CLINICAL STUDY PROTOCOL

STUDY TITLE:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG-3019 in Patients with Idiopathic Pulmonary Fibrosis
PROTOCOL NUMBER:	FGCL-3019-067
SPONSOR:	FibroGen, Inc. 409 Illinois Street San Francisco, California 94158 USA
IND NUMBER:	11212
EudraCT NUMBER:	2014-005658-20
INVESTIGATIONAL PRODUCT:	FG-3019
INDICATION:	Idiopathic Pulmonary Fibrosis
FIBROGEN MEDICAL MONITOR:	Name: [redacted] Title: [redacted] Work Phone: [redacted] Cell Phone: [redacted] E-mail Address: [redacted]
ORIGINAL PROTOCOL / DATE:	15 January 2013
AMENDMENT 1.0:	09 December 2014
AMENDMENT 2.0:	09 March 2015
AMENDMENT 3.0:	28 May 2015
AMENDMENT 5.1:	12 December 2016 (Regional: Australia, Bulgaria, India, New Zealand and South Africa)

CONFIDENTIALITY STATEMENT

STUDY ACKNOWLEDGEMENT

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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 drug and the study.

I will conduct the trial in accordance with the guidelines of GCP including the archiving of essential documents, the Declaration of Helsinki, the International Conference on Harmonisation (ICH) E6 Guideline for GCP, the FDA, any applicable local health authority, and Institutional Review Board (IRB) requirements.

Investigator Name (Printed)	Institution
Signature	Date

CONFIRMATION OF PROTOCOL APPROVAL

Original: 15 January 2013
Amendment 1.0: 09 December 2014
Amendment 2.0: 09 March 2015
Amendment 3.0: 28 May 2015

Amendment 5.1: 12 December 2016

This protocol is approved by FibroGen.

[redacted]

Date

FibroGen Inc.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AEs	adverse events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
BMPs	bone morphogenetic proteins
BP	blood pressure
CCN	cysteine-rich 61/CTGF/nephroblastoma overexpression
CFR	Code of Federal Regulations
CPAP	continuous positive airway pressure
CRF	case report form
CTGF	connective tissue growth factor
DLCO	diffusing capacity of the lung for carbon monoxide
DNA	deoxyribonucleic acid
DMC	Data Monitoring Committee
ECG	electrocardiogram
ECM	extracellular matrix
EMT	epithelial-mesenchymal transition
EOS	end of study
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FG-3019	FibroGen-3019 (recombinant human monoclonal antibody)
FVC	forced vital capacity
GCP	Good Clinical Practice
HAHA	human anti-human antibody
HRQoL	health-related quality of life
Hb	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HRCT	high resolution computed tomography
HSPG	heparin sulfate proteoglycans
ICF	informed consent form
ICH	International Conference on Harmonisation
IND	Investigational New Drug

INR	international normalized ratio
IL-1β	interleukin-1 beta
IL-4	interleukin-4
IL-10	interleukin-10
IL-13	interleukin-13
IL-17	interleukin-17
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IV	intravenous, intravenously
kDa	kilodalton
LRP	lipoprotein receptor-related protein
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NAC	N-acetylcysteine
NCI	National Cancer Institute
NCI CTCAE, v4.0	NCI Common Terminology Criteria for Adverse Events, Version 4.0
NSAIDs	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
OTC	over-the-counter
PDGF	platelet-derived growth factor
PFTs	pulmonary function tests
PP	per protocol
SAEs	serious adverse event(s)
SaO_2	oxyhemoglobin saturation
SAP	statistical analysis plan
SGRQ	Saint George's Respiratory Questionnaire
SPARC	secreted protein acidic and rich in cysteine
TE-AE	treatment-emergent adverse event
TE-SAE	treatment-emergent serious adverse event
TGF-β	transforming growth factor-β
TLC	total lung capacity
TNF-α	tumor necrosis factor-α
UIP	usual interstitial pneumonia
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
WHODrug	World Health Organization Drug Dictionary

AMENDMENT 5.1: KEY CHANGES FROM AMENDMENT 3.0

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

Key Change	Rationale	Sections Affected
The Follow Up / End of Study Visit is now scheduled at 4 weeks after the last dose of study drug (instead of 10 weeks).	The change in the schedule of the Follow Up/End of Study Visit is supported by pamrevlumab's drug PK characteristics and available safety data.	Protocol Synopsis, Sections 4 and 11, Appendix 2 and Appendix 3.

PROTOCOL SYNOPSIS

Study Title:	A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of FG-3019 in Patients with Idiopathic Pulmonary Fibrosis
Protocol Number:	FGCL-3019-067, Amendment 5.1
Investigational Product:	FG-3019
Target Population:	Male or female subjects, 40 to 80, years old who have IPF diagnosed in accordance with criteria published in the 2011 international consensus guidelines. Subjects who have failed or are intolerant of products approved for treating IPF are eligible.
IND Number:	011212
Study Phase:	Phase 2
Study Centers Planned:	Approximately 60 centers in the United States and other countries
Number of Subjects Planned:	Approximately 136
Objective:	The overall objective of this study is to evaluate the safety, tolerability, and efficacy of FG-3019 in subjects with IPF
Primary Safety Objective:	• To determine the safety and tolerability of FG-3019 administered at a dose of 30 mg/kg by intravenous (IV) infusion every 3 weeks
Primary Efficacy Objective:	• To determine the effect of FG-3019 on forced vital capacity (FVC) (percent of predicted value) in the target population
Secondary Efficacy Objectives:	• To evaluate the effect of FG-3019 on the extent of pulmonary fibrosis as measured by high resolution computed tomography (HRCT) scans of the chest • To evaluate the relationship between changes in quantified scores of pulmonary fibrosis and clinical outcomes • To evaluate the effect of FG-3019 on progression of IPF and the frequency of respiratory-related hospitalizations and respiratory-related mortality • To evaluate the effect of FG-3019 on health-related quality of life (HRQoL)

Exploratory Efficacy Objectives:	• To evaluate the effect of FG-3019 on FVC (liters) • To evaluate the effect of FG-3019 on a panel of serum and plasma biomarkers • To evaluate the relationship between known chromosomal loci associated with IPF and the response to FG-3019
Study Design:	This is a Phase 2, randomized, double-blind, placebo-controlled multicenter study. Subjects who have failed or are intolerant of products approved for treating IPF are eligible. Other 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 may be randomized to placebo. <u>Randomized Treatment Period</u> Subjects who sign informed consent will undergo screening visits to determine their eligibility. Eligible subjects who provide written informed consent will be stratified based on prior therapy with nintedanib and/or pirfenidone (yes/no) and randomized (1:1) to one of two treatment arms: Arm A: FG-3019, 30 mg/kg Arm B: Matching placebo Treatment should begin within 42 days of the first screening visit. Study Drug (FG-3019 [30 mg/kg] or placebo) will be administered by IV infusion every 3 weeks for a total of 16 infusions over 48 weeks. At the time of roll over into the Extended Treatment Period, the study subject treatment assignment will be unblinded only to designated personnel not associated with the study at FibroGen Inc. <u>Extended Treatment Period</u> *Subjects Enrolled under the Original Protocol and Assigned to Arm A: FG-3019* All subjects in Arm A whose FVC percent predicted value shows less than 3% absolute decrease from baseline in the Randomized Treatment Period will be offered participation in an Extended Treatment Period. These subjects may continue treatment until FVC percent predicted decreases 3% or more on two consecutive scheduled evaluations compared to the original pre-treatment baseline. *Subjects Enrolled Under Amendment 1 or Subsequent Amendments and Assigned to Arm A: FG-3019* All subjects in Arm A whose FVC percent predicted value is greater than the original pre-treatment baseline in the Randomized

