to disease progression, defined as absolute FVCpp decline of ≥10% or death, whichever occurs first
- Change in Quantitative Lung Fibrosis (QLF) volume from baseline at Week 48
- Time to any component of the clinical composite endpoint, whichever occurs first: acute IPF exacerbation, respiratory hospitalization, or death
- Time to first acute IPF exacerbation during study
- Time to all-cause mortality during study
- Time to first respiratory hospitalization during study

Exploratory Endpoints:

- Time to composite of: respiratory hospitalization, absolute FVCpp decline ≥10%, or death, whichever occurs first
- Change in absolute FVCpp from baseline at Week 48
- Change in relative FVCpp from baseline at Week 48
- Change in St. George's Respiratory Questionnaire (SGRQ) score from baseline at Week 48
- Change in University of California San Diego – Shortness of Breath Questionnaire (UCSD-SOBQ) score from baseline at Week 48
- Change in Leicester Cough Questionnaire (LCQ) from baseline at Week 48
- Exploratory biomarkers

Safety Assessments:

Adverse events (including serious adverse events), clinical laboratory parameters, vital signs, immunogenicity (Human Anti-Human Antibody [HAHA] formation), and hypersensitivity/anaphylactic reactions.

STUDY DESIGN

This is a Phase 3, randomized, double-blind, placebo-controlled, multi-center trial to evaluate the efficacy and safety of pamrevlumab in subjects with idiopathic pulmonary fibrosis (IPF).

Subjects who are not being treated with approved IPF therapies (i.e., nintedanib or pirfenidone) may be eligible for screening. Examples of reasons subjects may not be treated with approved IPF therapies include but are not limited to:

- Intolerant or not responsive to approved IPF therapies
- Ineligible to receive these therapies
- Subject voluntarily declines to receive approved IPF therapies after being fully informed of the potential benefits/risks

NOTE: No subject should discontinue an approved IPF therapy for the purpose of enrolling in this study.

Approximately 340 eligible subjects will be randomized at a 1:1 ratio to Arm A or Arm B, respectively:

- Arm A: Pamrevlumab, 30 mg/kg IV, Day 1 and every 3 weeks thereafter
- Arm B: Matching placebo IV, Day 1 and every 3 weeks thereafter

Randomization will be stratified by:

- Prior treatment with an approved IPF therapy (Yes/No)
- GAP stage (I, II, III) derived from GAP score obtained at screening (See Appendix 5).

  NOTE: For calculation of the GAP score: Use the Best-Test Review (BTR) assessment provided by the spirometry vendor over-reader of the screening value (see Section 6.2.5 and Appendix 5).

The intent of this study is to evaluate the efficacy and safety profile of pamrevlumab as monotherapy in subjects with IPF who were either treated with an approved therapy in the past, but discontinued that therapy (possible reasons for discontinuation of approved therapy could include, but are not limited to, intolerance or disease progression); or who decided voluntarily to forego such treatment, after being fully informed of the potential benefits/risks.

During the treatment period, co-administration of an approved IPF therapy (i.e., pirfenidone or nintedanib) is acceptable if clinically indicated in the Investigator's opinion, provided that the Investigator assesses the potential risks/benefits of combining approved IPF therapies with blinded study treatment.

Subjects who complete the Week 48 visit of the main study (regardless of the number of study drug infusions received) will be eligible to participate in the optional, open-label, extension (OLE) phase of the study that offers continuing access to pamrevlumab regardless of randomization assignment in the main study. Details of this OLE phase are outlined in Appendix 6.

Subjects who discontinue study treatment for any reason should be encouraged to remain in the study and be followed for all study visits and assessments.

The following assessments will be assessed centrally:

- Pulmonary function tests (PFTs)
- High-resolution computed tomography (HRCT)
- Acute IPF exacerbations and respiratory hospitalizations

STUDY PERIODS

The study consists of the following study periods:

- **Main (double blind, placebo-controlled) phase:**
  - Screening period: Up to 6 weeks
  - Treatment period: 48 weeks
- **Optional, open label extension (OLE) phase of pamrevlumab:**
  - Access to pamrevlumab will be available until the last subject completes 48 weeks of treatment in the OLE phase, or pamrevlumab is commercially available for the indication of IPF, or the Sponsor decides to end the OLE phase, whichever occurs first.
- **Follow-up period/final safety assessments:**
  - 28 days after last dose
  - 60 days after last dose: follow-up phone call, for a final safety assessment

SUBJECT ELIGIBILITY CRITERIA

Inclusion Criteria:

1. Age 40 to 85 years, inclusive, at screening initiation.
2. Diagnosis of IPF as defined by ATS/ERS/JRS/ALAT guidelines (Raghu 2018).
3. IPF diagnosis within the past 7 years, with onset defined as the date of the first recorded diagnosis of IPF by HRCT and/or surgical biopsy (SLB) or other appropriate tissue sample (e.g., cryobiopsy) in the medical history.
4. Interstitial pulmonary fibrosis defined by HRCT scan at screening, with evidence of ≥10% to <50% parenchymal fibrosis (reticulation) and <25% honeycombing, within the whole lung. **NOTE**: this requires confirmation by an Independent Radiology Imaging Review Group, prior to randomization. If a recent HRCT scan (within 3 months prior to screening) is available, it can be utilized for screening purposes, provided it is submitted and evaluated by the Independent Radiology Imaging Review Group, is adhering to the imaging parameters detailed in the Imaging Core Manual (ICM), and is using the same accredited scanner as the on-study HRCT scans.
5. FVCpp value >45% and <95% at screening **and** Day 1 (prior to randomization).
6. Diffusing capacity of the lungs for carbon monoxide (DLCO) percent predicted and corrected by Hb value ≥25% and ≤90% at screening (determined locally). If a DLCO is available within 3 months prior to screening, it can be utilized for screening purposes.
7. Both FVC and DLCO testing must be representative of the IPF underlying disease (i.e., have been obtained in absence of an acute respiratory event [e.g., lung infection, cold]

or other events that are known to affect PFT testing results (e.g., broken rib, chest pain, other).

8. Not currently receiving treatment for IPF with an approved therapy (i.e., pirfenidone or nintedanib) for any reason, including prior intolerance or lack of response to an approved IPF therapy, or choice to forego treatment with an approved IPF therapy after a full discussion with the Investigator regarding risks/benefits of such therapy. **NOTE**: no subject should discontinue approved therapy for the purpose of enrolling in this study.
9. Male subjects with partners of childbearing potential and female subjects of childbearing potential (including those <1 year postmenopausal) must use a highly effective method of contraception per Clinical Trial Facilitation Group (CTFG) recommendation (see protocol section 5.2.3 for details) during the conduct of the study, and for 3 months after the last dose of study drug. Women not of childbearing potential are defined as:
    a. Post-menopausal women (defined as at least 12 months with no menses without an alternative medical cause); in women < 45 years of age, a high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy; OR
    b. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; OR
    c. Have a congenital or acquired condition that prevents childbearing.
10. Able to understand and sign a written informed consent form.

Exclusion Criteria:

1. Previous exposure to pamrevlumab.
2. Evidence of significant obstructive lung disease by any of the following criteria: (1) forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio <0.70, or (2) extent of emphysema greater than the extent of fibrosis on HRCT. **NOTE**: this requires confirmation by an Independent Radiology Imaging Review Group, prior to randomization.
3. Female subjects who are pregnant or nursing.
4. Smoking within 3 months of screening and/or unwilling to avoid smoking throughout the study.
5. Interstitial lung disease (ILD) other than IPF, including but not limited to any of the other types of idiopathic interstitial pneumonias; lung diseases related to exposure to fibrogenic agents or other environmental toxins or drugs; other types of occupational lung diseases; granulomatous lung diseases; pulmonary vascular diseases; systemic diseases, including vasculitis, infectious diseases and connective tissue diseases. In cases of uncertain diagnosis, serological testing and/or review by multi-disciplinary team should be performed to confirm diagnosis of IPF vs. other types of ILD.

6. Sustained improvement in the severity of IPF during the 12 months prior to screening, based on changes in FVC, DLCO, and/or HRCT scans of the chest.
7. History of other types of respiratory diseases, including diseases or disorders of the airways, lung parenchyma, pleural space, mediastinum, diaphragm, or chest wall that, in the opinion of the Investigator, would impact the primary protocol endpoint or otherwise preclude the subject's participation in the study.
8. Medical conditions (e.g., MI/stroke within the past 6 month), or logistical challenges that in the opinion of the Investigator preclude the subject's adequate participation in the study.
9. Poorly controlled chronic heart failure (NYHA Class 3 or above); clinical diagnosis of cor pulmonale requiring specific treatment; or severe pulmonary arterial hypertension requiring specific treatment that, in the opinion of the Investigator, would preclude the subject's participation in the study.
10. Clinically important abnormal laboratory tests (including serum creatinine ≥1.5 x upper limit of normal [ULN], hemoglobin (Hb) <10 g/dL, white blood cells <3,000/mm^3, platelets less than 100,000/mm^3, serum total bilirubin >1.5 x ULN, serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 x ULN, or serum alkaline phosphatase ≥2 x ULN.
11. Ongoing acute IPF exacerbation, or suspicion of such process during screening or randomization, including hospitalization due to acute IPF exacerbation within 4 weeks prior to or during screening.
12. High likelihood of lung transplantation (in the opinion of the Investigator) within 6 months after Day 1.
13. Use of any investigational drugs or unapproved therapies, or participation in a clinical trial with an investigational new drug, within 30 days prior to screening. Or use of approved IPF therapies (i.e., pirfenidone or nintedanib) within 1 week prior to screening.
14. Daily use of PDE-5 inhibitor drugs (e.g., sildenafil, tadalafil) except for treatment of severe pulmonary artery hypertension.
15. Any current malignancy (this does not include localized cancer such as basal or squamous cell carcinoma of skin). Any history of malignancy likely to result in mortality, or requiring significant medical or surgical intervention within the next year.
16. History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies, or to any component of the excipient.
17. Any condition (other than IPF) that is likely to result in the death of the patient within the next year.
18. The Investigator judges that the subject will be unable to fully participate in the study and complete it for any reason, including inability to comply with study procedures and treatment, addiction, or any other relevant medical or psychiatric conditions.

STUDY TREATMENT

Dose and Mode of Administration:

Main Phase (Double-Blind, Placebo-Controlled):

Pamrevlumab or placebo, 30 mg/kg, IV, Day 1 and every 3 weeks thereafter, up to Week 48, for a total of up to 17 infusions.

Optional, Open Label Extension (OLE) Phase of Pamrevlumab:

Pamrevlumab (30 mg/kg) every 3 weeks

Other Important Information:

Other medications and therapies intended to treat IPF, other than approved IPF therapies (pirfenidone or nintedanib), will not be allowed during the study except for some protocol-specified exceptions.

Study drug should not be administered to subjects with a history of allergic or anaphylactic reaction to human, humanized, or chimeric monoclonal antibodies, or to any of the components of the excipient.

STATISTICAL METHODS

Sample Size Calculations:

This study will enroll approximately 340 subjects with a 1:1 randomization ratio to either pamrevlumab or placebo.

A sample size of 340 subjects will have at least 90% power, based on a two-sided alpha level of 0.05 for a two-sample t-test, to detect a treatment difference of 120 mL in the primary efficacy endpoint, change from baseline in FVC (L), assuming a standard deviation of 300 mL.

Statistical Analysis Methods:

The primary efficacy endpoint, change from baseline to Week 48 in FVC (L), will be analyzed using a random coefficient model (RCM) with treatment, visit, visit-by-treatment interaction, randomization stratification, baseline FVC volume, age, sex, height as fixed effects; the intercept and linear slope of visit are random effects.

For the other efficacy endpoints, unless stated otherwise, the RCM model will be used for pulmonary function test variables; the Mixed Model for Repeated Measure (MMRM) model will be used for patient reported outcome questionnaires and other continuous variables; and the Cox regression model will be used in time-to-event variables. The analysis models will include the stratification factors and appropriate baseline factors.

Safety Analyses:

All subjects who received any dose of study treatment will be included in the safety analyses. Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs) will be summarized by treatment arm.

Clinically significant changes from baseline in vital signs and laboratory tests will be identified and summarized by treatment arm. Additionally, hypersensitivity/anaphylactic and immunogenicity reactions will be monitored and assessed.

Safety data collected during the OLE phase will be summarized descriptively.

OPTIONAL BLOOD DRAWS

Optional Pharmacokinetics (PK) and Genomic Analyses:

Two optional sub-studies, one for PK assessment, and one for genomic analyses, will be performed in a subset of subjects at select sites. Such subjects will provide their consent to these optional sub studies prior to their participation in these sub-studies. PK assessments will continue to be optional except in the case of suspected hypersensitivity/anaphylactic reactions (see Section 6.2.4.2.3 for more detail).

This study will be conducted in accordance with the guidelines of Good Clinical Practice (GCP) and the applicable regulatory requirement(s), including the archiving of essential documents.

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2. INTRODUCTION

2.1. Description of Pamrevlumab

Pamrevlumab is a recombinant fully human immunoglobulin G1 (IgG) kappa monoclonal antibody that binds to connective tissue growth factor (CTGF) and is being developed for treatment of diseases in which tissue fibrosis has a major pathogenic role, as hepatitis induced liver fibrosis, idiopathic pulmonary fibrosis, certain fibrotic cancers and Duchenne muscular dystrophy (DMD). Pamrevlumab (MW ~150 kDa) is produced by mammalian Chinese hamster ovary (CHO) fed-batch cell culture system. Pamrevlumab contains 1,326 amino acids and binds with high affinity to domain 2 of CTGF (dissociation constant: Kd=0.1–0.2 nM).

2.2. Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive fatal lung disease of unknown etiology characterized by fibrotic interstitial infiltrates that are consistent with the histopathologic pattern of usual interstitial pneumonia (Gross, 2001, Raghu, 2018). IPF is the most common of seven recognized types of idiopathic interstitial pneumonia (Kim, 2006, Travis, 2013).

The pathogenesis of IPF has not been clearly defined. The long-held view that fibrosis in IPF is triggered by chronic inflammation (alveolitis) has given way to the current belief that IPF is a disorder caused by repetitive epithelial injury (Selman, 2001, Selman, 2006, Wilson, 2009). The recurrent, subclinical epithelial injury superimposed on accelerated epithelial aging leads to aberrant repair of the injured alveolus and deposition of interstitial fibrosis by myofibroblasts (Lederer 2018). According to this hypothesis, alveolar cell injury and activation initiate a dysregulated, exaggerated fibrotic healing process characterized by myofibroblast proliferation and progressive deposition of extracellular matrix (ECM) in genetically susceptible individuals (Agostini, 2006, Gross, 2001, Selman, 2004, Selman, 2006, Willis, 2006). ECM deposition and other pathologic processes in IPF, including epithelial basement membrane disruption, angiogenesis, smooth muscle cell proliferation, infiltration of mononuclear cells, accumulation of loose connective tissue, and cyst formation, eventually remodel the normal lung architecture and impair the lung's ability to perform gas exchange.

Exogenous and endogenous insults to the alveolar epithelium have been proposed as possible stimuli of the fibrotic process in IPF, but conclusive associations have not been established. The most commonly cited exogenous triggers of alveolar injury are exposure to cigarette smoke (Baumgartner, 1997, Flaherty, 2004) and environmental and occupational dusts (Hubbard, 2001, Taskar, 2006), viral infection (Kelly, 2002, Tang, 2003), and gastroesophageal reflux (Raghu, 2006). Alveolar epithelial cell apoptosis and failure of alveolar re-epithelialization (Barbas-Filho, 2001, Li, 2004, Selman, 2001, Selman, 2006), resistance of myofibroblasts to apoptosis (Thannickal, 2006), shortened telomeres, oxidative injury, proteostatic dysregulation and endoplasmic reticulum stress, and mitochondrial dysfunction lead to decreased alveolar epithelial-cell proliferation and secretion of profibrotic mediators (Beeh, 2002, Cantin, 1987, Daniil, 2008, Hunninghake, 2005, Waghray, 2005, Alder 2008, Selman 2014). Additionally, activation of the coagulation cascade (Chambers, 2008, Selman, 2001), and circulating bone marrow-derived fibroblast precursors (fibrocytes) (Andersson-Sjoland, 2008, Hashimoto, 2004) have also been implicated in the pathogenesis of IPF. Genetic factors may play a role, as gene

mutations account for some cases of familial IPF (Lawson, 2006), including mutations in the gene encoding surfactant protein C and telomerase genes that are responsible for telomere length shortening (Armanios, 2007, Loyd, 2008, Tsakiri, 2007).