	Treatment Period will be offered participation in an Extended Treatment Period and may continue treatment until FVC percent predicted is equal to or less than the pre-treatment baseline on two consecutive scheduled evaluations. *Subjects Enrolled Under the Original Protocol, Amendment 1 or Subsequent Amendments Assigned to Arm B: Placebo* All subjects assigned to Placebo (Arm B) will be offered participation in the Extended Treatment Phase for 45 weeks. Placebo subjects in the extension study are treated identically to subjects randomized to FG-3019 in Amendment 1, except for the fact that the baseline for these patients is the time at which they are enrolled into the extension phase (Baseline for Placebo subjects is Week 48 value). Change in FVC percent predicted during the extended treatment phase will be compared to this new baseline. Those subjects whose FVC percent predicted value at Week 48 of the Extension Period is greater than the new baseline may continue treatment with FG-3019 until FVC percent predicted is equal to or less than the baseline on two consecutive scheduled evaluations. See Section 4.2.3 for details regarding the Extended Treatment Period.
Study Periods	Screening Period (up to 6 weeks) Randomized Treatment Period (48 weeks) Extended Treatment Period (sub-set of subjects [see definition above]; duration based on changes in FVC (Section 4.2.3) Follow-Up Period (all subjects will undergo a final safety assessment at 4 weeks after last dose of study drug.)
Study Population	Male or female subjects 40 to 80 years old who have IPF diagnosed in accordance with criteria published in the 2011 international consensus guidelines.
Diagnosis and Main Eligibility Criteria	**Inclusion Criteria:** 1. Age 40 to 80 years, inclusive. 2. Diagnosis of IPF as defined by current international guidelines (Raghu, 2011). Each subject must have one of the following: (1) *Usual Interstitial Pneumonia* (*UIP) Pattern* on an available HRCT scan; or (2) *Possible UIP Pattern* on an available HRCT scan and surgical lung biopsy within 4 years of Screening showing *UIP Pattern* (HRCT criteria for *UIP Pattern* and *Possible UIP Pattern* and histopathological criteria for *UIP Pattern* are described in Appendix 4). 3. History of IPF of ≤5 years duration with onset defined as the date of the first diagnosis of IPF by HRCT or surgical lung

	biopsy. 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, as determined by the HRCT central reader. 5. FVC percent of predicted value ≥55% at Screening. 6. Female subjects of childbearing potential and male subjects with female partners of childbearing potential are required to use double barrier contraception methods during the conduct of the study and for 3 months after the last dose of study drug. **Exclusion Criteria**: 1. Female subjects who are pregnant or nursing. 2. Infiltrative lung disease other than IPF, including any of the other types of idiopathic interstitial pneumonias (Travis, 2013); 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 and connective tissue diseases. 3. HRCT scan findings at Screening are inconsistent with *UIP Pattern*, as determined by the HRCT central reader (a definition of "Inconsistent with *UIP Pattern*" is provided in Appendix 4). 4. Pathology diagnosis on surgical lung biopsy is anything other than *UIP Pattern*, as determined by the local pathologist (Appendix 4). 5. The Investigator judges that there has been sustained improvement in the severity of IPF during the 12 months prior to Screening, based on changes in FVC, diffusing capacity of the lung for carbon monoxide (DLCO), and/or HRCT scans of the chest. 6. 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 endpoints in the protocol or otherwise preclude the subject's participation in the study. 7. History of any other respiratory, cardiovascular, renal, hepatic, metabolic, neurologic, hematologic, or other medical conditions that, in the opinion of the Investigator, would preclude the subject's participation in the study. 8. 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. 9. Upper or lower respiratory tract infection of any type within 4 weeks of Screening. 10. Acute exacerbation of IPF within 3 months of Screening. 11. Evidence of obstructive lung disease by any of the following criteria: forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.70 or extent of emphysema on HRCT greater than the extent of fibrosis on HRCT. 12. DLCO <30% of predicted value. 13. High likelihood of lung transplantation (in the opinion of the Investigator) within 6 months after Day 1. 14. Poorly controlled chronic heart failure; clinical diagnosis of cor pulmonale requiring specific treatment; or severe pulmonary hypertension requiring specific treatment that, in the opinion of the Investigator, would preclude the subject's participation in the study. 15. Use of medications to treat IPF within 5 half-lives of Day 1 dosing. If monoclonal antibodies were used, the last dose of the antibody must be at least 4 weeks before Day 1 dosing. 16. Use of any investigational drugs, including any investigational drugs for IPF, within 4 weeks prior to Day 1 dosing. 17. History of cancer diagnosis of any type in the 3 years preceding Screening, excluding non-melanomatous skin cancer, localized bladder cancer, or in situ cancers. 18. Clinically significant trauma or surgical procedures within 4 weeks prior to dosing. 19. Planned elective surgery during the study including 4 weeks following the final dose of Study Drug. 20. History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies. 21. 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. 22. Body weight >130 kg. 23. Previous treatment with FG-3019. 24. Inadequate IV access.

Concomitant Medications/Therapies	Oral prednisone or equivalent oral corticosteroid (up to 10 mg daily) and N-acetylcysteine (NAC) (up to 1800 mg daily) are allowed. Medications that, in the opinion of the Investigator, are required for the treatment of acute exacerbations of IPF during the Treatment Period are acceptable. Female subjects of childbearing potential and male subjects with female partners of childbearing potential are required to use double barrier contraception methods during the conduct of the study and for 3 months after the last dose of study drug.
Investigational Product, Dose, and Mode of Administration	FG-3019 is a fully human IgG_1 kappa monoclonal antibody that binds to connective tissue growth factor (CTGF). It will be administered at a dose of 30 mg/kg by IV infusion in a total volume of 250 mL (up to 400 mL if necessary) normal saline every 3 weeks.
Reference Therapy (and/or Placebo), Dose, and Mode of Administration	Placebo (identical to the FG-3019 vehicle) will be handled and administered in a manner that is identical to FG-3019.
Safety Endpoints and Assessments	• Adverse events and serious adverse events (SAEs) • Laboratory test abnormalities • 12-lead ECGs • Physical examinations • Human anti-human antibodies (HAHA)
Efficacy Endpoints and Assessments	**Primary efficacy endpoint** • Change from baseline in FVC (percent of predicted value) at Week 48. **Secondary efficacy endpoints** • Change in pulmonary fibrosis score by quantitative HRCT at Week 24, Week 48, and later time points. • Change from baseline in HRQoL at Week 24, Week 48, and later time points. • Progression of IPF, defined as time from Day 1 to any one of the following: o Death from any cause o Absolute decline FVC percent of predicted value of ≥10% not due to intercurrent illness, confirmed by repeat spirometry

	○ Clinical diagnosis of IPF progression. • Proportion of subjects with at least one respiratory-related hospitalization. • Proportion of subjects with respiratory-related death, censored at Week 52. • Categorical assessment of absolute change from baseline in FVC percent of predicted value at Week 48. **Exploratory efficacy endpoints** • Change from baseline to Week 24 and from baseline to Week 48 in FVC (liters). • Change from Day 1 to Week 48 in a panel of serum and plasma biomarkers that will be determined by FibroGen. • Relationship between known chromosomal loci associated with IPF and the response to FG-3019.
Statistical Methods:	This study is planned to enroll approximately 136 subjects, who will include a target of 110 subjects who are seeking first-line therapy and approximately 26 subjects who failed pirfenidone and/or nintedanib treatment. First line therapy is defined as no prior therapy with pirfenidone and/or nintedanib or <10% relative decrease in FVC % predicted while receiving either pirfenidone or nintedanib. Pirfenidone and/or nintedanib failure is defined as having ≥10% relative decrease in FVC % predicted during prior pirfenidone and/or nintedanib treatment. The effect of first-line treatment is the primary interest of the study and is the basis for sample size estimates. Assuming a 10% dropout rate and a common standard deviation of 7.3, a sample size of 55 subjects per arm in the primary analysis population provides approximately 80% power to detect a treatment difference of 4.2 in change from baseline to Week 48 in percent predicted FVC, using a two-sample t-test at the two-sided significance level of 0.05. If the treatment effect in the pirfenidone and/or nintedanib treatment failure group is similar to that in the general population, the two subgroups will be combined to achieve higher power. The primary efficacy analysis is to compare the treatment arms in change from baseline to Week 48 in FVC % predicted. A rank ANCOVA model will be used. A repeated measures model utilizing all observed data will be used for sensitivity analyses. Logistic regression and Fisher's exact test will be used to compare categorical endpoints. The Cox regression model will be used in time-to-event endpoints. All efficacy and safety data will be summarized descriptively by treatment arm.

	Treatment effect will be evaluated in various subgroups of interest. Unblinded analyses will be performed after all subjects have either completed the Week 48 assessments or discontinued the study.

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.

1 INTRODUCTION

1.1 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, 2011). 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). 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). Extracellular matrix 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, 2006a). 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), oxidant stress (Beeh, 2002, Cantin, 1987, Daniil, 2008, Hunninghake, 2005, Waghray, 2005), 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 a key cytokine thought to drive the fibrotic process in IPF (Agostini, 2006, Bergeron, 2003). Other cytokines, 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 have been implicated in this complex process of cellular interactions among activated epithelial cells, myofibroblasts, fibroblasts, macrophages, endothelial cells, and lymphocytes (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 are gaining increased attention

(Lama, 2006, Strieter, 2009, Willis, 2006). Connective tissue growth factor has been shown to be a central mediator of tissue remodeling and fibrosis and has been reported to be a downstream mediator that is essential for the fibrotic activity of TGF- β (Blom, 2002, Grotendorst, 1997).

The epidemiology of IPF is not clearly defined. Retrospective data from a large health care claims database suggest that the prevalence of IPF ranges from 14.0 to 42.7 per 100,000 and the annual incidence ranges from 6.8 to 16.3 per 100,000, depending on the strictness of the diagnostic criteria employed (Raghu, 2006b). Among persons aged 18 and older in the United States, as many as 89,000 people have been diagnosed with IPF, and as many as 34,000 are newly diagnosed each year (Raghu, 2006b). A recent 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). The prevalence of IPF increases with age, and most IPF patients are age 60 or older at the time of diagnosis. 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 forced expiratory volume in 1 second (FEV_1/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, characterized by worsening dyspnea over one month or less, new diffuse lung infiltrates and ground-glass opacities on HRCT, and worsening hypoxemia in the absence of pulmonary infection or other identifiable causes, punctuate the natural course of the disease, especially in its pre-terminal phase (Collard, 2007, Hyzy, 2007, Kim, 2006, Walter, 2006). These exacerbations are often fatal events (Hyzy, 2007, Kim, 2006, Martinez, 2005). The etiology of acute exacerbations of IPF is unknown, and its pathogenesis is not well understood (Collard, 2007). IPF-related exacerbations occurred at a rate of 0.13 per person-year in the Olmstead County population-based study reported above (Fernandez Perez, 2010). 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, reticular infiltrates with basal predominance, honeycombing, and absence of the features suggesting a different diagnosis) in the appropriate clinical setting (Raghu, 2011). Surgical lung biopsy, long considered the gold standard for diagnosis of IPF, is now performed in a minority of cases because of the morbidity associated with the procedure and increasing acceptance of diagnosis by HRCT (Raghu, 1999). Nevertheless, combined clinical, radiologic, and pathologic correlation is recommended as the optimal approach to diagnosis.

The histopathologic pattern of UIP is a heterogeneous, patchy involvement of lung parenchyma with areas of relatively normal lung tissue adjacent to areas that display architectural distortion ("spatial heterogeneity"), infiltrates of fibroblasts and myofibroblasts, collagen deposition, honeycombing, Type II pneumocyte hyperplasia, smooth muscle hyperplasia, and buds of young proliferating fibroblasts adjacent to alveoli called "fibroblastic foci" (Raghu, 2011, Selman, 2006, Visscher, 2006). 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, 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 recent 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), but most IPF patients are not eligible for transplantation because of their age or comorbid conditions.

The natural course of IPF is variable. Patients with IPF typically experience slowly progressive worsening of lung function over time, but some experience rapid declines and frequent hospitalizations in the late stage of the disease (Martinez, 2005). In two Phase 3 clinical trials examining the safety and efficacy of pirfenidone in patients with IPF, the mean decline in percent predicted FVC 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. The median survival is about 7 years after the onset of

symptoms and 3 years after the initial clinic visit (King, Jr., 2001). In patients over the age of 70, the median survival is about 15 months after the initial clinic visit (King, Jr., 2001).

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). The high mortality rate of IPF and the modest efficacy of approved drugs to treat IPF underscore the need to explore new pharmacologic approaches to manage this devastating disease.

1.2 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). 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 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).

1.3 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.

1.4 Investigational Product FG-3019

FG-3019 is a fully human, recombinant DNA-derived, IgG_1 kappa monoclonal antibody that binds to CTGF in the N-terminal domain 2, with high affinity (K_d = 0.1–0.2 nM). The antibody, which has a molecular weight of approximately 150 kDa and contains 1326 amino acids, has been shown to interfere with the activity of CTGF. For additional information on FG-3019, please refer to the current Investigator's Brochure.

1.5 Clinical Trial Experience with FG-3019

The clinical trial experience with FG-3019 includes seven clinical studies that are described in the Investigator's Brochure (Version 13, 18 December 2014). Overall safety experience with FG-3019 has been favorable in studies involving subjects with IPF, pancreatic cancer, liver fibrosis due to hepatitis B, and diabetic kidney disease.

In the Investigator Brochure, exposure of subjects to FG-3019 is displayed in Table 1. Twenty one subjects with IPF received a single dose of FG-3019, 89 subjects with IPF received multiple doses in an open label trial, and 27 subjects with IPF have received multiple doses of blinded study drug (FG-3019 or placebo) in the current trial Overall, FG-3019 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 FG-3019 treatment groups. Infusions of FG-3019 have been well tolerated. No infusion has been stopped due to AEs. There is no apparent pattern to the SAEs observed during clinical trials, and all SAEs, except one case of pain in extremity, were considered by the Sponsor as unrelated to study drug. See the Investigator Brochure for additional information.

1.6 Rationale for FG-3019 in Idiopathic Pulmonary Fibrosis

The observations that CTGF is a central mediator in the process of fibrosis suggest a potential role for FG-3019 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).

A murine model of chronic lung fibrosis demonstrated that FG-3019 attenuated radiation-induced lung remodeling (Huber, 2010). In mice treated with FG-3019 for 8 weeks starting 3 or 16 weeks after irradiation, no tissue remodeling or fibrosis was observed 30 weeks after irradiation, and lung function, as measured by partial pressure of oxygen in arterial blood, was normalized compared with mice in the irradiated control groups. Mice treated with FG-3019 starting 16 weeks after irradiation displayed a significant reversal of lung density, which was measured by computed tomography. FG-3019 also improved survival in most groups that received FG-3019. Mice that received FG-3019 starting 3 weeks after irradiation had a survival rate of 70% at the end of the study (48 weeks after irradiation) compared with 0% survival in the irradiated controls (Huber, 2010). In another study, administration of FG-3019 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 FG-3019 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 FVC percent of predicted value (Raghu, 2012). In 2012, the FDA granted Orphan Drug Designation to FG-3019 for the treatment of IPF. A randomized, double-blind, placebo-controlled trial of FG-3019 30 mg/kg is warranted at this time to further assess safety, tolerability, and efficacy in subjects with IPF.

2 OBJECTIVES

The overall objective of this study is to evaluate the safety and tolerability of FG-3019 in subjects with IPF, and the efficacy of FG-3019 for attenuating fibrosis and loss of FVC in these subjects.

2.1 Primary Safety Objective

To determine the safety and tolerability of FG-3019 administered at a dose of 30 mg/kg by IV infusion every 3 weeks.

2.2 Primary Efficacy Objective

To determine the effect of FG-3019 on FVC (percent of predicted value) when administered at a dose of 30 mg/kg by IV infusion every 3 weeks for 45 weeks in the target population.

2.3 Secondary Efficacy Objectives

1. To evaluate the effect of FG-3019 on the extent of pulmonary fibrosis as measured by HRCT scans of the chest.
2. To evaluate the relationship between changes in quantified scores of pulmonary fibrosis and clinical outcomes.
3. To evaluate the effect of FG-3019 on progression of IPF and the frequency of respiratory-related hospitalizations and respiratory-related mortality.
4. To evaluate the effect of FG-3019 on health-related quality of life (HRQoL).

2.4 Exploratory Efficacy Objectives

1. To evaluate the effect of FG-3019 on FVC (liters).
2. To evaluate the effect of FG-3019 on a panel of serum and plasma biomarkers.
3. To evaluate the relationship between known chromosomal loci associated with IPF and the response to FG-3019.

3 ENDPOINTS AND ASSESSMENTS

3.1 Safety Endpoints and Assessments

- AEs and SAEs
- Laboratory test abnormalities (graded by NCI Common Terminology Criteria for Adverse Events [NCI CTCAE, v4.0])
- 12-lead electrocardiograms (ECGs)
- Physical examinations
- Human anti-human antibody (HAHA)

3.2 Efficacy Endpoints and Assessments

3.2.1 Primary Efficacy Endpoint

- Change from baseline in FVC (percent of predicted value) at Week 48.

3.2.2 Secondary Efficacy Endpoints.

- Change in pulmonary fibrosis score by quantitative HRCT at Week 24, Week 48, and later time points.
- Change from baseline in HRQoL at Week 24, Week 48, and later time points.
- Progression of IPF, defined as time from Day 1 to any one of the following:
  - Death from any cause
  - Absolute decline in FVC % of predicted value of ≥10% not due to intercurrent illness, confirmed by repeat spirometry.
  - Clinical diagnosis of IPF progression.
- Proportion of subjects with at least one respiratory-related hospitalization.
- Proportion of subjects with respiratory-related death, censored at Week 52.
- Categorical assessment of absolute change from baseline in FVC percent of predicted value at Week 48.