Transforming growth factor-beta (TGF-β) is considered a key cytokine that is thought to drive the fibrotic process in IPF (Agostini, 2006, Bergeron, 2003). However, many other proteins have been implicated in regulation of the complex process of cellular interactions among activated epithelial cells, myofibroblasts, fibroblasts, macrophages, endothelial cells, and lymphocytes, including connective tissue growth factor (CTGF), platelet-derived growth factor (PDGF), tumor necrosis factor-alpha (TNF-α), endothelin-1, interleukin (IL)-1β, IL-4, IL-10, IL-13, IL-17, osteopontin, matrix metalloproteases, and multiple chemokines (Agostini, 2006, Ask, 2006, Pardo, 2006, Selman, 2004, Selman, 2006, Strieter, 2007, Wilson, 2009). The roles of epithelial-mesenchymal transition (EMT) and circulating fibrocytes and other extrapulmonary fibroblast progenitor cells in expanding the myofibroblast population within the lung have been the subject of active debate (Lama, 2006, Strieter, 2009, Willis, 2006, Kage 2012). Connective tissue growth factor is a central mediator of tissue remodeling and fibrosis and has been reported to be essential for the fibrotic activity of TGF- β (Blom, 2002, Grotendorst, 1997, Wang 2011, Lipson, 2012).

The epidemiology of IPF is not clearly defined. A report of a population-based study of adults with IPF in Olmstead County, Minnesota, from 1997 to 2005, revealed a prevalence of IPF of 27.9 to 63 cases per 100,000, and an incidence of 8.8 to 17.4 cases per 100,000, again depending on the diagnostic criteria (Fernandez Perez, 2010). In the United States, the prevalence of IPF has been reported to range from 10 to 60 cases per 100,000, although in one study, the prevalence was 494 cases per 100,000 in 2011 among adults over the age of 65 years, which was twice as high as the prevalence recorded 10 years earlier (Lederer, 2018). The prevalence of IPF increases with age, and most IPF patients are age 60 or older at the time of diagnosis, although it is unclear whether this reflects increased recognition or a true increase in incidence (Lederer, 2018) The disease is more common in men than in women (Fernandez Perez, 2010). Most patients are current or former smokers. A familial form of IPF may account for as many as 20% of cases of IPF (Loyd, 2008).

Patients with IPF suffer from progressive dyspnea and cough, and most have been symptomatic for several years by the time of their initial presentation. Delayed diagnosis is therefore common. Physical examination often reveals bibasilar inspiratory crackles, but it may be normal. Digital clubbing is observed in about one quarter of IPF patients (King, Jr., 2001). The chest radiograph reveals non-specific bilateral, reticular infiltrates in the periphery of the lower lung zones, often with findings suggestive of pulmonary hypertension. Pulmonary function tests demonstrate reduced lung volumes, proportionate reduction in the pulmonary diffusing capacity, and a normal to increased FEV1/FVC ratio (Martinez, 2006). Arterial hypoxemia, oxyhemoglobin desaturation, and an increased alveolar-arterial oxygen gradient that worsens with exercise are typically observed in patients with IPF (Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS), 2000, King, Jr., 2001). High resolution computed tomography (HRCT) scans display subpleural reticular abnormalities and honeycombing, especially in the lung bases (Kim, 2006). Traction bronchiectasis is a common finding. The presence of extensive ground glass opacities, peribronchial and perivascular predominance of infiltrates, discrete lung cysts, small nodules, air trapping, mosaic attenuation, and consolidation suggest alternative

diagnoses (Misumi, 2006). The sensitivity and specificity of HRCT for the diagnosis of IPF in the hands of expert radiologists approach 90% and 80%, respectively (Kim, 2006, Raghu, 1999).

Acute exacerbations of IPF, defined as an acute, clinically significant respiratory deterioration (acute worsening or development of dyspnea typically <1 mo duration) characterized by evidence of new widespread alveolar abnormality (computed tomography with new bilateral ground-glass opacity and/or consolidation superimposed on a background pattern consistent with usual interstitial pneumonia pattern), not fully explained by cardiac failure or fluid overload (Collard, 2016). These exacerbations are the leading cause of hospitalization and death in patients with IPF (Kondoh, 2010, Daniels 2008, Kim, 2015). The etiology of acute exacerbations of IPF remains uncertain, and its pathobiology may be related to intrinsic biological dysfunction of the lung that makes individuals with IPF more susceptible to external insults than individuals without IPF (Collard, 2016). A meta-analysis of six clinical trials in patients with IPF revealed a weighted average of 4.1 acute exacerbations per 100 patient-years (Atkins, 2014). A less common, rapidly progressive form of IPF, which is common in actively smoking males, has been described (Selman, 2007).

The diagnosis of IPF is suspected when the clinical and radiographic features described above occur in a patient with no known risk factors for interstitial disease and after other types of idiopathic interstitial pneumonias have been excluded. Transbronchial lung biopsy and bronchoalveolar lavage are occasionally performed to rule other causes of lung infiltrates. The diagnosis of IPF is confirmed when HRCT demonstrates definite features of "usual interstitial pneumonia" (UIP) (Subpleural and basal predominant reticular infiltrates; distribution is often heterogeneous, Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis) in the appropriate clinical setting. For patients with newly detected Interstitial lung disease (ILD) of apparently unknown cause who are clinically suspected of having IPF and have an HRCT pattern of UIP, the current recommendation is to not perform Surgical Lung Biopsy (SLB) (strong recommendation). On the other hand, patients with an HRCT pattern of probable UIP, indeterminate, or an alternative diagnosis, SLB is recommended (conditional recommendation) (Raghu, 2018).

The histopathologic pattern of UIP is a dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing), predominant subpleural and/or paraseptal distribution of fibrosis, patchy involvement of lung parenchyma by fibrosis, fibroblast foci, and the absence of features to suggest an alternate diagnosis (Raghu, 2018). These histopathologic features are more commonly found in subpleural regions in the lower lung zones. Interstitial infiltrates of lymphocytes and plasma cells are usually not prominent (Visscher, 2006).

Pirfenidone and nintedanib are approved drugs for the treatment of IPF. In addition to these drugs, IPF patients are usually managed with supportive measures such as symptomatic treatment of cough and dyspnea, supplemental oxygen for hypoxemia, smoking cessation, pulmonary rehabilitation, and prophylaxis and control of respiratory tract infections (Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS), 2000, (Collard, 2004, Walter, 2006, Wuyts, 2009). Corticosteroids and the immunosuppressive drugs cyclophosphamide and azathioprine were commonly prescribed for IPF in the past, but there is no evidence that these drugs improve patient outcomes or alter the natural course of the disease (Collard, 2004, Walter, 2006). Furthermore, IPF subjects taking a combination of prednisone,

azathioprine, and N-acetylcysteine (NAC) in one arm of a three-arm multicenter Phase 3 clinical trial experienced increased risks of hospitalization and death compared with those taking NAC only or placebo only (Raghu, 2012). A multicenter Phase 3 randomized trial of warfarin in patients with progressive IPF was stopped because of increased mortality in subjects taking warfarin compared with those taking placebo (Noth, 2012). Lung transplantation is the only treatment that improves survival (Noth, 2007, Walter, 2006, Lancaster 2019), but most IPF patients are not eligible for transplantation because of their age or comorbid conditions.

In two Phase 3 clinical trials examining the safety and efficacy of pirfenidone in patients with IPF, the mean decline in percent predicted FVC (FVCpp) from baseline to 72 weeks was 12.4% in one group receiving placebo and 9.6% in the other placebo group (Karimi-Shah, B., 2010). As the interstitial fibrosis and architectural distortion advance in IPF, the lung becomes more noncompliant, and the work of breathing and dyspnea increase. Progressive pulmonary hypertension and cor pulmonale often characterize the late course of the disease.

Several retrospective studies suggest that the median survival time from diagnosis is 2–3 years (Raghu, 2011). The 5-year survival rate of patients with IPF is approximately 20% to 40% (Kim, 2006), which is worse than that of all major cancers except cancer of the lung, pancreas, and esophagus (Siegel, 2012). Mortality from IPF was reported to have increased 28% in men and 41% in women between 1992 and 2003 (Olson, 2007). The majority of IPF patients die from complications of the disease, such as respiratory failure, pulmonary hypertension, and pneumonia, or from coronary artery disease (Daniels, 2008, Gross, 2001, Martinez, 2005, Olson, 2007).

2.3. Connective Tissue Growth Factor

Connective tissue growth factor is a 38 kDa secreted matricellular glycoprotein of the cysteine-rich 61/CTGF/nephroblastoma overexpression (CCN) family (Perbal, 2004, Rachfal, 2005) which was recently renamed cellular communication network family (Perbal 2018). It is produced by many cells, including fibroblasts, myofibroblasts, endothelial cells, mesangial cells, and stellate cells.

The name “connective tissue growth factor” implies a mechanism of action akin to that of classical growth factors, which signal through specific cell-surface receptors. However, experimental evidence does not support this concept. Instead, CTGF and the other members of the CCN family have activities associated with matricellular proteins that function in a more subtle modulatory fashion. Matricellular proteins, with prototypical representatives including secreted protein acidic and rich in cysteine (SPARC), osteopontin, and thrombospondins, are a subclass of ECM proteins that modulate cellular functions and signaling pathways through multiple mechanisms depending on cell type and the cellular context (Bornstein, 2002). These proteins are generally expressed at high levels during development and in response to injury; they typically bind to multiple cell-surface receptors, ECM components, growth factors, and cytokines. Connective tissue growth factor fits squarely within this definition (Chen, 2009). The cellular functions that can be modulated by CTGF include secretion and/or organization of ECM, cell proliferation, survival, adhesion, migration and EMT. Modulation of cellular signaling appears to occur through interactions of CTGF with 1) cell surface components such as integrins or the low density lipoprotein receptor-related protein (LRP)-1 (a multifunctional endocytic and signaling receptor), 2) cytokines and cytokine inhibitors, and 3) matrix components such as

heparin sulfate proteoglycans (HSPGs) and fibronectin. Interactions with HSPGs may displace other HSPG-binding proteins such as vascular endothelial growth factor (VEGF) and bone morphogenetic proteins (BMPs). It is believed that binding of cytokines to CTGF may either sequester them in an inactive conformation, or help to present cytokine binding partners to their receptors.

Connective tissue growth factor is a central mediator of tissue remodeling and fibrosis (Lipson, 2012). Connective tissue growth factor is essential for the fibrotic activity of TGF-β (Mori, 1999, Wang, 2011) but it may also act independently of TGF-β. While much has been made of the role of TGF-β in fibrosis, studies of the role of fibronectin in pulmonary fibrosis showed that the activity of TGF-β is dependent on cellular fibronectin to induce myofibroblast differentiation and that cellular fibronectin may have a fundamental role in activation of latent TGF-β (Muro, 2008). Shi-wen and colleagues showed that critical activities of TGF-β in the fibrotic process are dependent on CTGF expression, including EMT and ECM deposition, supporting the idea that CTGF over-expression is critical for activities attributed to TGF-β (Shi-wen, 2006).

Connective tissue growth factor has been shown to be an important mediator of pulmonary fibrosis in a mouse model of bleomycin-induced pulmonary fibrosis (Bonniaud, 2004). Lasky and coworkers observed upregulation of CTGF messenger ribonucleic acid (mRNA) gene expression in a mouse model of bleomycin-induced pulmonary fibrosis, suggesting a possible role of CTGF in the pathogenesis of lung fibrosis (Lasky, 1998).

2.4. Connective Tissue Growth Factor in Idiopathic Pulmonary Fibrosis

Transcripts of genes for TGF-β1 and CTGF were reported to be approximately 7-fold and 4-fold higher, respectively, in transbronchial lung biopsy specimens of patients with IPF compared with normal (Ziesche, 1999). TGF-β is expressed at fibrogenic foci in IPF (Broekelmann, 1991). Increased CTGF gene expression has been described in transbronchial biopsy specimens and in bronchoalveolar lavage fluid in patients with IPF (Allen, 1999, Pan, 2001). Allen and coworkers also reported that CTGF mRNA expression is increased 10-fold in bronchoalveolar lavage fluid in patients with IPF, compared with healthy control subjects (Allen, 1999). Connective tissue growth factor in plasma was reported to be elevated in IPF patients and the abundance correlated with change in FVC (Kono, 2011). These observations suggest that CTGF may have a role in the pathogenesis of IPF.

2.5. Clinical Trial Experience with Pamrevlumab

The clinical trial experience with pamrevlumab is presented in the current Investigator's Brochure (IB).

Overall, pamrevlumab has been well-tolerated. Adverse events (AEs) have been generally mild or moderate in severity and transient in duration. The AEs have been typical of the subjects' underlying medical condition(s) and, in placebo-controlled studies, were equally distributed between the placebo and pamrevlumab treatment groups. Infusions of pamrevlumab have been well tolerated.

Duration of exposure to pamrevlumab by indication is described in the IB.

See the IB for additional information.

2.6. Rationale for Pamrevlumab in Idiopathic Pulmonary Fibrosis

The observations that CTGF is a central mediator in the process of fibrosis suggest a potential role for pamrevlumab in interfering with the activity of CTGF and thereby preventing or reversing fibrotic lung damage in IPF. Connective tissue growth factor is considered a potential target for therapeutic intervention in pulmonary fibrosis (Antoniou, 2007, Ask, 2006, Blom, 2002, Bonniaud, 2004, Grotendorst, 1997).

In a mouse model of radiation-induced pulmonary fibrosis (Bickelhaupt et al, 2017), pamrevlumab at 10 mg/kg or placebo was administered by IP injection 3 times a week for 8 weeks starting before or up to 16 weeks after the irradiation. Pamrevlumab-treated mice demonstrated better survival compared with untreated irradiated mice. Pamrevlumab attenuated lung remodeling, improved pulmonary function, and improved lung density in a schedule dependent manner. Additional observations in gene-expression changes in the lungs also indicated that pamrevlumab can disrupt physiological tissue remodeling after the process has begun. In particular, pamrevlumab appears to disrupt a CTGF autocrine loop in mesenchymal cells like myofibroblasts that reduces their recruitment of leukocytes like macrophages, mast and dendritic cells via chemokine secretion. This disruption results in collapse of the cellular crosstalk that drives tissue remodeling (Sternlicht et al, 2018).

In another study, administration of pamrevlumab to mice with bleomycin-induced pulmonary fibrosis significantly inhibited lung hydroxyproline content, a marker of lung collagen content (FibroGen, 2003, data on file).

These preclinical findings are supported by preliminary efficacy data in the FGCL-3019-049 study, which suggest that treatment of subjects with IPF with pamrevlumab 15 mg/kg and 30 mg/kg IV every 3 weeks is associated with improvement or stability in quantified scores of whole lung fibrosis in approximately 45 percent of subjects at 24 weeks (Raghu, 2012). Changes from baseline in these scores were significantly correlated with changes in FVCpp value (Raghu, 2012).

In 2012, the Food and Drug Administration (FDA) granted Orphan Drug Designation to pamrevlumab for the treatment of IPF. Additionally, results from the Phase 2, randomized, double-blind, placebo-controlled trial of pamrevlumab in IPF (Study 067) has shown a statistically significant difference from placebo for the primary efficacy endpoint of FVCpp change from baseline to week 48 favoring pamrevlumab. Other important efficacy endpoints favoring pamrevlumab include: proportion of subjects with disease progression, time to disease progression, change from baseline in lung fibrosis (QLF, FIB) score to Week 48 measured by quantitative HRCT, patient-reported quality of life measurements using the SGRQ (positive trends) and the UCSD-SOBQ, as well as favorable trend in all-cause mortality.

These results of an open-label Phase 2 study and a randomized placebo-controlled Phase 2 study suggest pamrevlumab slows the progression of IPF as measured by change in FVCpp, quantitative analysis of fibrosis, and time to disease progression or death.

2.6.1. Clinical Studies in IPF

FibroGen has sponsored 5 studies in idiopathic pulmonary fibrosis (IPF), three Phase 1 / 2 studies that are completed, and two Phase 3 studies that are ongoing.

Study FGCL-MC3019-002, was a Phase 1 open-label, dose-escalation study to determine the safety, pharmacokinetics, immunogenicity, and bioactivity of escalating single doses of pamrevlumab in subjects with IPF; a total of 21 subjects were treated with pamrevlumab.

Study FGCL-3019-049, was an open-label, Phase 2 study to evaluate the safety, tolerability, and efficacy of pamrevlumab in subjects with IPF; subjects were treated with 2 doses of pamrevlumab every 3 weeks: 15mg/kg and 30mg/kg. Subjects who met extension criteria continued to receive pamrevlumab treatment every 3 weeks until disease progression. Results of the 049 study were published (Raghu et al. 2016, Clukers et al. 2018).

Study FGCL 3019-067 (PRAISE Study), was a Phase 2, randomized, double-blind, placebo-controlled study in subjects with IPF to evaluate the safety and efficacy of pamrevlumab administered at 30 mg/kg by IV infusion every 3 weeks for 45 weeks for a total of 16 infusions. Following the double-blind randomized treatment period, qualifying subjects had the option to enter an open-label extended treatment period to receive pamrevlumab 30 mg/kg every 3 weeks. Fifty subjects were randomized to pamrevlumab and fifty-three were randomized to placebo in the main study. The study was amended to include an additional subset of subjects (called "sub-study" to differentiate from the "main" study) receiving background IPF approved therapy with pirfenidone or with nintedanib in a stratified manner. For the sub-study, the randomized double-blind placebo-controlled treatment period was 24 weeks with no extended treatment period.

For details on studies 049 and 067 (main study, extended treatment period, and the sub-study) see Section 2.6.3 below, and the current version of the IB. Results of the PRAISE study were published (Richeldi et al, 2019).