3.2.3 Exploratory Efficacy Endpoints

- Change from baseline to Week 24 and from baseline to Week 48 in FVC (liters).
- Change from Day 1 to Week 48 in a panel of serum and plasma biomarkers that will be determined by FibroGen.
- Relationship between known chromosomal loci associated with IPF and the response to FG-3019.

4 STUDY DESIGN

4.1 Study Population

Male or female subjects, 40 to 80, years old who have IPF diagnosed in accordance with criteria published in the 2011 international consensus guidelines. Subjects who have failed or are intolerant of products approved for treating IPF are eligible.

4.2 Description of the Study

This is a Phase 2, randomized, double-blind, placebo-controlled multicenter study. Subjects who have failed or are intolerant of products approved for treating IPF are eligible. Other 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 may be randomized to placebo.

Subjects who sign informed consent will undergo screening visits to determine their eligibility. Eligible subjects will be stratified based on prior therapy with nintedanib and/or pirfenidone (yes/no) and randomized (1:1) to one of two treatment arms:

Arm A: FG-3019, 30 mg/kg

Arm B: Matching placebo

Approximately 60 centers in the United States and other countries will participate in this clinical trial.

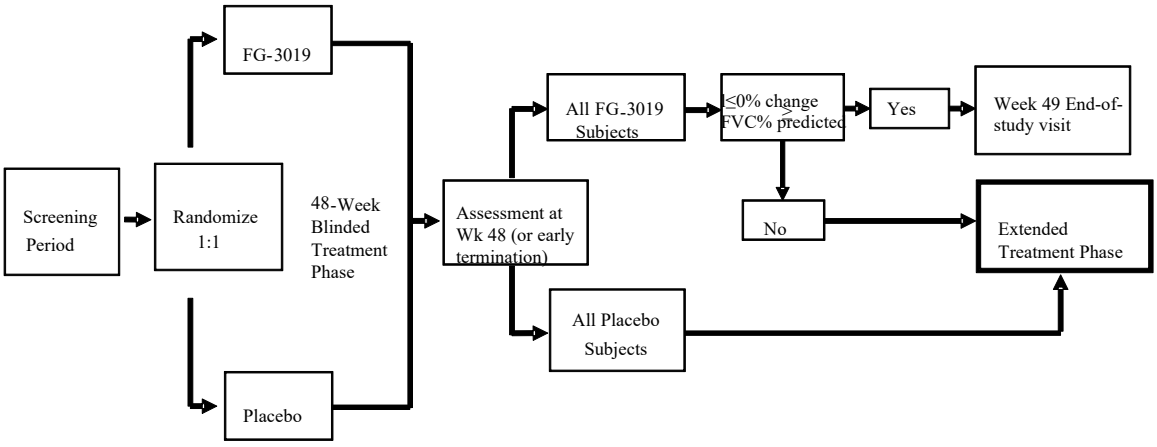
4.2.1 Study Periods

There are four study periods:

- Screening Period (up to 6 weeks)
- Randomized Treatment Period (48 weeks)
- Extended Treatment Period (sub-set of subjects [see definition above]; duration based on changes in FVC (Section 4.2.3)
- Follow-Up Period (all subjects will undergo a final safety assessment at 4 weeks after last dose of study drug.)

A schematic overview of the trial is provided in Figure 1.

Figure 1. Study Schema



4.2.2 Randomized Treatment Phase

Treatment should begin within 42 days of the first screening visit. Study Drug (FG-3019 [30 mg/kg] or placebo) will be administered by IV infusion every 3 weeks for a total of 16 infusions over 48 weeks.

The schedule of assessments of safety and efficacy are provided in Appendix 1 and Appendix 2. Safety and tolerability will be monitored closely by FibroGen. Cumulative safety experience will be evaluated by FibroGen on a regular basis. Final efficacy assessment is in Week 48. Subjects who do not enter the Extended Treatment Phase will undergo end-of-study (EOS) assessment (Appendix 3) on Week 49 (4 weeks after last dose of study drug).

After all subjects complete Week 48 evaluations or prematurely discontinue the study, data will be cleaned and locked for the primary analysis of efficacy and safety.

4.2.3 Extended Treatment Period (Weeks Identified with –EX Suffix)

At the time of roll over into the Extended Treatment Period, the study subject treatment assignment will be unblinded only to designated personnel not associated with the study at FibroGen Inc. To continue to maintain the study blind, the first dose for all subjects in the Extended Treatment Period will be administered over approximately 2 hours.

4.2.3.1 Subjects Enrolled under the Original Protocol and Assigned to Arm A: FG-3019

All subjects in Arm A whose FVC percent predicted value shows less than 3% absolute decrease from baseline in the Randomized Treatment Period will be offered participation in an Extended Treatment Period. These subjects may continue treatment until FVC percent predicted decreases 3% or more on two consecutive scheduled evaluations compared to the original pre-treatment baseline.

4.2.3.2 Subjects Enrolled Under Amendment 1 or Subsequent Amendments and Assigned to Arm A: FG-3019

All subjects in Arm A whose FVC percent predicted value is greater than the original pre-treatment baseline in the Randomized Treatment Period will be offered participation in an Extended Treatment Period and may continue treatment until FVC percent predicted is equal to or less than the pre-treatment baseline on two consecutive scheduled evaluations.

4.2.3.3 Subjects Enrolled Under the Original Protocol or Amendment 1 and Subsequent Amendments Assigned to Arm B: Placebo

All subjects assigned to Placebo (Arm B) will be offered participation in the Extended Treatment Phase for 45 weeks. Placebo subjects in the extension study are treated identically to subjects randomized to FG-3019 in Amendment 1, except for the fact that the baseline for these patients is the time at which they are enrolled into the extension phase (Baseline for Placebo subjects is Week 48 value). Change in FVC percent predicted during the extended treatment phase will be compared to this new baseline. Those subjects whose FVC percent predicted value is either equal to or greater than the new baseline may continue treatment with FG-3019 until FVC percent predicted is equal to or less than the baseline on two consecutive scheduled evaluations. See Section 4.2.3 for details regarding the Extended Treatment Period.

4.2.4 End of Treatment and Follow-up

4.2.4.1 Randomized Treatment Phase

- Subjects assigned to either FG-3019 or placebo who discontinue treatment before week 48 should undergo end of treatment and safety assessment visits (Appendix 3).
- Subjects who were assigned to FG-3019 complete 48 weeks of treatment and are not going on to the Extended Treatment Period should undergo a Safety Assessment visit (Appendix 3); Week 48 evaluation is identical to End of Treatment visit. Thus, subjects who complete Week 48 and are not eligible for the extension study only need the final safety assessment. Subjects who enter the Extended Treatment Period do not need a final safety assessment because they are continuing treatment).
- Subjects who were assigned to placebo who complete 48 weeks of treatment but do not enter the Extended Treatment Period should undergo a safety assessment as described in Appendix 3.

4.2.5 Extended Treatment Phase

- Subjects who were assigned to FG-3019 and continue in the Extended Treatment Period will undergo early termination and safety assessment visits (Appendix 3) at the time they discontinue treatment **unless** they discontinue treatment at Week 48 EX. In this case, they only undergo the safety assessment visit. This is applicable whether subjects stop before or after week 48 EX.
- Subjects who were assigned to placebo, and receive FG-3019 in the Extended Treatment Phase and then discontinue treatment at Week 48 of the Extended Treatment Period should undergo a Safety Assessment visit (Appendix 3).

- Subjects who were assigned to placebo, and receive FG-3019 in the Extended Treatment Phase who discontinue treatment prior to Week 48 of the extended treatment period will undergo early termination and safety assessment visits (Appendix 3) at the time they discontinue treatment.

4.2.6 Placebo Control Group

In order to evaluate the effect of treatment with FG-3019 on the endpoints described in Section 3, approximately 50% of subjects will be randomized to placebo treatment (Arm B).

The placebo control is appropriate for this trial given the population of participating subjects. Enrolled subjects are those who have failed or are intolerant of approved therapies and who refuse to receive approved therapies. For these subjects the only treatment option is best supportive care, which is available to them within this protocol, and optionally experimental treatment. Therefore, placebo control, which provides for the best supportive care, is appropriate and ethical. Additionally, subjects who are randomized to placebo will be offered crossover treatment to the active arm after completion of the initial 48-week treatment period.