2.6.2. Dose Rationale

Pamrevlumab has been tested in a Phase 1 single-ascending dose study (FGCL-MC3019-002) and two repeat-dose Phase 2 studies (Study 049 and Study 067) in IPF patients. The single-dose study utilized intravenous infusions of 1, 3, or 10 mg/kg. Study 049 was an open-label study testing 15 mg/kg and 30 mg/kg every 3 weeks for 45 weeks as monotherapy. Study 067 was a placebo-controlled study testing 30 mg/kg every 3 weeks for 45 weeks as monotherapy. All studies collected safety and tolerability data, samples for pharmacokinetic analyses and pulmonary function test measurements.

Prior to studying IPF, pamrevlumab was tested in a Phase 1 multiple ascending dose study in combination with gemcitabine and erlotinib in advanced pancreatic cancer patients using IV doses of 3 mg/kg up to 45 mg/kg every 2 weeks, and weekly doses up to 22.5 mg/kg. The Phase 1 study in pancreatic cancer included assessments of safety and tolerability, samples for pharmacokinetic analyses and measures of disease progression.

Collectively these studies have investigated repeat doses up to 30 mg/kg every three weeks in IPF and up to 45 mg/kg every 2 weeks in pancreatic cancer. The doses in all studies were found to be safe and tolerable and active doses were identified in each indication.

The combined data were analyzed via population pharmacokinetics (PopPK) to determine if the PK for the two indications were similar. The combined PopPK model was used to derive steady state trough exposures of pamrevlumab leading to exposure-response relationships for the two Phase 2 IPF studies. The efficacy measure was forced vital capacity FVCpp. Clinical trial simulations of FVCpp were also performed to evaluate the probability of success of

pamrevlumab versus placebo at different doses. Safety data for the two Phase 2 IPF studies were tabulated by dose group, and exposure-response relationships were explored for selected adverse events. These analyses form the basis for the Phase 3 dose in IPF patients and shows that an IV administration of 30 mg/kg of pamrevlumab every three weeks to IPF patients achieves better efficacy than placebo for FVCpp, and reaches the mean pamrevlumab trough where efficacy begins to plateau (approximately 150 μg/mL).

2.6.3. Safety Summary and Benefit/Risk Assessment

Overall, pamrevlumab has been well-tolerated. Three Phase 1/2 studies were completed in IPF: Study FGCL-MC3019-002 (N=21); Study FGCL-3019-049 (N=89; 53 receiving 15mg/kg and 36 receiving 30mg/kg pamrevlumab); and Study FGCL 3019-067 (N=103; 50 randomized to pamrevlumab 30mg/kg, 53 randomized to placebo). The majority of TEAEs reported were of respiratory nature and consistent with those reported for historical, comparable IPF populations (Richeldi, 2014). Across the IPF studies, the most common treatment emergent adverse event (TEAEs) by subject have been cough, fatigue, dyspnea, upper respiratory tract infection, bronchitis, and nasopharyngitis.

In study FGCL-MC3019-002, pamrevlumab was well tolerated across the range of doses studied; there were no dose-limiting toxicities, and adverse events were generally mild or moderate. A single TESAE, interstitial lung disease in the 10 mg/kg dose cohort, was reported during the study. No subject withdrew due to a TEAE.

During a post-PK long term follow up three subjects died: approximately two, six, and 11 months after the administration of pamrevlumab, respectively, due to disease progression. None of the deaths were considered related to pamrevlumab.

In study FGCL-3019-049, the most frequent TEAEs were cough, fatigue, dyspnea, upper respiratory tract infection and bronchitis, which are consistent with those AEs reported for historical, untreated controls in IPF populations in randomized, placebo-controlled studies (King 2009; Raghu et al, 2004; Zisman et al, 2010; King et al, 2014; Richeldi et al, 2014).

TEAEs were similar across cohorts and also similar when comparing these observed during the initial 48 weeks and during the extension. Approximately one-third of study subjects experienced TEAEs Grade ≥3 and these were of respiratory nature, related to IPF or its complications. TESAEs were reported in about one-third of subjects, mainly related to IPF or its complications. Treatment or study discontinuation was reported for 16 subjects, the most frequent cause being IPF progression. A total of 13 deaths have been reported during the entire study duration (including the first 48 weeks and the extension periods), 12 of them from respiratory causes. The mortality rate observed in this study is below the calculated expected mortality rate as per the GAP system (Ley et al, 2012).

In Study FGCL-3019-067, pamrevlumab was well tolerated, with a safety profile similar to that of placebo: 48 (96%) patients in the pamrevlumab group compared to 52 (98%) patients in the placebo group had at least one TEAE. TESAEs were observed in 12 patients (24%) in the pamrevlumab group and 8 (15%) in the placebo-group and were mostly respiratory-related; however, fewer patients in the pamrevlumab group discontinued study treatment because of a TESAE than did those in the placebo group: three (6%) versus seven (13%), and fewer patients in the pamrevlumab group (five [10%]) compared to placebo (seven [13%]) were hospitalized

following a respiratory-related TESAE. Nine patients died during the study: three (6%) in the pamrevlumab group and six (11%) in the placebo group. No safety concerns were identified in the analysis of clinical laboratory results or ECG parameters.

Regarding efficacy results in study 067, subjects receiving pamrevlumab showed a statistically significant difference from placebo for the primary efficacy endpoint of FVCpp change from baseline to week 48 favoring pamrevlumab. In addition, other efficacy results showed that pamrevlumab slowed the progression of IPF as measured by change in HRCT quantitative lung fibrosis, and time to disease progression as measured by 10% categorical decline in FVCpp or death.

In summary, across all completed phase 2 IPF studies, the observed TEAEs have been generally mild or moderate in severity and transient in duration, have been typical of the patients' underlying medical condition(s) and, in the placebo-controlled study, were equally distributed between the placebo and pamrevlumab treatment groups.

Therefore, based on the cumulative safety data and the potential benefit of pamrevlumab in IPF, the benefit/risk profile is considered overall favorable (Wells, 2019).

3. OBJECTIVES AND ENDPOINTS

3.1. Objective

The overall objective of this trial is to evaluate the efficacy and safety of 30 mg/kg IV infusions of pamrevlumab as compared to placebo in subjects with idiopathic pulmonary fibrosis.

3.2. Endpoints

3.2.1. Primary Endpoint:

- Change in FVC (L) from baseline at Week 48

3.2.2. Secondary Endpoints

Endpoints:

- Time to disease progression, defined as absolute FVCpp decline of ≥10% or death, whichever occurs first
- Change in Quantitative Lung Fibrosis (QLF) volume from baseline at Week 48
- Time to any component of the clinical composite endpoint, whichever occurs first: acute IPF exacerbation, respiratory hospitalization, or death
- Time to first acute IPF exacerbation during study
- Time to all-cause mortality during study
- Time to first respiratory hospitalizations during study

3.2.3. Exploratory Endpoints

Exploratory endpoints include:

- Time to composite of: respiratory hospitalization or death or absolute FVCpp decline ≥10%, whichever occurs first
- Change in absolute FVCpp from baseline at Week 48
- Change in relative FVCpp from baseline at Week 48
- Change in St. George's Respiratory Questionnaire (SGRQ) score from baseline at Week 48
- Change in University of California San Diego – Shortness of Breath Questionnaire (UCSD-SOBQ) score from baseline at Week 48
- Change in Leicester Cough Questionnaire (LCQ) from baseline at Week 48
- Exploratory biomarkers

3.2.4. Safety Assessment

Treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs), clinical laboratory parameters, vital signs, immunogenicity (Human Anti-Human Antibody [HAHA] formation), and hypersensitivity/anaphylactic reactions.

3.3. Overall Study Design

This is a Phase 3, randomized, double-blind, placebo-controlled multi-center trial to evaluate the efficacy and safety of pamrevlumab in subjects with IPF. Approximately 340 subjects will be enrolled in this trial.

Subjects must be fully informed of the potential benefits of approved products and make an informed decision that they prefer to participate in a clinical trial in which they could be randomized to placebo.

NOTE: Plans to re-screen a subject must be discussed with and approved by the Medical Monitor, prior to re-screening

Subjects will be randomized in a 1:1 ratio to one of the two study treatment arms:

- Arm A: pamrevlumab, 30 mg/kg IV, Day 1 and every 3 weeks thereafter
- Arm B: Matching placebo IV, Day 1 and every 3 weeks thereafter

Subjects will be stratified by:

- Prior treatment with an approved IPF therapy (Yes/No)
- GAP stage (I, II, III) derived from GAP score obtained at screening (See Appendix 5).

NOTE: For calculation of the GAP score: Use the Best-Test Review (BTR) assessment provided by the spirometry vendor over-reader of the screening value (See Section 6.2.5 and Appendix 5).

This study consists of the following study periods:

- **Main (double blind, placebo-controlled) phase**:
  - Screening period: Up to 6 weeks
  - Treatment period: 48 weeks
- **Optional, open label extension phase**:
  - Access to pamrevlumab will be available until the last subject completes 48 weeks of treatment in the OLE phase, or pamrevlumab is commercially available for the indication of IPF, or the Sponsor decides to end the OLE phase, whichever occurs first.
- **Follow-up period/final safety assessment**:
  - 28 days after last dose
  - 60 days after last dose: follow-up phone call, for a final safety assessment

The intent of this study is to evaluate the efficacy and safety profile of pamrevlumab as monotherapy in subjects with IPF who were either treated with an approved therapy in the past, but discontinued that therapy (possible reasons for discontinuation of approved therapy could include, but are not limited to, intolerance or disease progression); or who decided voluntarily to forego such treatment, after being fully informed of the potential benefits/risks.

NOTE: No subject should discontinue an approved therapy for the purpose of enrolling in this study.

During the treatment period, co-administration of one of the two approved IPF therapies, pirfenidone or nintedanib, is acceptable if clinically indicated in the Investigator's opinion, after assessment of potential risks / benefits of such combination with blinded study treatment. See also Section 5.1.10.

A schematic overview of the study is provided in Figure 1. A detailed overview of assessments and the timing of assessments is provided in Appendix 1. A detailed overview of the OLE assessments and procedures is provided in Appendix 6.

3.3.1. Study Duration

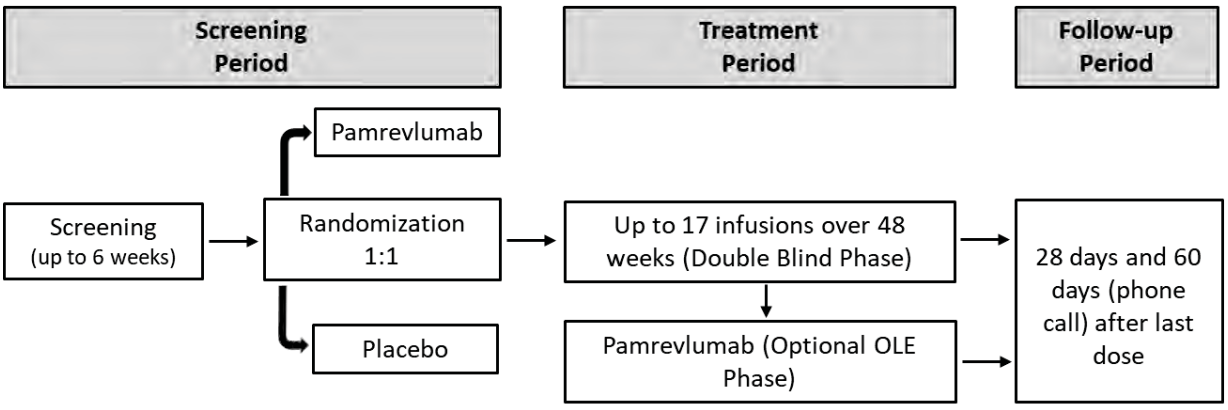
Subjects are encouraged to receive all 17 study drug doses in the main study. Subjects who do not receive all doses are encouraged to continue with study visits and assessments.

Subjects who complete the Week 48 visit (regardless of the number of study drug doses received) will be eligible for an open-label extension (OLE) phase, which will provide continuing access to pamrevlumab until the last subject completes 48 weeks of treatment in the OLE phase, or pamrevlumab is commercially available for the indication of IPF, or the Sponsor decides to end the OLE phase, whichever occurs first.

Subjects who withdraw from the main study early, for any reason, will need to return for an early termination (ET) visit as soon as feasible and 28 days after the last dose, with a follow-up phone call 60 days after the last dose for a final safety assessment. Such subjects should also be contacted by phone at weeks 24 and 48, to check the subject's vital status; such subjects will not be eligible for the OLE phase.

See also Section 4.3 for mandatory Study Withdrawal reasons, and Section 4.4 for procedures related to Early Study Withdrawal.

Figure 1: FGCL-3019-091 Study Schema



3.3.2. Placebo Control Group

In order to evaluate the effect of treatment with pamrevlumab on the endpoints described in Section 3.2, 50% of subjects will be randomized to placebo treatment.

A placebo control is appropriate and ethical for this trial given the intended population of participating subjects: those who have not responded to or are intolerant of approved IPF therapies, or who decided voluntarily to forego such treatment, after being fully informed of the potential benefits/risks. For these subjects the best treatment option is supportive care, which is available to them within this protocol. In addition, they have the option of receiving treatment with an approved IPF therapy any time after randomization, if clinically indicated in the Investigators opinion, without the need to end study participation. All study subjects who complete Week 48 visit (regardless of the number of study drug infusions received) will be offered participation in the optional OLE phase which provides continuing access to pamrevlumab treatment (Appendix 6).

NOTE: No unblinding of subject's treatment assignment in the main study will occur for purposes of OLE participation.

3.4. Randomization and Treatment Assignment

3.4.1. Randomization

Approximately 340 subjects will be randomized 1:1 to receive either pamrevlumab or placebo, resulting in approximately 170 subjects per treatment arm. Each subject will receive a unique study ID number during screening.

Subjects will be stratified by:

- Prior treatment with an approved IPF therapy (Yes/No)
- GAP stages (I, II, III), derived from the GAP scores obtained at screening (See Section 6.2.5 and Appendix 5).

Automated randomization and treatment assignments will be performed by an Interactive Response System (IXRS or IRT).

3.4.2. Treatment Assignment

Subjects will be randomized 1:1 to one of two treatment arms:

- **Arm A**: Pamrevlumab
- **Arm B**: Placebo

3.5. Blinding

This is a double-blind, placebo-controlled study. The Investigator, study site staff, subjects, selected Sponsor clinical team and designees are blinded to study drug assignment. Blinded

treatment with a placebo control is the gold standard method for obtaining unbiased assessments of safety and efficacy in clinical trials of investigational drugs such as pamrevlumab.

3.5.1. Maintenance of Blinding

The study blind will be maintained for all parties specified above throughout the study with the exception of the scenarios outlined in Section 3.5.2. Pamrevlumab and placebo are identical in appearance, packaging, and labeling in order to maintain the study blind.

3.5.2. Request for Unblinding of Treatment Assignment

Breaking the blind during the study (for a single subject) should be considered only when knowledge of the treatment assignment is deemed essential by the Investigator due to immediate safety concerns, or is considered essential for the immediate subject management. The responsibility to break the blind (for a single subject) in emergency situations resides solely with the Investigator. It is the Investigator's responsibility to promptly document and explain any unblinding to the Sponsor.

Such emergency unblinding will be done by the Investigator using the automated Interactive Response System (IXRS or IRT) which ensures rapid unblinding in emergency situations.

4. SELECTION AND WITHDRAWAL OF SUBJECTS

4.1. Subject Inclusion Criteria

In order to be eligible for inclusion in this trial, a subject must meet all of the following:

1. Age 40 to 85 years, inclusive, at screening initiation.
2. Diagnosis of IPF as defined by ATS/ERS/JRS/ALAT guidelines (Raghu 2018).
3. IPF diagnosis within the past 7 years, with onset defined as the date of the first recorded diagnosis of IPF by HRCT and/or surgical lung biopsy (SLB), or other appropriate tissue sample (e.g., cryobiopsy) in the medical history.
4. Interstitial pulmonary fibrosis defined by HRCT scan at screening, with evidence of ≥10% to <50% parenchymal fibrosis (reticulation) and <25% honeycombing, within the whole lung. **NOTE**: this requires confirmation by an Independent Radiology Imaging Review Group, prior to randomization. If a recent HRCT scan (within 3 months prior to screening) is available, it can be utilized for screening purposes, provided it is submitted and evaluated by the Independent Radiology Imaging Review Group, is adhering to the imaging parameters detailed in the Imaging Core Manual (ICM), and is using the same accredited scanner as the on-study HRCT scans.
5. FVCpp value >45% and <95% at Screening **and** Day 1 (prior to randomization).
6. Diffusing capacity of the lungs for carbon monoxide (DLCO) percent predicted and corrected by Hb value ≥25% and ≤90% at screening (determined locally). If a DLCO is available within 3 months prior to screening, it can be utilized for screening purposes.
7. Both FVC and DLCO testing must be representative of the IPF underlying disease (i.e., have been obtained in absence of an acute respiratory event [e.g., lung infection, cold] or other events that are known to affect PFT testing results. [e.g., broken rib, chest pain, other]).
8. Not currently receiving treatment for IPF with an approved therapy for IPF (i.e., pirfenidone or nintedanib) for any reason, including prior intolerance or lack of response to an approved IPF therapy, or choice to forego treatment with an approved IPF therapy after a full discussion with the Investigator regarding risks/benefits of such therapy. **NOTE**: no subject should discontinue approved therapy for the purpose of enrolling in this study.
9. Male subjects with partners of childbearing potential and female subjects of childbearing potential (including those <1 year postmenopausal) must use a highly effective method of contraception per Clinical Trial Facilitation Group (CTFG) recommendation (see protocol section 5.2.3 for details) during the conduct of the study, and for 3 months after the last dose of study drug. Women not of childbearing potential are defined as:
    a. Post-menopausal women (defined as at least 12 months with no menses without an alternative medical cause); in women < 45 years of age, a high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. OR

b. Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening; OR
c. Have a congenital or acquired condition that prevents childbearing.