4.3 Treatment Assignment

Subjects are stratified by prior therapy with pirfenidone and/or nintedanib (yes/no) and randomized 1:1 to FG-3019 or placebo using an Interactive Web Response System (IWRS).

4.4 Blinding

4.4.1 Rationale for Blinding

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 FG-3019.

4.4.2 Maintenance of Blinding

A statistician who is not otherwise affiliated with the study prepared the randomization code and the code is not available to study staff. The subjects, clinical site staff, and the FibroGen Medical Monitor and Clinical Operations staff will be blinded to whether a subject is randomized to FG-3019 or placebo. Study drug (FG-3019 or placebo) are provided in coded vials that are identified by serial number only.

4.4.3 Unblinding of Treatment Assignment

Treatment assignment of individual subjects will be unblinded during the study if this information is required to manage a SAE. Study documentation provides details on the procedures for unblinding treatment assignment by investigators. For planned assessments of efficacy, treatment assignment by groups will be unblinded but individual subject treatment assignments will not be unblinded. Treatment will be unblinded for each subject after completion of the Week 48 evaluations by unblinded FibroGen personnel. Subject eligibility for the Extended Treatment Phase will be communicated to the site.

Unblinding will also occur at the time of enrollment of subjects into the at Extended Treatment Period, after all week 48 assessments are complete **only** for designated individuals at FibroGen Inc. who are not associated with the conduct of this study. The Investigators, subjects and study teams will remain blinded till the study is complete.

4.5 Study Treatment with FG-3019

Subjects will receive FG-3019 at a dose of 30 mg/kg by IV infusion in normal saline (unless volume is >250mL in which case the study drug can be administered undiluted) every 3 weeks. The maximum dose of FG-3019 at any infusion will be capped at 3,900 mg.

4.6 Concomitant Medications, Procedures and Nondrug Therapies

4.6.1 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 Screening Visit 1 through the End-of-Study (EOS) Visit.

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 management of idiopathic pulmonary fibrosis and that subjects may be treated with concomitant medications for their various medical conditions. Optimal medical care must be provided, and Investigators should ensure, for example, that subjects maintain stable vital signs and laboratory test values during the course of the study.

Oral prednisone or equivalent oral corticosteroid (up to 10 mg daily) and NAC (up to 1800 mg daily) will be allowed during the study.

Prohibited medications include approved 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, pirfenidone, nintedanib, azathioprine, cyclophosphamide, cyclosporine, interferon gamma 1b, D penicillamine, methotrexate, leflunomide, colchicine, bosentan, ambrisentan, aminobenzoate, mycophenolate mofetil, imatinib, relaxin, etanercept, adalimumab, infliximab, anakinra, abatacept, and rituximab. If sildenafil is used for erectile dysfunction the dosage regimen should be no more than three times a week. Immunosuppressives and monoclonal antibodies used for other diseases such as rheumatoid arthritis are allowed but the indication should be clearly documented. Indications for concomitant medications should be clearly documented in the subjects clinical record (use for IPF or other diseases).

Any medications to treat IPF should be terminated within 5 half-lives of Day 1 dosing. If monoclonal antibodies are used the last dose must be at least 4 weeks before Day 1 dosing (Exclusion criterion 15).

Questions about concomitant medications should be addressed to the attention of the FibroGen Medical Monitor or designee.

4.6.2 Contraception

Female subjects of childbearing potential and male subjects with female partners of childbearing potential are required to use double barrier contraception methods during the conduct of the study and for 3 months after the last dose of study drug.

Pregnancy, spontaneous or therapeutic abortion, or events related to pregnancy must be reported (Section 11.3.6).

4.7 Safety Plan

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, complete and focused physical examinations, 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.

4.8 Independent Data Monitoring Committee

4.8.1 Safety Monitoring

Safety data in this double-blind placebo-controlled study will be monitored on a regular basis by a Data Monitoring Committee (DMC) that is independent of the FibroGen Medical Monitor and Clinical Operations staff. FibroGen is responsible for the establishment of this DMC, the development of a DMC charter, and supporting DMC meetings.

5 ELIGIBILITY CRITERIA

FibroGen will not grant waivers to Inclusion Criteria and Exclusion Criteria in this protocol.

5.1 Inclusion Criteria

1. Age 40 to 80 years, inclusive.
2. Diagnosis of IPF as defined by current international guidelines (Raghu, 2011). Each subject must have one of the following: (1) *Usual Interstitial Pneumonia* (*UIP) Pattern* on an available HRCT scan; or (2) *Possible UIP Pattern* on an available HRCT scan and surgical lung biopsy within 4 years of Screening showing *UIP Pattern* (HRCT criteria for *UIP Pattern* and *Possible UIP Pattern* and histopathological criteria for *UIP* Pattern described in Appendix 4).
3. History of IPF of ≤5 years duration with onset defined as the date of the first diagnosis of IPF by HRCT or surgical lung biopsy.
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, as determined by the HRCT central reader.
5. FVC percent of predicted value ≥55% at Screening.
6. Female subjects of childbearing potential (including those <1 year postmenopausal) and male subjects with female partners of childbearing potential, must use double barrier contraception methods during the conduct of the study, and for 3 months after the last dose of study drug.

5.2 Exclusion Criteria

1. Female subjects who are pregnant or nursing.
2. Infiltrative lung disease other than IPF, including any of the other types of idiopathic interstitial pneumonias (Travis, 2013); 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 and connective tissue diseases.
3. HRCT scan findings at Screening are inconsistent with *UIP Pattern*, as determined by the HRCT central reader (a definition of Inconsistent with *UIP Pattern* is provided in in Appendix 4).
4. Pathology diagnosis on surgical lung biopsy is anything other than *UIP Pattern*, as determined by the local pathologist (Appendix 4).
5. The Investigator judges that there has been sustained improvement in the severity of IPF during the 12 months prior to Screening, based on changes in FVC, diffusing capacity of the lung for carbon monoxide (DLCO), and/or HRCT scans of the chest.

6. 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 endpoints in the protocol or otherwise preclude the subject's participation in the study.
7. History of any other respiratory, cardiovascular, renal, hepatic, metabolic, neurologic, hematologic, or other medical conditions that, in the opinion of the Investigator, would preclude the subject's participation in the study.
8. 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.
9. Upper or lower respiratory tract infection of any type within 4 weeks of Screening.
10. Acute exacerbation of IPF within 3 months of Screening (a definition of acute exacerbation of IPF is provided in Section 8.
11. Evidence of obstructive lung disease by any of the following criteria: forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC) ratio <0.70, or extent of emphysema on HRCT greater than the extent of fibrosis on HRCT.
12. DLCO <30% of the predicted value.
13. High likelihood of lung transplantation (in the opinion of the Investigator) within 6 months after Day 1.
14. Poorly controlled chronic heart failure; clinical diagnosis of cor pulmonale requiring specific treatment; or severe pulmonary hypertension requiring specific treatment that, in the opinion of the Investigator, would preclude the subject's participation in the study.
15. Use of medications to treat IPF within 5 half-lives of Day 1 dosing. If monoclonal antibodies were used, the last dose of the antibody must be at least 4 weeks before Day 1 dosing.
16. Use of any investigational drugs, including any investigational drugs for IPF, within 4 weeks prior to Day 1 dosing.
17. History of cancer diagnosis of any type in the 3 years preceding Screening, excluding non-melanomatous skin cancer, localized bladder cancer, or in situ cancers.
18. Clinically significant trauma or surgical procedures within 4 weeks prior to dosing.
19. Planned elective surgery during the study including 4 weeks following the final dose of Study Drug.
20. History of allergic or anaphylactic reaction to human, humanized, chimeric or murine monoclonal antibodies.
21. 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.
22. Body weight >130 kg.

23. Previous treatment with FG-3019.
24. Inadequate IV access.

6 STUDY DRUG/TREATMENT SUPPLY

6.1 FibroGen Investigational Product

FG-3019 is a fully human IgG1 kappa monoclonal antibody that binds to CTGF. It will be administered at a dose of 30 mg/kg by IV infusion in a total volume of 250 mL (up to 400 mL if necessary) normal saline every 3 weeks. The maximum dose of FG-3019 will be capped at 3,900 mg. Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfil Good Manufacturing Practice Annex 13 requirements for labelling. Label text will be translated into local language.

The patient emergency contact details will not be on the label, but can be found in the informed consent.

6.1.1 Formulation

FG-3019 is supplied in single-use glass vials containing 10 mL of a sterile, preservative-free solution. The solution is composed of 10 mg/mL FG-3019, 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.