10. Able to understand and sign a written informed consent form.

4.2. Subject Exclusion Criteria

Subjects will be ineligible for and excluded from this trial if any of the following apply:

1. Previous exposure to pamrevlumab.
2. Evidence of significant obstructive lung disease by any of the following criteria: (1) forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio <0.70, or (2) extent of emphysema greater than the extent of fibrosis on HRCT. **NOTE**: this requires confirmation by an Independent Radiology Imaging Review Group, prior to randomization.
3. Female subjects who are pregnant or nursing.
4. Smoking within 3 months of screening and/or unwilling to avoid smoking throughout the study.
5. Interstitial lung disease (ILD) other than IPF, including but not limited to any of the other types of idiopathic interstitial pneumonias; lung diseases related to exposure to fibrogenic agents or other environmental toxins or drugs; other types of occupational lung diseases; granulomatous lung diseases; pulmonary vascular diseases; systemic diseases, including vasculitis, infectious diseases and connective tissue diseases. In cases of uncertain diagnosis serological testing and/or review by multi-disciplinary team should be performed to confirm diagnosis of IPF vs. other types of ILD.
6. Sustained improvement in the severity of IPF during the 12 months prior to screening, based on changes in FVC, DLCO, and/or HRCT scans of the chest.
7. History of other types of respiratory diseases, including diseases or disorders of the airways, lung parenchyma, pleural space, mediastinum, diaphragm, or chest wall that, in the opinion of the Investigator, would impact the primary protocol endpoint or otherwise preclude the subject's participation in the study.
8. Medical conditions (e.g., MI/stroke within the past 6 month), or logistical challenges that in the opinion of the Investigator preclude the subject's adequate participation in the study.
9. Poorly controlled chronic heart failure (NYHA Class 3 or above); clinical diagnosis of cor pulmonale requiring specific treatment; or severe pulmonary arterial hypertension requiring specific treatment that, in the opinion of the Investigator, would preclude the subject's participation in the study.
10. Clinically important abnormal laboratory tests (including serum creatinine ≥1.5 x upper limit of normal [ULN], hemoglobin (Hb) <10 g/dL, white blood cells <3,000/mm^3, platelets less than 100,000/mm^3, serum total bilirubin >1.5 x ULN, serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥2 x ULN, or serum alkaline phosphatase ≥2 x ULN.

11. Ongoing acute IPF exacerbation, or suspicion of such process, during screening or randomization, including hospitalization due to acute IPF exacerbation within 4 weeks prior to or during screening.
12. High likelihood of lung transplantation (in the opinion of the Investigator) within 6 months after Day 1.
13. Use of any investigational drugs or unapproved therapies, or participation in any clinical trial with an investigational new drug within 30 days prior to screening. Or use of approved IPF therapies (i.e., pirfenidone or nintedanib) within 1 week prior to screening.
14. Daily use of PDE-5 inhibitor drugs (e.g., sildenafil, tadalafil), except for treatment of severe pulmonary artery hypertension.
15. Any current malignancy (this does not include localized cancer such as basal or squamous cell carcinoma of skin). Any history of malignancy likely to result in mortality, or requiring significant medical or surgical intervention within the next year.
16. History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies, or to any component of the excipient.
17. Any condition (other than IPF) that is likely to result in the death of the patient within the next year.
18. The Investigator judges that the subject will be unable to fully participate in the study and complete it for any reason, including inability to comply with study procedures and treatment, addiction, or any other relevant medical or psychiatric conditions.

4.3. Subject Study Withdrawal Criteria

Subjects who do not receive all study drug doses in the main study are encouraged to remain in the study and continue with the regular study visits and assessments. However, subjects may withdraw from the study at any time, for any reason. Reasons for discontinuing study drug treatment, as well as reasons for withdrawing from study, will be captured on CRF.

Mandatory reasons for withdrawing the subject from the study include the following:

- Any safety concern in the Investigator's opinion, that precludes further study participation, including infusion-associated reactions deemed life-threatening by the Investigator (see also/ Section 5.1.6)
- Lung transplant
- Pregnancy
- Major protocol deviation that substantially affects subject safety or assessment of efficacy endpoints
- Withdrawal of Consent

4.4. Subject Study Withdrawal Procedures/Assessments

Subjects who withdraw from the study early will have an early termination (ET) visit as soon as feasible. Subjects will return for a Safety Follow-up Visit 28 days after the last dose and will have a final Safety Follow-up Phone call 60 days after last dose for a final assessment of safety.

In addition, these subjects should also be contacted by phone for vital status at weeks 24 and 48.

At the Early Study Termination visit, PFTs do not have to be repeated, if the last one (excluding the screening visit) was performed within 8 weeks of this visit; HRCT does not have to be repeated, if the last one (excluding the screening visit) was performed within 4 months of this visit.

4.5. Replacement of Study Subjects

All randomized subjects will be included in the study. Subjects who terminate the study early will not be replaced.

4.6. Study Closure

FibroGen reserves the right to close any investigational site(s) or terminate the study at any time for any reason. Reasons for the closure of the study site or termination of the study by FibroGen may include (but are not limited to):

- Successful completion of the study at the investigational site
- The required number of subjects for the study has been recruited
- Failure of the Investigator to comply with the protocol, GCP guidelines or local requirements
- Safety concerns
- Inadequate recruitment of subjects by the Investigator

5. TREATMENT OF SUBJECTS

5.1. Study Treatment

5.1.1. Pamrevlumab or Placebo

Pamrevlumab is a fully human IgG1 kappa monoclonal antibody that binds to CTGF and is formulated as solution for administration by IV infusion.

Matching placebo is formulated as solution to be administered in a manner that is identical to pamrevlumab infusion.

5.1.2. Formulation

Pamrevlumab is supplied in single-use glass vials containing sterile, preservative-free solution (100 mg pamrevlumab/vial or 500 mg pamrevlumab/vial respectively). The solution is composed of 10 mg/mL pamrevlumab, 1.60 mg/mL L-histidine, 3.08 mg/mL L-histidine HCl, 8.01 mg/mL sodium chloride, and 0.05 mg/mL polysorbate 20, resulting in a solution with a tonicity of approximately 290 mmol/kg and a pH of 6.0.

The placebo formulation is of identical composition as the pamrevlumab formulation, except for the absence of pamrevlumab.

5.1.3. Study Drug Packaging and Labeling

Labels will be prepared and will comply with Good Manufacturing Practice requirements for labelling and local regulatory guidelines.

5.1.4. Study Drug Storage

All Investigational Product (IP) vials must be stored refrigerated (2°C to 8°C), in a temperature-controlled and monitored environment, protected from light, and in a securely locked area to which access is limited to appropriate study personnel. Documentation of the storage conditions must be maintained by the site for the entire period of study participation. Details regarding the reporting of temperature excursions can be found in the study Investigational Product (IP) Manual.

5.1.5. Study Drug Preparation

IP is infused undiluted after pooling the contents of the calculated number of vials in an empty infusion bag (total volume of fluid must not exceed **410 mL**) according to the Dose Preparation Instructions in the IP Manual.

Once prepared, the IP infusion is stable at room temperature for up to 6 hours. However, if prepared IP and stored refrigerated at 2 to 8ºC IP is stable for **48 hours.**

IP is administered by IV infusion, **using an infusion set with a 0.2 µm in-line filter**.

5.1.6. Study Drug Administration

Dosing is based on the weight obtained on Day 1 and every 12-weeks thereafter. The total dose **is not to exceed 4.1g**. The total **volume of fluid is not to exceed 410 mL**. Study Drug is administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (**0.2-micron pore size**). The infusion and post-infusion observation periods are provided in Table 1 below:

Table 1 Pamrevlumab (or placebo): Dose, Route, and Administration

Agent	Dose	Route	Infusion Rate	Frequency
Pamrevlumab/ matching placebo	30 mg/kg	IV	• First Infusion (including first infusion in OLE): Infuse over approximately 2 hours. • Second Infusion (including second infusion in OLE): If first infusion is well tolerated, infuse over approximately 1 hour. • Subsequent Infusions: If 1 hour infusion(s) are well tolerated, infuse over approximately 30 minutes. **For ALL infusions:** A Post-infusion observation period has to be included throughout the study: It is 1 hour for at least the first 3 infusions (including in OLE); this may be reduced to 30 minutes if there were no infusion-related AEs after the first 3 infusions.	Day 1 and Every 3 weeks thereafter **NOTE**: Infusions must be AT LEAST 10 days apart

NOTE: DO NOT ADMINSITER STUDY DRUG AS AN IV PUSH OR BOLUS INJECTION, OR CONCURRENTLY IN THE IV LINE WITH OTHER AGENTS.

The first infusion should be completed in approximately 2 hours. If the first infusion is well tolerated and no infusion-associated AEs are observed during the infusion and observation periods, the second infusion should be completed in approximately 1 hour. The subsequent infusion periods may be shortened to approximately 30 minutes if no infusion-associated AEs were observed during the initial two infusions.

If an infusion-associated AE occurs during any of the subsequent infusions, study drug will be administered over approximately 1 hour for the next three infusions. If no infusion-associated AEs are observed in any of these three infusions, the infusion may be decreased again, to approximately 30 minutes.

The Investigator or other qualified personnel must be either present, or immediately available, during all infusions and observation periods for each subject. If a subject has a significant infusion-associated AE, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If such a subject continues study drug dosing, a physician should be immediately available during all subsequent infusions and observation periods at the site.

Subjects who experience an infusion-associated AE will not be allowed to participate in Home Health Care (HHC). In addition, if a subject experiences a life-threatening (per Section 7.3.3) infusion-associated AE, study drug treatment must be permanently discontinued (see Section 4.3).

The Investigator has the option to use premedication (e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs)) for a subsequent infusion; this may be discussed with the FibroGen Medical Monitor.

Infusions are to be continued until the total volume has been administered. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. This post-infusion observation period may be reduced to 30 minutes if the subject has had no infusion-associated AEs during the first three infusions.

Study drug will be administered at a hospital or ambulatory setting with adequate facilities for managing medical emergencies. Medications for the treatment of acute reactions, including anaphylaxis, must be available to study site staff for immediate use. There is no specific treatment for a pamrevlumab overdose or infusion-associated AEs. Signs and symptoms should be managed with appropriate standard of care treatment.

The Sponsor may consider the use of properly trained home health care staff to administer the infusions of study drugs at the subject's home and corresponding study assessments during the conduct of the study (after the completion of at least three 30 minute infusions without safety concerns), consistent with institutional regulations and policies. See Section 5.1.7 for details.

COVID-19 Vaccine and Study Drug Administration

If a subject receives a COVID-19 vaccine during the study, it is recommended that a time separation of at least 48 hours is maintained between administration of the COVID-19 vaccine (single/multiple dose) and study drug infusion. The time separation may allow for better interpretation of any adverse events and their relationship to the vaccine or study drug.

The following procedures must be performed prior to each infusion:

- Vital signs (blood pressure [BP], pulse, and temperature) within 30 minutes before starting the infusion
- Query subject and assess AEs and SAEs
- Record concomitant medications

The following procedures must be performed after each infusion:

- Vital signs (BP, pulse, and temperature) within 30 minutes after completion of the infusion
- Query subject and assess AEs and SAE's

5.1.7. Home Health Care

The Sponsor may consider the use of properly trained and qualified home health care staff in specific regions/countries, depending on local acceptance and adoption of home visits, to administer study drug at the subject's home, after completion of at least the first 3 infusions without safety concerns. Home Health Care (HHC) is optional and the decision to utilize this service is determined by the site, consistent with institutional regulations and policies.

NOTE: Subjects who experience a significant infusion-associated AE may not receive HHC. In addition, if a new safety concern arises during a home infusion, the subject has to attend an on-site visit for an Investigator assessment as soon as feasible. HHC support will only be on weeks

with study drug infusions and no scheduled study assessments. Visits that include collection of PFT, ePRO, safety labs or HRCT must be performed on-site. Medications and supplies to treat suspected hypersensitivity/anaphylactic reactions must be available for immediate use for all study drug infusion visits.

5.1.8. Missed Dose

Every attempt should be made to complete all study visits within the windows as outlined in the Schedule of Assessment (SOA) (Appendix 1).

Scheduled visit dates are determined from the time of the first dose, which is defined as Day 1. A visit schedule is provided in Section 6.1.2 and the SOA (Appendix 1). Visits conducted outside the visit windows will be recorded as a protocol deviation. Missed doses are not to be made up through extra visits. If a subject misses more than two infusions in any 18-week period throughout the study, or two sequential infusions, the FibroGen Medical Monitor should be notified. The reason for missed doses must be documented in the subject's clinical record.

If a dose is missed due to a missed visit see section 6.1.4 and 6.1.5.

Refer to the case report form (CRF) completion guidelines for additional information on CRF completion requirements for missed visits.

5.1.9. Study Drug Handling and Disposal

All study drug provided by the Sponsor should be retained at the site until otherwise instructed in writing by the Sponsor (or designee). If local/regional/institutional policies do not allow the site to retain study drug, the site must provide the Sponsor (or designee) their drug destruction SOP/process for review and approval. The Sponsor (or designee) will perform drug accountability and reconciliation for all study drug received at the site prior to approving study drug return/destruction. Upon completion of accountability/reconciliation or upon completion of the study or termination of the investigational site, all used, unused, partially used study drug, and all study drug that was not dispensed will be shipped to a destruction site designated by the Sponsor (or designee) for destruction. IV bags used to infuse study drug can be disposed of per institutional policy. Please refer to the IP Manual for additional information on study drug materials, management and accountability.

5.1.10. Co-Administration of an Approved IPF Therapy

During the treatment period, co-administration of an approved IPF therapy (i.e., pirfenidone or nintedanib) is acceptable if clinically indicated in the Investigator's opinion, provided that the Investigator assesses the potential risks/benefits of combining approved IPF therapies with blinded study treatment.

Dosing of approved IPF therapy, and safety monitoring while receiving such therapy, must be in accordance with the approved therapy's local label.

5.1.11. Treatment Compliance

All treatments are administered at the investigational site by qualified personnel and documented in the corresponding case report form (CRF).

5.2. Concomitant Medications

5.2.1. Permitted Concomitant Medications

Concomitant medications (any prescription and/or over-the-counter [OTC] preparation) and procedures or nondrug therapies (e.g., physical therapy, acupuncture, continuous positive airway pressure [CPAP]) used by a subject while participating in this clinical trial must be recorded from the Screening Visit through the Safety Follow-Up Visits.

Other than the restrictions that follow, concomitant medications may be given at the discretion of the Investigator. It is expected that Investigators will provide optimal medical care for the subject's various co-existing medical conditions. The Investigator should ensure optimal medical care is provided during the course of the study.

Oral prednisone or equivalent oral corticosteroid: up to 10 mg daily for chronic use is permitted, as long as such use is for a condition other than IPF, and has to be documented accordingly. Higher doses for acute conditions are permitted. N-acetylcysteine (NAC): up to 1800 mg daily, is also permitted during the study.

5.2.2. Prohibited Concomitant Medications

Pirfenidone and nintedanib are permitted as approved IPF therapies, if clinically indicated during the study. For details, see Section 5.1.10.

Prohibited medications include any other (off-label or investigational) agents for the treatment of interstitial lung diseases including IPF. The list of prohibited concomitant medications for treatment of IPF includes, but is not limited to, the following:

- sildenafil: if used for erectile dysfunction the frequency of administration should be no more than two times a week,
- azathioprine,
- cyclophosphamide,
- cyclosporine,
- interferon gamma 1b,
- D penicillamine,
- methotrexate,
- leflunomide,
- colchicine,
- bosentan,
- ambrisentan,
- aminobenzoate,
- mycophenolate mofetil,
- imatinib,

- relaxin,
- etanercept,
- adalimumab,
- infliximab,
- anakinra,
- abatacept,
- rituximab

If any of these treatments are prescribed for their approved indications, for other co-existing medical conditions such as systemic inflammatory disease (e.g., rheumatoid arthritis), severe pulmonary hypertension, etc.), such uses are allowed. All indication needs to be clearly documented in the subject's clinical record.

Questions about concomitant medications should be discussed with the FibroGen Medical Monitor.

5.2.3. Contraception Requirements

A non-clinical study evaluating the potential effects of pamrevlumab on embryo-fetal development has been conducted (rabbit embryo-fetal development study 352021017). The pamrevlumab systemic exposure levels at 200 mg/kg to the pregnant female rabbits which resulted in fetal external and skeletal abnormalities are approximately 20-fold greater than the systemic exposure levels in humans at doses of 30mg/kg or 35 mg/kg in our current protocols.

No adverse effects of pamrevlumab administration were observed in a study of rat male and female fertility.

Therefore, female subjects of childbearing potential and male subjects who have partners with reproductive potential are required to use a highly effective method of contraception per Clinical Trial Facilitation Group (CTFG) recommendation (for reference see section 13) during the study and for 3 months after the last dose of study drug as follows:

• Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:

- oral
- intravaginal
- transdermal

• Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:

- oral
- injectable
- implantable[2]

• Intrauterine device (IUD)[2]

• Intrauterine hormone-releasing system (IUS)[2]

- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to women of childbearing potential with infrequent or irregular menstrual cycles.

[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method (see section 4.3 of the CTGF guidance document).

[2] Contraception methods that in the context of the CTGF guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of the CTGF guidance sexual abstinence is considered a highly effective method only if 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 trial and the preferred and usual lifestyle of the subject.

6. ASSESSMENTS OF EFFICACY

6.1. Study Assessments

A signed and dated IRB/IEC-approved informed consent must be obtained before any study-specific assessments are performed. Assessments that are part of routine care are not considered study-specific and may be used at screening to determine eligibility. All subjects will be screened for eligibility before randomization. Only eligible subjects will be randomized into the study.

6.1.1. Screening Period

All screening procedures must be performed within 6 weeks. Plans to rescreen a subject should be discussed with the medical monitor. Study procedures to be performed during the screening period can be found in the SOA (Appendix 1).

6.1.2. Treatment Period

The study procedures and assessments are presented for the Treatment phase in Appendix 1.

The treatment period begins on Day 1 (first study drug infusion) and continues through Week 48. Visit windows are within ±7 days of the scheduled visit date for Weeks 3 through 48; however, visits should be at least 10 days apart, to ensure intervals of at least 10 days between study drug infusions.

Subjects who complete the Week 48 visit may be eligible to participate in an optional OLE period where all subjects are offered continuing access to pamrevlumab treatment. The details of procedures and assessments, including visit window for OLE are described in Appendix 6.

6.1.3. Safety Follow-Up

Safety assessments will be performed at the following two time points:

- 28 days after last dose
- 60 days after last dose: follow-up phone call, for a final safety assessment

The visit windows for the safety assessments are: 28 days +7 days and 60 days +7 days (phone call) after the last dose.

After this protocol-required reporting period, the Investigator does not need to actively monitor subjects for SAEs. However, if the Investigator becomes aware of an SAE/death that may be possibly related to study treatment after the protocol-required reporting period, the Investigator may report the event to FibroGen as outlined in Section 7. SAEs reported outside of the protocol-required reporting period will be captured within the safety database only as clinical trial cases for the purposes of expedited reporting.

6.1.4. Missed Visits

Scheduled visit dates are determined from the time of the first dose, which is defined as Day 1. Protocol-defined visits conducted outside the study visit window (see Section 6.1.2) will be recorded as a protocol deviation unless there is an AE/SAE/intercurrent illness or other

extenuating circumstance (such as during the COVID-19 pandemic), resulting in missed visit(s). Refer to Section 5.1.8 for additional details. For missed visits, the subject will be asked to resume the planned visit schedule at the next scheduled visit.

NOTE: In accordance with FDA Guidance: During the COVID-19 pandemic, the visit modality (e.g.: in-person versus remotely) and scheduling maybe adjusted and conducted at the discretion of the Investigator, in accordance with the site's rules and recommendations, and using all necessary precautions. If a visit has to be done remotely, it can be conducted with any technology available to the site and study subjects, such as via tele-health visits, phone calls, etc.

Subjects who do not receive all study drug doses, but complete the Week 48 visit, are considered study completers, and may be considered for participation in the OLE of pamrevlumab (see also Appendix. 6).

6.1.5. Unscheduled Visits

Unscheduled visits/assessments may be scheduled as needed. Unscheduled visit data will be captured accordingly in the clinical database.

Unscheduled PFTs: Subjects who are unable to perform a PFT on a scheduled visit, or are missing a visit with a scheduled PFT, need to do an unscheduled PFT assessment at the next scheduled visit.

If the subject is unable to perform PFT at the Week 48 visit, the subject must have an unscheduled visit at the nearest possible date to perform the end of treatment (EOT) PFT assessment.

NOTE: In accordance with FDA Guidance: During the COVID-19 pandemic, the visit modality (e.g.: in-person versus remotely) and scheduling maybe adjusted and conducted at the discretion of the Investigator, in accordance with the site's rules and recommendations, and using all necessary precautions. If a visit has to be done remotely, it can be conducted with any technology available to the site and study subjects.

6.2. Assessments

Refer to the SOA (Appendix 1) for details regarding the timing and frequency of study assessments. Spirometry, laboratory evaluations and patient reported outcomes assessments should be performed prior to infusions.

6.2.1. Vital Signs (including Weight and Height)

Vital signs to be collected include; heart rate, blood pressure and temperature:

- Heart rate should be collected as beats/min
- Systolic and diastolic blood pressure should be collected from subjects in seated position (mmHg)
- Temperature should be taken as oral or tympanic and captured as °F or °C

Weight is collected during screening, Day 1 and every 12 weeks thereafter. Height is collected during screening only.

6.2.2. Physical Exam

Full physical exams (PEs) will be performed according to the SOA (Appendix 1). In addition, PEs may be performed throughout the study as needed, if clinically indicated.

6.2.3. Electrocardiogram (ECG or EKG)

12-lead ECGs will be performed in accordance with institutional standards and according to the SOA (Appendix 1). In addition, ECGs may be performed throughout the study as needed, if clinically indicated.

6.2.4. Laboratory Evaluations

Details regarding sample collection, preparation and transport can be found in the central lab manual.

6.2.4.1. Central Laboratory Evaluations

The following labs will be evaluated by a central laboratory in accordance with the SOA (Appendix 1):

Table 2: Laboratory Tests

CBC:	Chemistry Panel:
Absolute neutrophil count (ANC)	Bicarbonate
Eosinophils	BUN
Erythrocyte count (RBC)	Calcium
Hematocrit %	Creatinine
INR	Chloride
PT/PTT	Magnesium
Hemoglobin	Glucose
WBCs (Leukocyte count)	ALP
Lymphocytes	ALT
Mean corpuscular volume	AST
Monocytes	Bilirubin, total
Neutrophils	Albumin
Platelets	Phosphorous
Basophils	Potassium
	Sodium
	Cholesterol
	Total Protein
	GGT
	Triglycerides
Pregnancy Test: Urine; Serum hCG at screening and to confirm a positive urine test	
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = Gamma-glutamyltransferase; BUN = blood urea nitrogen; CBC = complete blood count; INR = international normalized ratio; PT/PTT = prothrombin time/partial thromboplastin time; RBC = red blood cell; WBCs = white blood cells; hCG =Human chorionic gonadotropin.	

Central lab results obtained during the screening period will be used to determine subject eligibility for participation in the trial. Central lab results will be reviewed by the Investigator for clinical significance and to determine appropriate reporting of adverse events (see Section 7.3). A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

Local laboratory assessments are not required for this study, but the results of any local laboratory assessments may be used to assess subject safety. If a local lab abnormality is reflective of an AE, report the etiology, if known, as per section 7.3.7. Local laboratory results will not be captured in the clinical database.

NOTE: Local laboratory assessments may also be used in case of Central Laboratory supply shortages or shipment delays. If local laboratory assessments are used instead of central labs, the following points need to be considered:

- In case of local screening labs, the Investigator needs to review the results with respect to Exclusion #10.

- For on-study laboratory assessments, only laboratory abnormalities that are considered clinically significant in the Investigator's assessment need to be reported as TEAEs, as per Protocol Section 7.3.7. In such a case, if possible, the etiology of a lab abnormality should be reported as TEAE, not the abnormal lab value.

6.2.4.2. Pharmacokinetics (PK) and Pharmacodynamics

Additional samples will be collected to evaluate PK, HAHA, HAHA-NA, CTGF, exploratory biomarkers and genomics in accordance with the SOA in Appendix 2. The central laboratory will manage the storage of these samples while analysis will be performed at a specialty lab.

6.2.4.2.1. Pharmacokinetics (Optional)

An optional PK assessment will be performed in a subset of subjects at select sites. PK assessments will continue to be optional except in the case of suspected hypersensitivity/anaphylactic reactions (see Section 6.2.4.2.3 for more detail). Plasma samples will be collected for estimates of PK parameters using population PK and exposure-response analysis, if possible, according to the SOA in Appendix 2. A specialty laboratory will measure plasma pamrevlumab levels using a validated assay. For the population PK analysis, it is critical to accurately record the dosing time and date in addition to the sampling collection time and date. Both pre-dose and post-dose samples are required for PK. The pre-dose PK sample should be taken within 2 hours prior to dosing, the post-dose PK sample should be between 1-4 hours after the end of dosing.

6.2.4.2.2. Human Anti-Human Antibodies (HAHA)

Plasma samples will be collected for evaluation of human anti-human antibodies (HAHA) in all subjects according to the SOA in Appendix 2. A specialty laboratory will measure HAHA titers using a validated assay.

Samples with positive HAHA results will be tested for neutralizing antibody (HAHA-NA). The prevalence and duration of binding and neutralizing antibodies and the effect of these antibodies on the pharmacokinetics, pharmacodynamics markers, efficacy, and safety of pamrevlumab will be assessed.

6.2.4.2.3. Suspected Hypersensitivity or Anaphylactic Reactions

Any immunogenic reactions, including drug-related hypersensitivity or anaphylaxis, should have PK, HAHA, HAHA-NA, CTGF and tryptase drawn within 24 hours of a suspected reaction from pamrevlumab (see Appendix 2 for more detail). This is in addition to timepoints in which PK, HAHA, and HAHA-NA and CTGF were drawn pre-infusion and post-infusion.

This will not be considered optional for the subject unless there is local institutional guideline consideration for total blood volume collection on the same day as a standard blood draw timepoint, which could preclude the subject from having this collection take place within 24 hours. The Tryptase sample should be drawn within 1 to 6 hours of immunogenic reaction, and all other samples should be collected within 24 hours of the immunogenic reaction. See Appendix 2 for more detail.

6.2.4.2.4. Exploratory Biomarkers

Serum and plasma samples will be collected in subjects according to the SOA in Appendix 2. These samples will be stored and used to explore additional biomarkers of pamrevlumab's effects in the context of the current clinical trial.

Exploratory biomarkers to be analyzed may include markers of inflammation such as CRP, TNF, IL-6, IL-8 and CCL18; markers of fibrosis and collagen synthesis such as TGF-beta, PINP and PIIINP, as well as other markers of tissue remodeling and angiogenesis such as angiopoietins, VEGF, MMP7 and KL-6.

NOTE: Biomarker samples will be collected for subjects, except in countries where the Regulatory Agencies do not allow collection of these markers.

6.2.4.2.5. DNA for Genomic Analysis (Optional)

A genome-wide association study was performed in subjects with fibrotic idiopathic interstitial pneumonias (N = 1616) and controls (N = 4683) (Fingerlin, 2013) and determined an association of disease with TERT and MUC5B on chromosomes 5p15 and 11p15, respectively, the chromosome 3q26 region near TERC, and identified 7 novel chromosome loci. The novel loci include FAM13A (4q22), DSP (6p24), OBFC1 (10q24), ATP11A (13q34), DPP9 (19p13), and chromosomal regions 7q22 and 15q14-15. Their findings indicate that genes involved in host defense, cell-cell adhesion, and DNA repair contribute to the risk of fibrotic pulmonary disease. In this study, we plan to collect whole blood samples to isolate patient DNA and evaluate the relationship between clinical response to pamrevlumab and variants in loci such as those described above.

A whole blood sample will be collected for DNA analysis on Day 1 before dosing for all subjects who agree to DNA analysis. This testing is optional, requires specific consent by participating subjects and subjects may refuse DNA testing. Only tests for genetic loci associated with ILD, fibrosis or CTGF biology will be performed, and all samples will be destroyed after testing is completed.

NOTE: DNA samples for genomics analysis will be collected for subjects who consent, except in countries where the Regulatory Agencies do not allow collection of these samples.

6.2.5. High Resolution Computerized Tomography (HRCT) Scans and Spirometry

The key study procedures that measure efficacy are serial spirometries to assess lung function (refer to the PFT Procedure Manual for additional details) and serial HRCT assessments to evaluate fibrosis. These measurements will be performed in all patients according to the SOA in Appendix 1.

HRCT:

An Independent Radiology Review Group is assessing all HRCTs for:

- Quantitation of fibrosis, a secondary efficacy measure, and
- Confirmation of HRCT-related eligibility, specifically:
    - Inclusion # 4 and Exclusion # 2
    - Assessment of UIP pattern.

For the screening HRCT, the Independent Radiology Review Group is providing their assessment to study sites, in accordance with the Independent Radiology Review Imaging Charter. It is the responsibility of the Investigator to review this assessment prior to randomization, to make sure all HRCT-related eligibility criteria are met.

For the screening HRCT: if a recent scan, i.e., within 3 months prior to screening, is available, it can be utilized as the screening HRCT, provided it is submitted and evaluated by the Independent Radiology Imaging Review Group, is adhering to the imaging parameters detailed in the Imaging Core Manual (ICM), and is using the same accredited scanner as the on-study HRCT scans.

Spirometry:

Subjects must have an FVCpp value >45% and <95% at screening **and** Day 1 (prior to randomization), in order to be eligible for the study.

For the screening FVCpp value and GAP score calculation: the quality-controlled, Best-Test Review (BTR) assessment provided by the spirometry vendor over-reader, which is provided to sites within 48 hours after uploading the test, is to be used for eligibility assessment and GAP score calculation.

For the Day 1 (pre-randomization) FVCpp value: the real-time value obtained from the device is to be used for eligibility confirmation, without the need to wait for the BTR assessment.

BTR assessments of all spirometries are conducted for statistical purposes, and will be provided to the site, for quality feedback.

NOTE: For spirometries deemed "unacceptable" by the spirometry vendor over-reader, the test has to be repeated.

6.2.6. Patient Reported Outcomes (PROs)

Patient reported outcome (PRO) data will be collected in all subjects to evaluate specific patient reported symptoms, treatment related symptoms and functional impacts that may be responsive to treatment. All questionnaires will be administered as specified in the SOA (see Appendix 1) in the same order at Week 48 as was done at baseline. On weeks where both questionnaires and spirometry are performed, the PFT should be completed prior to administering the PRO.

6.2.6.1. St. Georges Respiratory Questionnaire (SGRQ)

The St. Georges Respiratory Questionnaire is a disease-specific instrument designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airways disease.

6.2.6.2. University of California, San Diego – Shortness of Breath Questionnaire (UCSD-SOBQ)

The UCSD-SOBQ is a self-administered rating of dyspnea associated with activities of daily living (ADLs). The questionnaire is designed to assess severity of shortness of breath during specific ADLs and to assess the limitations due to shortness of breath, fear of harm from overexertion and fear of shortness of breath.

6.2.6.3. Leicester Cough Questionnaire (LCQ)

The Leicester Cough Questionnaire is a self-administered instrument designed to monitor individual patients cough, assess different aspects of health affected in patients and detect changes in health status within an adult chronic cough population (Birring, 2003).

7. ASSESSMENTS OF SAFETY

7.1. Background

Adverse event reports from Investigators are the critical building blocks to the development of the safety profile of the Study Drug. Subjects will be asked non-leading questions in general terms to determine the occurrence of AEs, according to the schedule outlined in Appendix 1. In addition, all AEs reported spontaneously during the course of the study will be recorded. The Investigator must immediately (within 24 hours of awareness) report to the Sponsor or designated safety management vendor all SAEs, regardless of whether the Investigator believes they are related to the study drug.

7.2. Definitions

7.2.1. Definition of an Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The Investigator is responsible for ensuring that any adverse events observed by the Investigator or reported by the subject as defined in the study protocol are recorded in the subject's medical record. The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (e.g., diabetes, migraine headaches and gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not worsened during the study or involves an intervention, such as elective cosmetic surgery, or a medical procedure while on study, is not considered an adverse event.

7.2.2. Definition of a Serious Adverse Event (SAE)

A serious adverse event is any adverse event or suspected adverse reaction that results in any of the following outcomes:

- Death,
- A life-threatening AEs (i.e., if in the view of the Investigator or Sponsor, the subject was at immediate risk of death at the time of the event). Life-threatening does not refer to an event which hypothetically might have caused death if it were more severe,
- Inpatient hospitalization or prolongation of existing hospitalization,
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions,
- A congenital anomaly or birth defect, or
- Is considered a medically important event not meeting the above criteria, but which may jeopardize a subject or may require medical or surgical intervention to prevent one of the other criteria listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or

at home, and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

Please note that death is an outcome, not an event; the primary cause of death would be the adverse event.