6.2 Reference Therapy (Placebo)

Placebo (identical to the FG-3019 vehicle) is handled and administered in a manner that is identical to FG-3019.

6.2.1 Formulation

Placebo is a sterile, aqueous solution of pH 6.0 for dilution into 0.9% serum chloride injection USP prior to IV infusion. The solution formulation contains 8.01 mg/mL sodium chloride, 3.08 mg/mL L-histidine HCL, 1.60 mg/mL L-histidine, and 0.05 mg/mL polysorbate 20. The solution is free of preservatives as the content of each vial is intended for single use. Each vial delivers a nominal volume of 10 mL.

6.3 Preparation of Dose and Administration

The dose of Study Drug (FG-3019 [30 mg/kg] or placebo) for each infusion will be based on the Day 1 weight for the first 12 weeks. Total volumes of <250 mL must be diluted in 0.9% Sodium Chloride Injection according to the Dose Preparation Instructions in the Study Reference Manual. Total volumes of >250 mL FG-3019 can be infused undiluted. The dose should be prepared in a volume of fluid that does not exceed 400 mL. Study Drug will be administered as soon as possible after release from the site's pharmacy and within 8 hours of preparation. Study Drug will be administered by IV infusion, using an infusion set with a sterile, nonpyrogenic, low-protein-binding in-line filter (0.2-micron pore size).

The first administration of Study Drug in any given subject in the Randomized Treatment Period as well as the Extended Treatment Period shall be completed in approximately 2 hours. If the first administration is well tolerated and no drug-related AEs are observed during the infusion or subsequent 1-hour observation period, the second administration of Study Drug shall be completed in approximately 1 hour. All subsequent infusion periods, including those in the Extended Treatment Phase, may be shortened to approximately half an hour. If a drug-related AE occurs during the first or a subsequent infusion, Study Drug will be administered over

approximately 1 hour for the next three infusions. If no drug-related AEs are observed in any of these three infusions, the duration of infusion may be decreased to approximately half an hour.

A physician must be immediately available during the first Study Drug infusion and observation period for each subject. If a subject has a significant infusion reaction, the infusion rate may be slowed or temporarily stopped, depending on the severity of symptoms. If a subject experiences a significant infusion reaction and continues Study Drug dosing, a physician should be immediately available during all subsequent infusions and observation periods. If the Investigator wishes to use premedication, e.g., antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs) for a subsequent infusion, this should be discussed with the FibroGen Medical Monitor or designee. Infusions are to be continued until the total volume of the infusion has been administered. Subjects will remain at the study site for 1 hour after the end of the infusion for clinical observation. The post-infusion observation period may be reduced to 30 minutes if the subject has had no infusion-related AEs after three infusions. The IV line should remain in place and maintained per site procedures until the end of this post-treatment observation period.

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 an FG-3019 overdose or infusion reaction. Signs and symptoms should be managed with appropriate standard of care treatment.

The following procedures must be performed during each infusion:

Vital signs (blood pressure [BP], pulse, respiration rate, and temperature) every 30 minutes (± 10 minutes)

Query subject and assess AEs and SAEs

Record concomitant medications, including any pre-medication pre-approved by the FibroGen medical monitor or designee

The following procedures must be performed after each infusion:

Vital signs (BP, pulse, respiration rate, and temperature) every 30 minutes (± 10 minutes) for a minimum of 30 minutes after completion of the infusion (see above)

Query subject and assess AEs and SAEs

Record concomitant medications

6.4 Storage

Vials of Study Drug must be stored refrigerated (2°C to 8°C), temperature-controlled and monitored, 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.

7 STUDY PROCEDURES-ALL COHORTS UNLESS OTHERWISE SPECIFIED

7.1 Study Procedures

The study procedures and assessments are presented for the Randomized Treatment phase in Appendix 1, for the Extended Treatment phase in Appendix 2, and for End-of-Treatment and Follow-up periods in Appendix 3. See the Study Reference Manual for additional details.

The treatment period in the Randomized Treatment Phase begins on Day 1 (first infusion of Study Drug) and continues through Week 48. Visit windows are within ± 3 days of the scheduled visit date for Weeks 3 through 48.

After completion of Week 48 assessments and reporting of all AEs, subjects may be eligible to continue to open label treatment in the Extended Treatment Phase. All other subjects undergo the EOS assessments.

Eligible subjects from the Randomized Treatment Phase of the study are offered participation in the Extended Treatment Phase as described under Section 4.2.3 and illustrated in Figure 1. A Transition Period of up to 3 weeks between the Week 48 Visit in the Randomized Treatment Period and Day 1-EX in the Extended Treatment Phase is provided in order to determine subject eligibility for the Extended Treatment Phase and to arrange scheduling of the Day 1-EX Visit. The total interval between the Week 45 Visit in the Randomized Treatment Phase and the Day 1-EX Visit in the Extended Treatment Phase should not exceed 6 weeks. If necessary, an unscheduled visit should be performed to obtain repeat pulmonary function tests (FVC) if the interval between the Week 45 Visit in the Randomized Treatment Phase and the Day 1-EX Visit in the Extended Treatment Phase is expected to exceed 6 weeks.

The treatment period in the Extended Treatment Phase begins on Day 1-EX (first infusion of FG-3019) and continues until progression or withdrawal. Visit windows are within ± 3 days of the scheduled visit date.

7.2 Serial PFT and HRCT

The key study procedures that measure efficacy are serial PFT measurements to look at spirometry (see Procedure Manual for PTF for additional details) and serial HRCT assessments to look for fibrosis (see Site Manual for HRCT and Appendix 5).

7.3 Blood Volume

The total amount of blood taken is approximately 13 tablespoons (195 ml) in the Randomized Treatment Phase and 10 tablespoons (150 ml) per year in the Extended Treatment Phase (total 23 tablespoons (345ml) for two years. Subjects who continue Extended Treatment beyond one year will give approximately 150 mL of blood per year.

7.4 Missed Visits

Every attempt should be made to complete all study visits within window as outlined in the Schedule of Assessments (Appendix 1, Appendix 2, and Appendix 3).

Scheduled visit dates are determined from the time of the first dose, which is defined as Day 1. Protocol-defined visits conducted outside the ± 3 day study visit window will be recorded as a protocol deviation unless there is an AE/SAE/intercurrent illness. If a dose is delayed due to an AE/SAE/illness, the next dose should occur as soon as possible when the patient is stable so that

the dosing interval is close to 3 weeks. No subject should receive more than one dose in any 7-day period. Missed doses are not to be made up through undertaking 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. Subjects who miss three sequential doses or more than one instance of two sequential doses will not be allowed to continue in the study and will be terminated early. The reason for missed doses should be documented in the subject's clinical record.

For missed visits without an AE/SAE/intercurrent illness, the subject will be asked to resume the planned visit schedule and return for the next scheduled visit. If the subject is unable to perform PFTs at a scheduled visit the PFT can be performed at the next scheduled visit.

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

7.5 Unscheduled Visits

Unscheduled Visit assessments may be required at the discretion of the Investigator. These should be recorded on the appropriate CRF.

Subjects who, in the judgment of the PFT technician or investigator, are unable to perform PFTs adequately on a scheduled visit should undergo PFT assessment at the next scheduled visit or sooner if feasible.

7.6 Assessments

7.6.1 Central Laboratory

All laboratory tests of blood and/or urine specimens will be performed by a central laboratory or FibroGen, as appropriate. A Central Laboratory Manual with instructions on specimen collection, processing, storing, and shipping to the central laboratory will be provided to all participating sites.

7.6.2 Local Laboratory(s)

A local laboratory will analyze urine (and blood, if necessary) samples for pregnancy testing only.

7.6.3 Other Reference Laboratories

Human anti-human antibody plasma level measurement will be performed at a specialty laboratory.

7.6.4 Exploratory Biomarkers

Serum and plasma samples will be stored and used to explore additional biomarkers of FG-3019's effects. The final selection of these biomarkers will be made by FibroGen, based upon the best scientific data available at that time.

7.6.5 DNA for Genomic Analysis

Fingerlin et al performed a genome-wide association study 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 FG-3019 and variants in these specific chromosomal loci.

A whole blood sample will be collected for DNA analysis on Day 1 before dosing or at subsequent visits for subjects already enrolled in the study 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 IPF will be performed and all samples will be destroyed after testing is completed.

8 SUBJECT DISCONTINUATION

Subjects who discontinue the study early should be strongly encouraged to complete the End-of-Treatment and Follow-up Visit (Appendix 3).