Surgical procedures, per se, are not SAEs. The condition requiring the surgical procedure, however, may be a SAE.

Scheduled or pre-planned hospitalization or prolongation of a hospitalization due to standard of care assessments and procedures (including elective procedures) do not warrant reporting as adverse events unless resulting observations are deemed by the Investigator to meet the definition of an adverse event.

7.3. Procedures for Eliciting, Recording, and Reporting Adverse Events

7.3.1. Adverse Event Reporting Period

The safety reporting period begins after the subject has signed the informed consent and ends 60 days after the last dose of study drug. It is only required that SAEs be reported prior to first dose, while all AEs (serious and non-serious) be reported thereafter. The Investigator should notify FibroGen of any death or other SAEs occurring after a subject has discontinued or terminated study participation that may reasonably be related to this study (Section 7.3.5). Pregnancy reporting requirements are outlined in Section 7.3.6.

Adverse events will be followed until resolved, stable, or until the subject's last study visit or subject is lost to follow-up.

7.3.2. Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will actively seek information from each subject at each visit to collect any AEs occurring since the previous visit. All AEs will be collected in response to a general question about the subject's well-being and any possible changes from the BL or previous visit. There will be no directed questioning for any specific AE. This does not deter the site from collecting and recording any AEs reported by the subject to site personnel at any other time.

Whenever possible, diagnoses should be recorded when signs and symptoms are due to a common etiology, as determined by qualified medical study staff. The Investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values. In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event. The Investigator is expected to follow reported adverse events until stabilization or reversibility.

The following attributes must be assigned to each AE:

- Description (Investigator's verbatim term describing the event)

- Dates of onset and resolution
- Severity
- Relationship to study drug
- Outcome
- Action taken regarding study drug
- Other treatment required
- Determination of "seriousness"

7.3.3. Assessing Adverse Event Severity

AEs, including abnormal clinical laboratory values, should be graded using the most current National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) guidelines. For terms not specified as part of NCI CTCAE, the following guidelines should be used to determine grade:

All AEs will be assessed for severity using the following criteria:

- **Grade 1, Mild:** Asymptomatic or mild symptoms which the subject finds easily tolerated. The event is of little concern to the subject and/or of little-or-no clinical significance; intervention not indicated.
- **Grade 2, Moderate:** The subject has enough discomfort to cause interference with or change in some of their age-appropriate instrumental activities of daily living (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money); local or noninvasive intervention indicated.
- **Grade 3, Severe:** The subject is incapacitated and unable to work or participate in many or all usual activities. The event is of definite concern to the subject and/or poses substantial risk to the subject's health or well-being; likely to require medical intervention and/or close follow-up, including but not limited to hospitalization or prolongation of hospitalization.
- **Grade 4, Life-threatening:** The subject was at immediate risk of death from the event as it occurred.
- **Grade 5, Death**: Fatal AE.

7.3.4. Assessing the Adverse Event's Relationship to Study Drug

Most of the information about the safety of a drug prior to marketing comes from clinical trials; therefore, AE reports from Investigators are critically important. The assessment of whether an AE is causally related to the study drug(s) using an evidence-based approach is critical in order to appropriately describe the safety profile of the study drug(s). Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the study drug's safety profile.

The Investigator must provide an evidence-based assessment of the relationship of the AE to study drug in accordance with the guidance below. Absence of an alternative cause would not normally be considered sufficient evidence to assess an event as related to study drug.

- Related:
  - Any event for which there is sufficient evidence to suggest that the study drug may have caused the event. For example, an unanticipated medical condition occurs which resolves with study drug interruption and re-occurs with re-administration of study drug; another example is a typical drug-related medical condition such as a rash that occurred shortly after first dose of study drug.
- Not Related:
  - The event represents a pre-existing underlying disease that has not worsened on study
  - The event has the same characteristics of a known side-effect associated with a co-medication
  - The event is an anticipated medical condition of anticipated severity for the study population
  - The most plausible explanation for the event is a factor that is independent of exposure to study drug

7.3.5. Reporting Serious Adverse Events (SAEs)

The Investigator is responsible for ensuring that all SAEs observed by the Investigator or reported by the subject that occur after signing of the informed consent/assent through 60 days after the last dose of pamrevlumab are recorded in the subject's medical record and are submitted to FibroGen. All SAEs must be submitted to FibroGen within 24 hours following the Investigator's knowledge of the event via the SAE report form. Additionally, pamrevlumab related SAEs (including deaths) that occur after the Safety Follow-Up visits will be reported.

If a subject is permanently withdrawn from protocol required therapies because of a serious adverse event, this information must be submitted to FibroGen. FibroGen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, Investigators/institutions, and central IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice (GCP).

There is no requirement to monitor study subjects for serious adverse events following the protocol-required reporting period or after end of study. However, these serious adverse events can be reported to FibroGen if the Investigator becomes aware of them. If serious adverse events are reported, the Investigator is to report them to FibroGen within 24 hours following the Investigator's knowledge of the event. Serious adverse events reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting; these cases will not be included in the clinical study report.

To report an SAE, the Investigator must complete an SAE Report Form and fax or email the completed form to the Sponsor or its designated safety management vendor.

Full details of the SAE should also be recorded on the medical records and in the CRF. The following minimum information is required:

- Subject number, sex and age
- The date of report
- A description of the SAE (event, seriousness of the event)
- Causal relationship to the study drug

Follow-up information for the event should be sent promptly.

For each SAE observed, the Investigator should obtain all of the information available about the event, including (but not limited to): hospital discharge diagnoses, hospital discharge note, death certificate, appropriate laboratory findings (including autopsies and biopsy results), and clinical examinations (including radiological examinations and clinical consultations).

7.3.5.1. Reporting Serious Adverse Events to the Institutional Review Board / Independent Ethics Committee

The Investigator is responsible for notifying his/her Institutional Review Board (IRB) or Ethics Committee (EC) of SAEs in accordance with local regulations. The Sponsor, or its designated safety vendor, will provide a copy of expedited safety reports to the Investigator that it intends to submit to global regulatory authorities.

7.3.5.2. Deaths

The Investigator will report the fatal event to the Sponsor's medical monitor. The Investigator must provide a causal assessment of the relationship of the event to the study drug according to the guidance in Section 7.3.4.

If the death occurred within the AE collection and reporting period (signed ICF to 60 days after last dose) and meets the reporting criteria, the Investigator must submit the SAE Report Form in the same manner as described above in Section 7.3.5. If the Investigator becomes aware of a death occurring after the AE reporting period and considers it related to pamrevlumab, it will be reported as an SAE.

7.3.6. Pregnancies: Reporting and Follow-up of Subjects and Female Partners of Subjects

The outcome of all pregnancies for female subjects or female partners of male subjects should be followed up and documented as described. If a female subject or a female partner of a male subject becomes pregnant while the subject is receiving study treatment or within 12 weeks after the last dose of study treatment, a Pregnancy Report Form must be completed and submitted to the Sponsor or designated safety management vendor within 24 hours of the Investigator becoming aware of the pregnancy. The Investigator must follow-up to completion of the pregnancy to ascertain its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur during the pregnancy or birth. The outcome of the pregnancy must be reported by the Investigator on a Pregnancy Outcome Report Form, which should be sent to the Sponsor and/or its designated safety vendor within 24 hours of the Investigator becoming aware of the outcome.

Pregnancy itself is not an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Pregnancies are followed up to outcome even if the subject was discontinued from the study. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

If a lactation case occurs while the female subject is taking protocol-required therapies, or within 60 days after the last dose of study treatment, report the lactation case to FibroGen. In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 60 days after the last dose of pamrevlumab. Any lactation case should be reported to FibroGen's Safety within 24 hours of the investigator's knowledge of event.

7.3.7. Laboratory or other Test Abnormalities/ Findings

A laboratory or other test abnormality (e.g., spirometry, HRCT) in the absence of any signs or symptoms is not necessarily an AE. The Investigator must review and assess all test results provided by the central laboratory or other vendors throughout the study in a timely manner, and determine whether any abnormal values/test results are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Such abnormalities should be considered CS if they are associated with new signs or symptoms, if they occur after taking study medication, reflect a meaningful change from the screening value(s), or require active management (e.g., requiring treatment, additional testing, study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

Clinically significant laboratory abnormalities will be reported as AEs. If the abnormal laboratory finding is accompanied by signs or symptoms, report the signs and symptoms as the AE in lieu of the abnormal laboratory value. If a diagnosis is available, report the diagnosis.

7.3.8. Hypersensitivity/Anaphylactic Reactions:

Hypersensitivity and anaphylactic reactions will be monitored throughout the study, using the criteria below as defined per Sampson et al. 2006 (Sampson, 2006).

Anaphylaxis is highly likely when the following criteria is fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula).

And at least one of the following criteria:

   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   b. Reduced BP or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)

2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):

   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula)

b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)

c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence)

d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)

3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):

a. Systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline

7.3.9. Safety Monitoring

Safety will be assessed throughout the study. A medically complete baseline profile of each subject will be established through medical history, a complete physical examination including vital signs, laboratory tests, PFTs, and a 12-lead ECG. During the course of the study, vital signs, laboratory tests, and PFTs will be performed at frequent intervals as described in Appendix 1 and Appendix 2. Any medically significant changes from baseline will be monitored throughout the study and appropriate interventions will be taken accordingly. Safety and tolerability will be monitored closely by FibroGen.

7.3.9.1. Special Reporting Situations

Special Reporting Situations on FibroGen investigational product pamrevlumab (or placebo) that require safety evaluation include:

- Overdose (any dose greater than 4.1g)
- Suspected abuse/misuse
- Inadvertent or accidental exposure
- Medication error (e.g., incorrect dose administered)
- Drug-drug interactions

Report special situations to FibroGen's Safety within 24 hours of the investigator's knowledge of the event. See Study Reference Manual for detailed reporting instructions.

7.3.9.2. Data Monitoring Committee (DMC)

A Data Monitoring Committee (DMC) will be utilized and will be composed of external experts. Composition and responsibilities of the DMC will be defined in a separate DMC charter. The DMC responsibilities will include review of the safety data.

8. STATISTICS

8.1. Sample Size Determination

This study will enroll approximately 340 subjects with a 1:1 randomization ratio to pamrevlumab or placebo, respectively.

A sample size of 340 subjects will have at least 90% power, based on a two-sided alpha level of 0.05 for a two-sample t-test, to detect a treatment difference of 120 mL in the primary efficacy endpoint, change from baseline in FVC (L), assuming a common standard deviation of 300 mL.

The rationale for these sample size assumptions are as follows. In the phase 2 study FGCL-3019-067, a treatment difference of 178 mL was observed in change from baseline in FVC to Week 48. For this study, a conservative treatment difference of 120 mL is assumed. The standard deviation is estimated based on published results from other IPF studies.

8.2. Analysis Populations

8.2.1. Intent to Treat (ITT) Population

The ITT population is defined as all randomized subjects. Subjects will be analyzed according to the treatment as randomized.

8.2.2. Safety Population

The safety population is defined as all subjects who have received the study medication. Subjects will be analyzed according to the treatment as received.

8.3. Statistical Analysis

8.3.1. General Considerations

The primary efficacy endpoint will be tested at the significance level of 0.05. Upon observing a significant treatment difference in the primary endpoint, the secondary endpoints will be tested sequentially in a fixed sequence according to the order listed in section 3.2.2, taking into consideration the adjustment for the family-wise error-rate of 0.05. The testing will continue with the significance level of 0.05 in sequential fashion until the test fails to show statistical significance for a secondary endpoint.
Baseline characteristics, safety, efficacy, and biomarker data will be summarized by treatment arm, based on available data in the ITT and/or Safety Population.

All study parameters will be presented in the data listings and summarized descriptively by visit. Descriptive statistics for continuous variables include: n, mean, standard deviation or standard error (SE), median, minimum, and maximum. Categorical variables will be presented by frequency count of subjects and percentage. Two-sided 95% confidence intervals will be provided.

Efficacy and safety analyses for formal treatment arm (pamrevlumab vs placebo) comparisons will only be based on data observed during the main study that is double-blind and placebo-controlled. Data from the OLE period will be summarized descriptively.

8.3.2. Subject Enrollment and Disposition

The number (%) of subjects who completed or discontinued the study, and reasons for early discontinuation, will be summarized by treatment for subjects in the ITT population.

8.3.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for subjects in the ITT population.

8.3.4. Efficacy Analyses

Unless stated otherwise, analyses performed using the random coefficient model (RCM), mixed model for repeated measurements (MMRM), and time to event model are under the same set of estimand and estimator descriptions as the primary endpoint. The analysis population is all randomized subjects to reflect the intent-to-treat (ITT) principle for all analyses.

8.3.4.1. Primary Endpoint Analysis

The primary estimand is intended to provide a population level estimate of the treatment effects of the pamrevlumab on a continuous endpoint, regardless of participants compliance with the IP dosing. Under estimand framework, the analysis of primary endpoint includes the following components:

Population: Male and female patients aged 40 to 85 years, inclusive at screening initiation with IPF diagnosis made with 7 years prior to screening under American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (Raghu 2018), and not currently receiving treatment with the 2 approved antifibrotic standard of care medications. All subjects in ITT population will be included.

Endpoint: Change from baseline in FVC (L) assessments at Week 48.

Treatment of interest: The randomization study treatment (pamrevlumab or placebo).

Handling of intercurrent events: The treatment policy strategy will be adopted for primary analysis. Details on handling missing values will be defined in SAP.

Population-level summary for the endpoint: Absolute LSMeans difference between pamrevlumab and placebo in change from baseline to Week 48 in FVC (L) estimated from a random coefficient model (RCM), the primary analysis approach. RCM model includes treatment, visit (as a continuous variable), visit-by-treatment interaction, randomization stratification factors, baseline FVC volume, age, sex, height as fixed effects, and the intercept and linear slope of visit as random effects. Details of RCM model will be defined in SAP.

Additional sensitivity and supplemental analyses on primary endpoint will be defined in SAP. The following analysis will be performed including, but not limited to:

1. With alternative model using quadratic assumption of FVC decline
2. Alternative assumptions for missing data (imputation method):
    a. Missing not at random: Pattern mixture model (e.g., control-based imputation)
    b. Missing not at random: Tipping point analysis (e.g., delta-adjusting pattern imputation)

8.3.4.2. Secondary Endpoint Analysis

The secondary estimands are intended to provide a population level estimate of the treatment effect of the pamrevlumab on time-to-event endpoints and continuous endpoint, regardless of participants compliance with the IP dosing. Under estimand framework, the analysis of secondary endpoint includes the following components:

Population: Same as primary estimand.

Endpoints:

- Time to disease progression, defined as absolute FVCpp decline of ≥10% or death, whichever occurs first
- Change in Quantitative Lung Fibrosis (QLF) volume from baseline at Week 48
- Time to any component of clinical composite endpoint, whichever occurs first: acute IPF exacerbation, respiratory hospitalization, or death
    - Time to first acute IPF exacerbation during study
    - Time to all-cause mortality during study
    - Time to first respiratory hospitalizations during study

Treatment of interest: Same as primary estimand.

Handling of intercurrent events:

For time-to-event endpoints, treatment policy strategy will be adopted. For death, composite strategy will be used if death is a component of the endpoint. Censoring rules will be defined in SAP.

For QLF, the same strategy as primary estimand will be applied.

Population-level summary for the endpoint:

For time-to-event endpoints: The hazard ratio and corresponding 95% CI from Cox proportional hazard model will be presented. P-value from stratified Log-rank test will also be reported. Details will be defined in SAP.

For QLF endpoint: treatment difference of Least-square mean (LSMean) and SE at week 48 between pamrevlumab and placebo and the corresponding 95% CI derived from a Mixed Model for Repeated Measure (MMRM) will be presented. The MMRM model includes treatment, visit, treatment-visit interaction, randomization stratification, and baseline endpoint value as fixed effects.

8.3.4.3. Exploratory Analyses

Patient reported outcomes (PROs) including SGRQ, UCSD-SOBQ and LCQ will be analyzed using same MMRM model as QLF. Absolute and relative FVCpp will be analyzed with similar RCM model as FVC excluding the covariates adjusted for FVCpp. Time to composite of respiratory hospitalization, absolute FVCpp decline ≥10%, or death will be analyzed similar to other secondary time-to-event endpoints. Biomarkers will be summarized.

8.3.5. Pharmacokinetic Analyses

A plan for population PK analysis will be provided in the SAP.

8.3.6. Safety Analyses

Safety data will be summarized based on the Safety population. TEAEs and TESAEs will be summarized by treatment arm.

Clinically significant changes from baseline in vital signs and laboratory tests will be identified and summarized by treatment arm. Additionally, hypersensitivity/anaphylactic reactions will be monitored and immunogenicity reactions, including neutralizing HAHA formation, will be assessed by treatment arm.

8.4. Interim Analysis

No interim analysis is planned for this study.

8.5. Statistical Analysis Plan

The Statistical Analysis Plan (SAP) will include detailed analysis methods, statistical models, definitions, missing data handling as well as other data handling rules. It will document detailed analyses of the primary, secondary, and additional exploratory endpoints that are not otherwise specified in the protocol. The SAP will be finalized prior to database lock and treatment unblinding.

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. Data Quality Assurance

Quality assurance and quality control systems will be implemented and maintained with Standard Operating Procedures by FibroGen and its designee(s), as appropriate, to ensure that this clinical study is conducted and data are generated, documented (recorded) and reported in compliance with the protocol, ICH E6 (GCP), and other applicable regulations.

This study will be monitored by FibroGen or designee in accordance with GCP, and may be audited or reviewed by an independent Quality Assurance department, IRB/IEC, and/or regulatory authorities. This implies that monitors and auditors/inspectors will have the right to inspect the study sites at any time during and/or after completion of the study and will have direct access to data/source documents, including the subject's file. By participating in this study, Investigators agree to this requirement.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate, complete, and verifiable from source documents.
- All data are collected, tracked, and submitted by the site to FibroGen or designee, including unscheduled and missed assessments
- The reported data are reconciled across all data sources (e.g., laboratory, safety, IRT, clinical databases).
- The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

Measures will be undertaken to protect the confidentiality of records that could identify subjects, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

9.2. Audit and Inspection

Authorized representatives of the Sponsor, a regulatory authority, and/or an IRB/IEC may visit the Investigator site to perform audits or inspections, including source data verification and source documentation review. The Investigator will allow the Sponsor auditor (or designee), regulatory authority or ethics committee representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts (e.g., medical records) and study source documents, and other records relative to study conduct.

The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH GCP guidelines, and any applicable regulatory requirements.

The Investigator must contact the Sponsor, or its third party representative (CRO), immediately if notified by a regulatory authority of an inspection pertaining to this study.

10. ETHICS

10.1. Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirements, the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), the Declaration of Helsinki, any other applicable regulatory requirements, and Institutional Review Board (IRB) or Independent Ethics Committee (IEC) requirements.

10.2. Communication with the Institutional Review Board or Independent Ethics Committee

This protocol, the Informed Consent Form, the IB, and any information to be given to the subject must be submitted to a properly constituted IRB/IEC by the Investigator for review and approved by the IRB/IEC before the study is initiated and before any investigational product is shipped to the investigator. In addition, any subject recruitment materials must be approved by the IRB/IEC before the material is used for subject recruitment.

The Investigator is responsible for obtaining reapproval by the IRB/IEC annually or as required by the policies and procedures established by the IRB/IEC. Copies of the investigator's annual report and other required reports submitted to the IRB/IEC and copies of the IRB/IEC continuance of approval must be furnished to FibroGen or designee. A copy of the signed FDA Form 1572 or other qualified Investigator statement (as required) must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB/IEC of any protocol changes or amendments, changes to the IB, and other safety-related communications from FibroGen or its designee. Written documentation of IRB/IEC approval must be received before the amendment is implemented.

Investigators must maintain a list of appropriate qualified persons to whom the Investigator has delegated significant trial-related duties and update the list as staff and their delegated responsibilities change.

10.3. Subject Information and Consent

Prior to participation in any study-specific procedures, the subject must sign (note: all references to "subject" in this section refers to the study subject or his/her legally acceptable representative) an IRB/IEC-approved written Informed Consent Form (ICF) in his/her native language. The approved written informed consent must adhere to all applicable laws in regards to the safety and confidentiality of the subjects. To obtain and document informed consent, the Investigator should comply with applicable regulations, and adhere to ICH GCP standards and the ethical principles in the Declaration of Helsinki (October 2008).

The language in the written information about the study should be as non-technical as practical and should be understandable to the subject. Before informed consent is obtained, the Investigator should provide the subject ample time and opportunity to inquire about the study and to decide whether or not to participate.

All questions about the study should be answered to the satisfaction of the subject. The written ICF should be signed and personally dated by the subject and the person who conducted the informed consent discussion, with any additional signatures obtained as required by applicable local regulations and IRB/IEC requirements. Each subject will be informed that participation is voluntary and that he/she can withdraw from the study at any time. All subjects will receive a copy of the signed and dated ICF.

If there are any changes to the IRB/IEC approved ICF during the subjects' participation in the study, the revised ICF must receive the IRB/IEC's written approval before use and subjects must be re-consented to the revised version of the ICF, if/as required by the IRB/IEC.

Each subject must provide his or her consent for the use and disclosure of personal health information in accordance with applicable regulatory requirements.

10.4. Subject Confidentiality

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

Subject medical information obtained as part of this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent or other disclosure authorization documents signed by the subject, unless permitted or required by applicable law.

11. DATA HANDLING AND RECORD KEEPING

11.1. Source Documents

Source documents are original documents, data, and records necessary for the reconstruction and evaluation of the clinical study. The Investigator or designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each subject enrolled in this clinical study. Source documents must be adequate to reconstruct all data transcribed onto the Case Report Forms (CRFs) and resolved queries.

11.2. Direct Access to Source Documents

The Investigator must provide direct access to source data and source documents for trial-related monitoring, audits, IRB/IEC review, and regulatory authority inspection. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information and medical records.

11.3. Data Collection, Handling, and Verification

All required data will either be entered onto CRFs by authorized site personnel or will be provided as a data transfer from authorized service providers (such as laboratory results from a central laboratory). Data will be entered or uploaded into a validated, clinical database compliant with 21 CFR Part 11 regulations.

All subject data will be reviewed by Sponsor and/or designee. Data that appear inconsistent, incomplete or inaccurate will be queried for site clarification.

Medical history, adverse events and medications will be coded using industry standard dictionaries (e.g., MedDRA and World Health Organization Drug [WHODrug]) Dictionary.

The Investigator is responsible for reviewing, verifying, and approving all subject data (i.e., CRFs and queries) throughout the duration of the study and prior to study completion, ensuring that all data are verifiable with source documents.

11.4. Protocol Deviations

Unless there is a safety concern, there should be no deviations or violations of the study protocol. In the event of a safety concern, the Investigator or designee must document and explain the reason for any deviation from the approved protocol. The Investigator may implement a deviation from, or a change to, the protocol to eliminate an immediate hazard to study participants without prior IRB/IEC approval. Immediately after the implemented deviation or change, the Investigator must submit a report explaining the reasons for the protocol violation or deviation to the IRB/IEC, FibroGen, and to the regulatory authorities, if required.

11.5. Retention of Data

A FibroGen representative will inform the Investigator in writing when it is acceptable to dispose of any study records. To enable evaluation and/or audits from regulatory authorities or FibroGen or designee, the Investigator agrees to keep records, including the identity of all participating subjects (e.g., subject identification code list and all source documents), all original signed ICFs, copies of all CRFs, original laboratory reports, detailed records of drug disposition and all essential documents for the conduct of a clinical study. To comply with international regulations, the records should be retained by the Investigator for 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, the Investigator may need to retain these documents for a longer period if required by applicable law, regulatory requirements or by an agreement with FibroGen whichever is longer.

11.6. Financial Disclosure

The Investigator's disclosable financial interests must be obtained prior to initiation of the study site, at completion of the study at the investigational site, and 1 year following study completion.

The Investigator should promptly update this information if any relevant changes occur during the above described period.

Disclosable financial interests will be recorded on the Investigator Financial Disclosure Form.

Any Investigator(s) added as investigational staff to the form FDA 1572 or other qualified investigator statement must complete the Investigator Financial Disclosure Form at the beginning of his/her participation in the study. The Investigator Financial Disclosure Form for any Investigator(s) leaving the clinical site prior to study completion will be obtained prior to study completion.

12. PUBLICATION POLICY

The data and results of the study will be owned solely by FibroGen and shall be confidential information of FibroGen, subject to the Investigator's publication rights, described below and if any outlined in the Clinical Trial Agreement. It is understood by the Investigator that FibroGen may use the information developed in this clinical study in connection with the development of its compounds and therefore, may disclose it as required to other clinical investigators, the Licensing Authority or to regulatory agencies of other governments. To allow for the use of the information derived from this clinical study, the Investigator understands that he/she has an obligation to provide and disclose test results and all data developed during this study to FibroGen.

Any publication or presentation of the results of this clinical study by the Investigator may only be made in strict compliance with the provisions of the Clinical Trial Agreement. Any publication relating to the study shall be made in collaboration with FibroGen. The Investigator should understand that it is not FibroGen’s intention to prevent publication of the data generated in the clinical study. However, FibroGen reserves the right to control the form and timing of such publication for commercial reasons. The Study Center and Investigator shall adhere to the publication language as outlined in both Clinical Trial Agreement and the protocol to the extent that if there is any conflict or ambiguity between Clinical Trial Agreement and the protocol, the publication terms in the Clinical Trial Agreement shall prevail.

13. REFERENCES

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14. APPENDICES

APPENDIX 1. MAIN STUDY SCHEDULE OF ASSESSMENTS

	Screening Period (Up to 6 Weeks) [a]	Dosing Period [b, c] (48 Weeks)																	Safety Follow-Up Period	
Study Week		Day 1 (First dose)		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48/ last dose/ ET	28 days after last dose [r]	60 days after last dose (phone call) [r]
Assessment		Pre-dose	Post-dose																		
Sign and date ICF	X																		X[s]		
Eligibility Assessment (Inclusion/Exclusion)	X	X																			
Demographics	X																				
Medical History	X																				
Labs	X	X					X				X				X				X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Exam [d, e]	X [d]	X [d]					X[d]				X[d]				X[d]				X[d]		
ECG [f]	X																		X		
Randomization		X																			
Infusions [g, h]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
	Screening Period (Up to 6 Weeks) [a]	Dosing Period [b, c] (48 Weeks)																	Safety Follow-Up Period	

Study Week		Day 1 (First dose)		3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48 /last dose/ ET	28 days after last dose [r]	60 days after last dose (phone call) [r]
Adverse Events [i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Procedures and Nondrug Therapies [j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
DLCO	X [k]																				
PFTs	X	X[l]			X[l]		X[l]		X[l]		X[l]				X[l]				X[l, t]		
HRCT of Chest	X[m]										X								X [t]		
SGRQ [n]		X					X				X				X				X	X	
UCSD-SOBQ [n]		X					X				X				X				X	X	
Leicester Cough Q [n]		X					X				X				X				X	X	
Pregnancy Test [o] (WOCBP)	X	X									X								X[p]	X	X
Assess vital status (in subject who terminate study early)											X[q]								X[q]		

Abbreviations: AE = adverse event; CBC = complete blood count; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; ET = early termination; hCG = human chorionic gonadotropin; HRCT = high resolution computed tomography; ICF = Informed Consent Form; PFTs = Pulmonary Function Test; SGRQ = Saint George's Respiratory Questionnaire; UCSD-SOBQ = University of California San Diego – Shortness of Breath Questionnaire;
WOCBP = Women of childbearing potential

a.) Plans to re-screen a subject must be discussed with, and approved by, the Medical Monitor prior to re-screening
b.) Visit window of ±7 days, Week 3 through Week 48. Missed visits are not to be made up between scheduled visits, subject is to return for the next scheduled visit
c.) Unscheduled visit assessments (procedures) performed as necessary. During the COVID 19 pandemic, the visit modality (e.g.: in-person versus remotely) and scheduling maybe adjusted and conducted at the discretion of the Investigator, in accordance with the site's rules and recommendations, and using all necessary precautions. If a visit has to be done remotely it can be conducted with any technology available to the site and study subjects.
d.) Height is measured only at screening. Weight is measured at screening, Day 1 (to calculate the starting dose), and every 12 weeks thereafter to determine the need for dose adjustment.
e.) Additional PE's may be performed as needed, if clinically indicated.
f.) Additional ECGs may be performed as needed, if clinically indicated.

g.) Study drug infusions are Q3W starting on Day 1. **NOTE**: infusions must be at least 10 days apart; missed doses are not to be made up between scheduled visits, subject is to return for the next scheduled visit/dose. Vital signs (blood pressure, pulse, and temperature) must be recorded prior to, and after each infusion, according to Section 5.1.6.
h.) If during a home infusion a new safety concern arises, the subject has to attend an on-site visit for an Investigator assessment as soon as feasible.
i.) See Section 7 for details on safety assessments and AE/SAE reporting.
j.) Concomitant medications and nondrug therapies must be reported starting with signing of informed consent and ending 28 days after the last dose. If the subject experiences an AE/SAE before the end of the final safety phone call (60 days after last dose), concomitant medications and nondrug therapies may also be collected, if part of the treatment of the AE/SAE.
k.) If a DLCO is available within 3 months prior to screening, it can be utilized for screening purposes.
l.) On-treatment PFTs, should be collected pre-dose.
m.) If a recent HRCT scan (within 3 months prior to screening) is available, it can be utilized for screening purposes, provided it is submitted and evaluated by the Independent Radiology Imaging Review Group, is adhering to the imaging parameters detailed in the Imaging Core Manual (ICM), and is using the same accredited scanner as the on-study HRCT scans.
n.) Questionnaires are obtained pre-dose. On weeks where both questionnaires and PFTs are obtained, PFT should be completed first.
o.) Pregnancy tests for women of childbearing potential (WOCBP) only: serum pregnancy test at Screening; urine pregnancy tests (pre-dose) during study visits. A positive urine pregnancy test must be confirmed by serum hCG. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.
p.) Urine pregnancy test to be done at Week 48 visit for women of childbearing potential only who consent to OLE. A positive urine pregnancy test must be confirmed by serum hCG.
q.) ET subjects will be contacted by phone at weeks 24 and 48 to check the subject's vital status.
r.) All subjects will attend a visit 28 days after the last dose for all the marked assessments, and will be contacted by phone 60 days after the last dose, for a final safety assessment. If the subject experiences an SAE during these 60 days, it must be reported within 24 hours of awareness (see Section 7.3 for details).
s.) Subjects eligible for the OLE are to be consented for the OLE at or before the Week 48 visit
t.) ET subjects: PFTs do not have to be repeated if the last one was performed within 8 weeks (excluding the screening visit) of the ET visit. HRCT does not have to be repeated if the last one performed was within 4 months (excluding the screening visit)

APPENDIX 2. PHARMACOKINETIC, BIOMARKER, IMMUNOGENICITY AND GENOMICS SAMPLING

Timepoint [a]	PK [g] (Plasma)	Biomarkers [b, f] (Serum and plasma)	CTGF [b] (Plasma)	HAHA/HAHA-NA [e] (Plasma)	Genomics [b,g] (Whole blood)	Tryptase (serum)
Day 1	X[c]	X	X	X[b]	X	
Day 8	X[d]					
Day 15	X[d]					
Week 3	X[c]					
Week 12	X[c]					
Week 24	X[c]	X	X	X[b]		
Week 36	X[c]		X	X[b]		
Week 48/Last Dose / ET	X[c,]	X	X	X[b]		
28 Days after Last Dose	X[d,]	X	X	X[b]		
Suspected Hypersensitivity/ Anaphylactic Reaction	X[h]		X[h]	X[h]		X[h]

Abbreviations: PK = Pharmacokinetic; CTGF = connective tissue growth factor; HAHA = human anti-human antibody; HAHA-NA = human anti-human antibody neutralizing antibody

a.) For all time points, the actual date and time of sample collection must be recorded, in addition to date and time of study treatment administration.
b.) Sample should be collected within 2 hours prior to dosing start.
c.) Both pre-dose and post-dose samples are required for PK. Pre-dose sample collection should be within 2 hours prior to dosing and post-dose should be between 1-4 hours after dosing end.
d.) Only one sample is required. A ±2 day window may be applied to the Day 8 and 15 sample.

e.) Samples with positive HAHA results will be tested for neutralizing antibody (HAHA-NA).

f.) Biomarkers will be collected for subjects in countries where the Regulatory Agencies allow collection of these samples
g.) PK and DNA samples will be collected for subjects who consent, except in countries where the Regulatory Agencies do not allow collection of these samples
h.) In the event of a suspected hypersensitivity/anaphylactic reaction, PK, HAHA, HAHA-NA, CTGF and tryptase. The Tryptase sample should be drawn within 1 to 6 hours of immunogenic reaction, and all other samples should be collected within 24 hours of the immunogenic reaction.

APPENDIX 3. HRCT CRITERIA AND HISTOPATHOLOGICAL CRITERIA FOR UIP PATTERN

HRCT Criteria for UIP Pattern

UIP Pattern

- Subpleural and basal predominant; distribution is often heterogeneous[1]
- Honeycombing with or without peripheral traction bronchiectasis or bronchiolectasis[2]

Probable UIP Pattern

- Subpleural and basal predominant; distribution is often heterogeneous
- Reticular pattern with peripheral traction bronchiectasis or bronchiolectasis
- May have mild ground-glass opacities (GGO)

Indeterminate for UIP

- Subpleural and basal predominant• Subtle reticulation; may have mild GGO or distortion ("early UIP pattern")
- CT features and/or distribution of lung fibrosis that do not suggest any specific etiology ("truly indeterminate for UIP")

Histopathological Criteria for UIP Pattern

UIP Pattern

- Dense fibrosis with architectural distortion (i.e., destructive scarring and/or honeycombing)
- Predominant subpleural and/or paraseptal distribution of fibrosis
- Patchy involvement of lung parenchyma by fibrosis
- Fibroblast foci
- Absence of features to suggest an alternate diagnosis

Probable UIP Pattern

- Some histologic features from column 1 are present but to an extent that precludes a definite diagnosis of UIP/IPF AND
- Absence of features to suggest an alternative diagnosis OR
- Honeycombing only

Indeterminate for UIP Pattern

- Fibrosis with or without architectural distortion, with features favoring either a pattern other than UIP or features favoring UIP secondary to another cause[3]
- Some histologic features from column 1, but with other features suggesting an alternative diagnosis[4]

[1] Variants of distribution: occasionally diffuse, may be asymmetrical.