Subjects may withdraw from the study at any time for any reason, whether during the Screening, Treatment, or Follow-up Periods. Completion of efficacy assessments as outlined in Appendix 3 is discretionary and must be discussed in advance with the FibroGen Medical Monitor.

The Investigator must remove a subject from study treatment for the reasons below. Removing a subject from study treatment is based on the judgment of the Investigator in consultation with the FibroGen Medical Monitor.

- Pregnancy in a female subject
- AEs, SAEs, repeated hospitalizations, or medical conditions that make further participation in the study a risk to the subject.
- Clear evidence of progression of IPF and or absolute decline in FVC % of predicted value of ≥10% in the absence of an intercurrent illness, documented by two consecutive spirometry tests.
- Receipt of a prohibited medication that cannot be discontinued.

Dosing may be temporarily suspended up to 4 weeks for:

- Acute exacerbation of IPF, defined as (1) worsening or newly developed dyspnea as reported by the subject (≤30 days); (2) new bilateral ground-glass opacities on HRCT superimposed on the UIP abnormalities that defined subject eligibility for the study (Section 5.1); and (3) worsening hypoxemia (in the judgment of the Investigator), in the absence of pulmonary infection, heart failure, or other identifiable causes for this finding.
- Any other intercurrent illness that temporarily precludes the subject receiving the study drug infusion.

The reasons for suspension of treatment should be clearly documented in the subject's clinical record.

8.1 Replacement of Subjects

At the Sponsor's discretion, the number of subjects who are enrolled may be increased to account for early dropouts if the dropout rate is projected to be greater than 10%.

9 STUDY TERMINATION BY FIBROGEN

FibroGen has the right to terminate this study or to close any site at any time.

FibroGen may also suspend enrollment temporarily at any time for business or other reasons.

If the planned interim analysis indicates a lack of efficacy, FibroGen will terminate the Extended Treatment Period and dosing will cease for all subjects.

10 STATISTICS

10.1 Sample Size Determination

This study is planned to enroll approximately 136 subjects, which will include a target of 110 subjects who are seeking first-line therapy and 26 subjects who failed pirfenidone and/or nintedanib treatment. First-line therapy is defined as no prior therapy with pirfenidone/nintedanib or <10% relative decrease in FVC % predicted while receiving either pirfenidone or nintedanib. Failure of pirfenidone and or nintedanib treatment is defined as having ≥10% relative decrease in FVC % predicted during prior pirfenidone/nintedanib treatment. The effect of first-line treatment is the primary interest of the study, and is the basis for sample size determination. Assuming a 10% dropout rate and a common standard deviation of 7.3, a sample size of 55 subjects per arm in the primary analysis population provides approximately 80% power to detect a treatment difference of 4.2 in change from baseline to Week 48 in percent predicted FVC, using a two-sample t-test at the two-sided significance level of 0.05. The expected treatment difference is estimated using data from study FG-3019-049 and placebo data from published studies. In Study FG-3019-049, a mean decline of 2.8 in % predicted FVC from baseline to Week 48 was observed. The expected decline of 7.0 % predicted FVC in the placebo arm is estimated based on the weighted average of published studies (Azuma, 2005, Daniels, 2010, Demedts, 2005, King, Jr., 2008, King, Jr., 2009, King, Jr., 2011, Meier-Kriesche, 2004, Noble, 2011, Noth, 2012, Raghu, 2004, Raghu, 2008, Raghu, 2012, Richeldi, 2011, Taniguchi, 2010, Zisman, 2010).

Second line therapy patients are evaluated in an exploratory fashion. If the treatment effect in the pirfenidone/nintedanib failure group is similar to that in the general population, the two subgroups will be combined to achieve higher power.

10.2 Analysis Populations

10.2.1 Safety Population

The Safety Population will consist of all randomized subjects who received any dose of study medication. If actual treatment received differs from the randomized treatment arm, the actual treatment arm will be used for safety data analysis.

10.2.2 Full Analysis Set Population

The Full Analysis Set (FAS) Population will consist of randomized subjects who received at least one dose of study drug and have evaluable FVC assessments at baseline and at least one evaluable post baseline. The FAS population will be used in the primary analyses of the PFT endpoints and other efficacy endpoints except for PFS.

10.2.3 HRCT Evaluable Population

The HRCT Evaluable (HE) Population will consist of randomized subjects who have evaluable HRCT fibrosis scores at baseline and at Week 24 or at a later time point. The HE population will be used in the analyses related to HRCT fibrosis scores.

10.3 Statistical Analysis

10.3.1 General Analysis Methods

Unless the planned interim analysis at the end of the Randomized Treatment Phase indicates a lack of efficacy, the study is completed when the last subject completes the last visit in the Extended Treatment Phase.

Baseline characteristics, safety, and biomarker data will be summarized based on available data in the Safety Population, except for the parameters indicated otherwise. The primary efficacy analyses will be based on the FAS population, except for the analysis of PFS, which will be based on the Safety Population. All safety, efficacy, and exploratory endpoints will be summarized by group of actual treatment received.

All randomized subjects will be included in the data listings.

Continuous variables will be presented by descriptive statistics: n, mean, standard deviation, or standard error, median, minimum, and maximum. Categorical variables will be presented by counts of subjects and percentage.

10.3.2 Subject Enrollment and Disposition

The total number of subjects who completed or discontinued the study, and reasons for early discontinuation will be summarized for all randomized subjects.

10.3.3 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized for subjects in different analysis populations and subgroups. Baseline data related to safety and efficacy assessments will be summarized with the post-baseline data in the corresponding safety and efficacy sections.

10.3.4 Efficacy Analyses

The primary efficacy analyses will be performed in subjects in the FAS population except for analyses of PFS, which will be based on the Safety Population. Rules of missing data imputation will be described in the SAP. Analyses based on observed data will be used for sensitivity analyses.

10.3.4.1 Primary Efficacy Analysis

The primary analysis will be to compare the treatment arms in change from baseline to Week 48 in FVC % predicted based on the FAS Population. A rank ANCOVA model will be used, with baseline FVC % predicted value as covariate, treatment group, stratification, and treatment by stratification interaction as fixed effects. Factors may be eliminated from the model if they are insignificant. If the interaction term is significant, the primary analysis will be based on the subgroup of subjects on first-line therapy.

The ranks of the primary endpoint will be based on observed data and on imputed data if observed data are not available. A detailed description of the rank assessment will be described in the statistical analysis plan. A repeated measures model utilizing all observed data will be used for sensitivity analysis.

Descriptive summaries of the primary efficacy parameter will include the following:

1. Median change from baseline by treatment and visit
2. % of subjects with no decline by treatment and visit
3. % of subjects with decline ≥10% by treatment and visit

10.3.4.2 Analyses of Secondary Efficacy Endpoints

Similar models to those described above will be applied to analyzing changes in other PFT parameters, HRCT fibrosis score, and patient-reported outcome.

10.3.4.3 Analysis of Progression Free Survival

PFS is defined as the time from randomization to the first occurrence of the following events during the study (whichever occurs first):

1. Death from any cause
2. Absolute decline FVC percent of predicted value of ≥10% not due to intercurrent illness confirmed by repeat spirometeetry
3. Clinical diagnosis of progression of IPF

The analysis of PFS will be based on the Safety Population. If no PFS event is observed during the study, then PFS is censored at the last PFT assessment.

Comparison between treatment arms in PFS will be performed using the Cox regression model with adjustment for baseline FVC % predicted value as well as stratification and stratification by treatment interaction.

10.3.4.4 Analysis of IPF DNA Markers

Exploratory analyses will be performed to evaluate the relationship between clinical response to FG-3019 and variants in the chromosomal loci listed in Section 7.6.5

10.3.5 Safety Analyses

Treatment-emergent adverse events (TEAEs), defined as new or worsening AEs that occur after the first dose of study drug and within 4 weeks of last dose of study drug, will be tabulated to examine their frequency, severity, organ systems affected and relationship to study treatment. Treatment emergent SAEs and TEAEs leading to study or treatment discontinuation will be listed or tabulated separately.

Clinically significant changes from baseline in vital signs, laboratory tests, physical examinations, and ECGs will be identified.

Human anti-human antibody data will be summarized in a separate report.

10.3.6 Interim Analyses

Unblinded analysis of changes in pulmonary function and in pulmonary fibrosis will be performed after all subjects have either completed Week 48 assessments or discontinued the study early (prior to week 48 of the Randomized Treatment Phase). This analysis may be performed before data lock for the primary analysis of safety and efficacy provided the relevant pulmonary function and pulmonary fibrosis data are cleaned. If there is a substantial gap in completion of enrollment between subjects on first-line therapy and the pirfenidone and or nintedanib treatment failures, unblinded subgroup analysis may be performed at different times.