[2] Superimposed CT features: mild GGO, reticular pattern, pulmonary ossification.

[3] Granulomas, hyaline membranes (other than when associated with acute exacerbation of IPF, which may be the presenting manifestation in some patients), prominent airway-centered changes, areas of interstitial inflammation lacking associated fibrosis, marked chronic fibrous pleuritis, organizing pneumonia. Such features may not be overt or easily seen to the untrained eye and often need to be specifically sought.

[4] Features that should raise concerns about the likelihood of an alternative diagnosis include a cellular inflammatory infiltrate away from areas of honeycombing, prominent lymphoid hyperplasia including secondary germinal centers, and a distinctly bronchiolocentric distribution that could include extensive peribronchiolar metaplasia.

APPENDIX 4. RADIATION RISK ASSESSMENT

The estimated radiation dose that results from participation in this study is based on an estimate is for a "standard patient" such as the MIRD phantom used in the ImPACT dose calculator spreadsheet. However, the ImPACT spreadsheet does not have a model for all CT platforms and for these the DLP*k method is used. For this method we assume a "standard sized" patient model, scan length is 25 cm (the length of the lungs for the MIRD Phantom) and a k factor of 0.014 mSv/mGy*cm for a thoracic scan (AAPM report 96 and European Guidelines 2000). For this study the expected doses are summarized in the table below.

Please NOTE that for each visit, one CT exam will be performed. That exam will consist of a required scan per imaging manual. Effective dose estimates provided: (For this study, visits occur at Baseline, Week 24 and Week 48 (i.e., 3 visits). Early Term scan is not required if a previous scan was completed within 4 months.

Summary	
TLC scan – CTDIvol	6.1 mGy
TLC scan – DLP (25 cm scan)	153 mGy*cm
TLC scan only – DLP	153 mGy*cm
Effective Dose per CT exam (TLC only)	2.14 mSv per exam
Effective Dose per year (TLC only) (assume 2 studies each calendar year)	4.28 mSv per year
Effective Dose over entire study (TLC only) (3 studies)	6.42 mSv over entire study

Average background radiation (excluding medical exposure to population):

For a comparison, the average annual exposure from background radiation:

Based on National Average:	
United States	3.0 mSv per year
Canada	1.8 mSv per year
United Kingdom	2.5 mSv per year
Australia	2.0 mSv per year
Germany	2.0 mSv per year
India	2-2.5 mSv per year

References:

ImPACT http://www.impactscan.org/ctdosimetry.htm

AAPM - American Association of Physicists in Medicine (2008). The measurement, Reporting and Management of Radiation Dose in CT. Report No. 96 of AAP M Task Group 23, (2008)

European Commission (2000). European guidelines on quality criteria for computed tomography. EUR 16262 EN. Luxembourg, Office for Official Publications of the European Communities.

U.S. NRC Fact Sheet on Biological Effects of Radiation

APPENDIX 5. GAP SCORE CALCULATION

NOTE: For the screening FVCpp value and GAP score calculation: the quality-controlled, Best-Test Review (BTR) assessment provided by the spirometry vendor over-reader, which is provided to sites within 48 hours after uploading the test, is to be used for eligibility assessment and GAP score calculation.

Use the FVCpp and DLCOpp that qualifies the subject for the study entry at screening
https://www.mdcalc.com/gap-index-idiopathic-pulmonary-fibrosis-ipf-mortality

		Points
Gender	Female	0
	Male	1
Age	≤ 60 years	0
	61-65 years	1
	> 65 years	2
Predicted Forced Vital Capacity (FVCpp)	> 75 %	0
	50-75%	1
	< 50%	2
Predicted Diffusing Capacity of the Lung for Carbon Monoxide (DLCOpp)	> 55%	0
	36-55%	1
	≤ 35%	2
	Unable to perform	3
Total possible points		8

GAP STAGE CALCULATION
(GAP Stage is derived from the GAP Score taken at screening)

Stage	Points
Stage I	0-3
Stage II	4-5
Stage III	6-8

APPENDIX 6. OPTIONAL, OPEN LABEL EXTENSION (OLE) PHASE OF PAMREVLUMAB

Objective:

This is an optional, open-label, single arm extension phase to provide continued access to pamrevlumab in subjects with IPF who completed the Week 48 visit of the main study and wish to participate in this OLE.

Efficacy Assessment:

The following efficacy assessments will be collected only as standard-of-care per each investigational site's real world practice and descriptively presented during the OLE period:

- FVC (L)
- FVC percent predicted (pp)
- Absolute FVCpp decline of ≥10%
- All-cause mortality
- Respiratory hospitalizations
- Acute IPF exacerbations
- Change in HRCT Quantitative Lung Fibrosis (QLF) volume (if HRCT is performed as part of routine patient care)

Safety Assessments:

Treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (TESAEs; including hypersensitivity/anaphylactic reactions) will be collected for 60 days after the last dose.

Design

This is a multi-center, single-arm, open-label extension (OLE) phase in which subjects who complete the Week 48 visit of the main study are eligible to participate, as per Eligibility Assessments below.

All subjects will receive pamrevlumab in an open-label manner. **NOTE**: No unblinding of subject's treatment assignment in the main study will occur for purposes of OLE participation.

During the OLE treatment period, co-administration of an approved IPF therapy (i.e., pirfenidone or nintedanib) is acceptable if clinically indicated in the Investigator's opinion, provided that the Investigator assesses the potential risks/benefits of combining approved IPF therapies with pamrevlumab. See also Section 5.1.10 of the main study for details.

Eligibility Assessments:

All subjects participating in the OLE phase must have completed the Week 48 visit of the main study. In addition, the Investigator must consider the subject to be suitable for continued participation in this phase, including ability to comply with study visits every 3 weeks for pamrevlumab infusions.

A signed and dated IRB/IEC-approved informed consent must be obtained before dosing start, and preferably at the Week 48 visit of the main study.

Male subjects with partners of childbearing potential and female subjects of childbearing potential (including those <1 year postmenopausal) must continue to use highly effective contraception methods (per Section 5.2.3) until 3 months after the last dose of study drug in the OLE phase.

Additional consideration for participation in the OLE

The following conditions are excluded for continued participation in this OLE phase:

- Female subjects who are pregnant or nursing.
- Use of any investigational drugs, or participation in a clinical trial with an investigational new drug, other than participation in the main study.
- History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies, or experienced an allergic or anaphylactic reaction to study drug or to any component of the excipient while participating in the main study.
- Subjects who withdrew informed consent while participating in the main study.
- The Investigator judges that the subject is not suitable for participation, or is unable to fully participate in the OLE phase and complete it for any reason, including inability to comply with study procedures and treatment, or any other relevant medical or psychiatric conditions

Study Duration

The OLE phase will end either after the last subject completes 48 weeks of treatment, or pamrevlumab is commercially for the indication of IPF, or the Sponsor decides to end the OLE phase, whichever occurs first.

Subjects may withdraw from the OLE at any time, for any reason; such subjects will have an early termination visits (EX ET) as soon as feasible. Subjects will have a Safety Follow-Up Visit 28 days after the last dose and have a final Safety Follow-Up Phone Call 60 days after the last dose.

Any assessments repeated as a part of main study, and all AEs prior to first dose in OLE are considered as a part of the main study.

Study Drug Dosing instructions and Visit Schedule

Each subject will receive pamrevlumab (30 mg/kg) every 3 weeks, using the weight obtained on Day 1 of the OLE phase (=EX Day 1), and every 24 weeks thereafter, for assessment of the

proper weight-based dosing regimen. EX Day 1 is expected to be scheduled 3 weeks (+7 days) after the Week 48 visit of the main study.

See Protocol Section 5 for detailed information on study drug infusions. Home infusions via home health care may be available during the OLE phase of the study at the discretion of the Investigator but such home infusions services will not be reimbursed by the Sponsor.

Important NOTE: The infusion durations and post-infusion observations periods have to be followed per Table 1 in Protocol Section 5.1.6, including the initial dosing and observations periods.

Visit windows are within ±7 days of the scheduled visit date from EX Week 3 through EX End of Treatment; however, visits should be at least 10 days apart, to ensure intervals of at least 10 days between study drug infusions.

All study visits will be performed in accordance with the OLE Schedule of Assessments presented in Appendix 6.

Missed Visits/Missed Doses

Scheduled visit dates are determined from the time of the first dose in OLE, which is defined as EX Day 1. If a subject misses a visit, the subject should resume the regular visit schedule at the next scheduled visit.

Missed doses are not to be made up through extra visits. If a subject misses more than two infusions in any 18-week period, or two sequential infusions, the FibroGen Medical Monitor should be notified. The reason for missed doses must be documented in the subject's clinical record.

NOTE: In accordance with FDA Guidance: During the COVID-19 pandemic, the visit modality (e.g.: in-person versus remotely) and scheduling maybe adjusted and conducted at the discretion of the Investigator, in accordance with the site's rules and recommendations, and using all necessary precautions. If a visit has to be done remotely, it can be conducted with any technology available to the site and study subjects.

Unscheduled Visits

Unscheduled visits/assessments will be captured accordingly in the clinical database

Subject Study Withdrawal Criteria

Subjects may withdraw from the OLE at any time, for any reason. Such subjects will have an early termination visit (EX ET) as soon as feasible. Study procedures to be performed during the EX ET visit can be found in the OLE Schedule of Assessments (SOA) presented in Appendix 6. Reasons for withdrawal will be captured on CRF.

Mandatory reasons for withdrawing from the OLE phase include:

- Any safety concern in the Investigator's opinion, that precludes further study participation
- Lung transplant

- Pregnancy
- Withdrawal of Consent

Safety Follow-Up

All subjects will have two Safety Follow-Up Visits:

- 28 days after the last dose
- 60 days after last dose: follow-up phone call, for a final safety assessment

The visit windows for the safety assessments are: 28 days +7 days and 60 days +7 days (phone call) after the last dose.

See OLE SOA in Appendix 6.

After the protocol-required reporting period (60 days after the last dose), the Investigator does not need to actively monitor subjects for SAEs. However, if the Investigator becomes aware of an SAE/death that may be possibly related to study treatment after the protocol-required reporting period, the Investigator may report the event to FibroGen as outlined in Section 7 of the main study. SAEs reported outside of the protocol-required reporting period will be captured within the safety database only as clinical trial cases for the purposes of expedited reporting.

Study Assessments:

All study assessments are done per the local standard of care with the exception of weight, pre and post infusion vital signs and pregnancy test. Refer to OLE SOA for details.

Vital Signs (including Weight) – Pre and Post pamrevlumab infusion

Vital signs to be collected include heart rate, blood pressure and temperature:

- Heart rate should be collected as beats/min
- Systolic and diastolic blood pressure should be collected from subjects in seated position (mmHg)
- Temperature should be taken as oral or tympanic and captured as °F or °C

Weight is collected at EX Day 1 and every 24 weeks thereafter for purposes of adjusting the weight-based dose if necessary.

Laboratory Evaluations

Local lab results, done as part of local standard-of-care, will not be recorded on CRF; local lab results will be reviewed by the Investigator for clinical significance and to determine appropriate reporting of adverse events (see Section 7.3.7 of the main study).

Pregnancy tests (performed pre-dose EX Day 1, and pre-dose at other times) for women of childbearing potential (WOCBP) only, via urine pregnancy test should be done by the site using site supplies. A positive urine pregnancy test must be confirmed by serum hCG using the site local labs for testing

PFTs and HRCT

PFTs and HRCTs are performed locally, and at a frequency according to local SOC, as determined by the Investigator. These tests will not be reimbursed by Sponsor.

All local spirometry results are entered into EDC.

If HRCT scans are done, they should be uploaded to the same Independent Radiology Review Group as for the main study.

Human Anti-Human Antibodies (HAHA)

Plasma samples will be collected for evaluation of human anti-human antibodies (HAHA), specific to the impact of neutralizing anti-drug antibodies (ADA) and the impact on immunogenicity, in all subjects participating in the OLE at the 28 days after last dose Safety Follow-Up Visit. A specialty laboratory will measure HAHA titers using a validated assay.

Samples with positive HAHA results will be tested for neutralizing antibody (HAHA-NA). The prevalence and duration of binding and neutralizing antibodies and the effect of these antibodies on the pharmacokinetics, pharmacodynamics markers, efficacy, and safety of pamrevlumab will be assessed.

Statistical Considerations:

Data collected during the extension period will be summarized descriptively.

OLE Schedule of Assessments

	Dosing Period [a, b]			Follow-Up Period [o]	
Study Week	EX-Day 1[c]	Q3 Weeks	Q24 Weeks / Last Dose / EX ET	28 Days after Last Dose[o]	60 Days after Last Dose (phone call)[o]
Assessment					
Weight	X [d]		X [d]		
Vital Signs [e]	X	X		X	
Infusions [e]	X	X			
AEs/SAEs [f]	X	X		X	X
Concomitant Medications [g]	X	X		X	X
Procedures and Nondrug Therapies [g]	X	X		X	X
PFTs (local) [h, i, j]	SOC		SOC		
Labs (local) [h, i, k]	SOC		SOC	SOC	
HRCT of Chest [i, l]	SOC		SOC	SOC	
Pregnancy Test (urine) (WOCBP) [m]	X		X	X	X
HAHA/HAHA-NA [n] (Plasma)				X	

Abbreviations: AE = adverse event; SAE = serious adverse event; ET = early termination; hCG = human chorionic gonadotropin; HRCT = high resolution computed tomography; PFTs = Pulmonary Function Test; (SOC) = not required at time-points noted above, but assessed per timing of local standard of care; EX = Extension; WOCBP = Women of childbearing potential; HAHA = human anti-human antibody ; HAHA-NA = human anti-human antibody neutralizing antibody

a.) Pamrevlumab is dosed Q3W starting with EX-Day 1. Visit windows of ±7 days, EX Week 3 through EX Follow-Up Period. Missed visits are not to be made up between scheduled visits, subject is to return for the next scheduled visit
b.) Unscheduled visit assessments (procedures) will be determined by the investigator. During the COVID-19 pandemic, the visit modality (e.g.: in-person versus remotely) and scheduling maybe adjusted and conducted at the discretion of the Investigator, in accordance with the site's rules and recommendations, and using all necessary precautions. If a visit has to be done remotely it can be conducted with any technology available to the site and study subjects.
c.) Ensure subject has signed the informed consent at or before Week 48 visit of the main study and eligibility considerations have been assessed prior to EX Day 1 infusion.
d.) Weight will be measured at EX Day 1 and every 24 weeks thereafter to determine dose for the subsequent 24-week interval.
e.) Infusions must be at least 10 days apart. Vital signs (blood pressure, pulse, and temperature) must be recorded prior to, and after each infusion.
f.) See Section 7 of the main protocol for safety assessments.
g.) Concomitant medications and nondrug therapies are recorded after signing of informed consent and ending 28 days after the last dose. Subjects will also be contacted by phone for a follow-up at 60 days after the last dose for a final safety assessment. If the subject experiences an SAE, it must be reported within 24 hours of awareness (see Section 7.3 for details). If an AE/SAE occurs during this timeframe, concomitant medications and nondrug therapies if used to treat the AE/SAE, are also collected.
h.) Local Labs and PFTs are performed pre-dose.
i.) Collected according to local standard of care.

j.) PFT will be done locally, and at a frequency per local SOC, and recorded on CRF whenever they are performed locally.
k.) Labs will be done locally and at a frequency per local SOC. Lab data will NOT be recorded on CRF. Clinically significant laboratory abnormalities will be reported in the context of AE reporting; do not report non-clinically significant lab abnormalities as AE
l.) HRCT scans will be performed at a frequency per local SOC. Any HRCT scan will be uploaded to central HRCT radiology vendor
m.) Pregnancy tests (performed pre-dose EX Day 1, and pre-dose at other times) for WOCBP only, via urine pregnancy test. A positive urine pregnancy test must be confirmed by serum hCG. In each case of delayed menstrual period (over one month between menstruations) confirmation of absence of pregnancy is strongly recommended. This recommendation also applies to WOCBP with infrequent or irregular menstrual cycles.
n.) All subjects participating in the OLE will have a HAHA sample taken 28 days after the last dose. Samples with positive HAHA results will be tested for neutralizing antibody (HAHA-NA).
o.) Subjects who withdraw from the study, for any reason, should attend a Follow-Up Period visit 28 days after the last dose. These subjects will also be contacted by phone for a follow-up at 60 days after the last dose for a final safety assessment. Such subjects will have an early termination visit (EX ET) as soon as feasible. If the subject experiences an SAE, it must be reported within 24 hours of awareness (see Section 7.3 for details).