10.4 Statistical Analysis Plan

The SAP will include detailed plans for presenting and analyzing study data, as well as documentation of changes in protocol-specified analysis plans.

11 ASSESSMENT OF SAFETY

11.1 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 outlines in Appendix 1, Appendix 2, and Appendix 3. 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 all SAEs, regardless of whether the Investigator believes they are related to the study drug.

The definitions of an AE, suspected adverse reaction, adverse reaction, and SAE are describe below in accordance with the FDA Final Rule Vol 75, No 188, September 29, 2010, and/or Article 18 of Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 and the International Conference on Harmonisation (ICH) E2A guidance.

11.2 Definitions

11.2.1 Definition of an Adverse Event (AE)

An AE can be any unfavorable and unintended sign (e.g., an abnormal and clinically significant laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition, or abnormal results of diagnostic procedures, including laboratory test abnormalities. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

An AE includes medical conditions, signs, and symptoms not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with an underlying condition that were not present prior to the AE reporting period (Section 11.3.1).

11.2.2 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
- Other medically important events

Based upon appropriate medical judgment, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. These events must be reported to the sponsor similar to SAEs.

- A clinical diagnosis of IPF progression and surgical procedures such as lung transplantation are expected in this patient population. Data for IPF progression is being collected an efficacy endpoint (Sections 3.2.2, 10.3.4.3). However, as these events are medically significant and may be associated with hospitalization, so they should be reported as SAEs.
- Other elective surgeries (example knee replacement, haemorroidectomy, mole removal etc.) may occur during the study period. They should not be reported as SAEs, but the diagnosis that warranted these procedures should be reported (especially if this is a worsening of a pre-existing medical history condition). Any complications of such procedures should be reported as AE/SAE based on seriousness criteria listed above.

11.2.3 Definition of a Suspected Adverse Reaction

Suspected adverse reaction means any AE for which there is a *reasonable possibility* that the drug caused the AE. The term "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than the term "adverse reaction".

11.2.4 Definition of an Adverse Reaction

An adverse reaction means any AE caused by a drug.

11.2.5 Special Situations

Safety events of interest ("Special Situations") on the medicinal products administered to the subject as part of the study (e.g., study drug, comparator, and background therapy) that may require expedited reporting and/or safety evaluation include, but are not limited to:

- Overdose of the medicinal product
- Suspected abuse/misuse of the medicinal product
- Inadvertent or accidental exposure to the medicinal product
- Medication error involving the medicinal product (with or without subject exposure to the Sponsor medicinal product, e.g., name confusion)
- Drug-drug interaction

11.3 Procedures for Eliciting, Recording, and Reporting Adverse Events

11.3.1 Adverse Event Reporting Period

The study period during which all AEs and SAEs must be collected begins after informed consent is obtained and ends 4 weeks after the last dose of study drug, except for pregnancy

reporting (Section 11.3.6). In addition, all AEs reported spontaneously by the subject to site personnel, outside the study period, may be recorded.

Adverse events will be followed until resolved, stable, or until the subject's last study visit or lost to follow-up. If an AE is not resolved or stabilized at the subject's last visit, it is up to the discretion of the Investigator and study Medical Monitor to determine if further monitoring of the event is warranted.

Adverse events collected prior to dosing of study drug will be considered "non-treatment emergent" while those reported after the first dose of study drug and up to 4 weeks after the last dose of study drug will be considered "treatment emergent" and will be assessed for relationship to study drug.

11.3.2 Adverse Event Eliciting/Reporting

During the AE reporting period, study site personnel will query each subject at each visit to actively solicit any AE 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 baseline or previous visit, but shall not be specifically solicited. There will be no directed questioning for any specific AE. This does not preclude 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. New indications for medications started after informed consent is obtained until 4 weeks after the last dose of study drug will be recorded as AEs; recurrence or worsening of medical history problems requiring new or changes in concomitant medication, will also be recorded as AEs. Abnormal, clinically significant laboratory results, physical examination findings, and ECGs will be recorded as AEs if they are deemed by the Investigator to meet criteria.

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"

11.3.3 Assessing Adverse Event Severity

Adverse Events, including abnormal clinical laboratory values, should be graded using the National Cancer Institute (NCI) Common Terminology Criteria for AE (CTCAE) guidelines (Version 4.03; http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). 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; clinical or diagnostic observations only; 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:** Death related to AE.

11.3.4 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. Moreover, appropriately deciding whether the AE meets the definition of a suspected adverse reaction is usually the most difficult determination, but it is critical to avoid the miscategorization of the product's safety profile.

Due to the historical tendency for assessment of relationship to default as possibly related, the FDA has issued new guidance that clarifies the intent of the phrase "reasonable possibility" in the definition of "associated with the use of the drug." Default reporting of individual events as possibly related is uninformative and does not meaningfully contribute to the development of the product safety profile.

The Investigator must provide an 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 enough evidence to assess an event as possibly related or related to study drug.

- **Related (Adverse Reaction):**
    - Any event for which there is evidence to conclude that the study drug caused the event
- **Possibly Related (Suspected Adverse Reaction):**
    - A single occurrence of an event that is uncommon and *known to be strongly associated with drug exposure,* such as angioedema, anaphylaxis, rhabdomyolysis, Stevens-Johnson syndrome, etc.
    - One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug, such as tendon rupture

- **Not Related:**
    - The event represents the underlying disease (e.g., disease-related symptoms, disease progression)
    - The event represents a comorbid condition present at the time the subject entered the study that has not worsened
    - The event represents a known adverse reaction associated with a co-medication received by the study subject
    - The event is common for the study population (e.g., cardiovascular events in an elderly population)

The Investigator must provide an assessment of the relationship of the event to study drug, as this information is very important to monitor the real-time safety of the study drug. However, as the manufacturer of the study drug, Beijing FibroGen is responsible for making the final causality assessment for individual reports, and for reporting suspected adverse reactions and adverse reactions to Health Authorities.

11.3.5 Reporting Serious Adverse Events on the SAE Report Form

All SAEs must be reported immediately to the Sponsor and/or its designated safety management vendor.

To report an SAE, the Investigator must fax an SAE Report Form to the Sponsor's designated safety management vendor within 24 hours of becoming aware of the serious event. In case of emergency or doubt, the Investigator shall call the Sponsor's Medical Monitor for guidance. Follow-up reports must be submitted in a timely fashion as additional information becomes available.

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 (within 7 days) as necessary.

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).

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

The Investigator is responsible for notifying his/her Institutional Review Board/Independent Ethics Committee (IRB/IEC) of SAEs in accordance with local regulations. Sponsor, or its safety representative, will provide to the Investigator a copy of any expedited safety reports that it intends to file with a regulatory authority.

11.3.5.2 Deaths

For any death or life-threatening event occurring during the subject's study participation regardless of attribution, the Investigator will report the death or life-threatening event immediately to the Sponsor's Medical Monitor. The Investigator must provide an assessment of the relationship of the event to the study drug according to the guidance in Section 11.3.4.

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.

If the death occurred within the SAE collection and reporting period (signed ICF to 28 days after last dose), the Investigator must submit the SAE Report Form in the same manner as described above in Section 11.3.5. Additionally, the site must complete the appropriate CRF page. This includes death attributed to progression of the subject's underlying disease.

11.3.6 Pregnancies: Reporting and Follow-up of Subjects

A pregnancy in a female subject must be confirmed by a positive serum β-HCG test. If a female 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 (by way of its designated safety management vendor) within 24 hours of the Investigator learning of the pregnancy. If applicable, a pregnant subject is immediately withdrawn from receiving study treatment. The Investigator must follow the pregnancy to completion to ascertain both its outcome (e.g., spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) and whether any AEs occur.

Pregnancy itself is not an AE. However, the Investigator should report the information to the Sponsor on the designated forms. Pregnancies are followed up to outcome even if the subject was discontinued from the study. 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 management vendor within 24 hours of the Investigator learning of the outcome.

Pregnancy of the subject's partners is not considered to be an AE. However, the outcome of all pregnancies should if possible be followed up and documented as described. To capture information about a pregnancy from the partner of a male subject, the male subject's partner consent must be obtained to collect information related to the pregnancy and outcome (will be handled on a case-by-case basis with IRB/IEC approval).

11.3.7 Abnormal Laboratory Findings

Laboratory values will be collected throughout the study to assess for safety. The Investigator must review and assess all laboratory results in a timely manner, and determine whether the abnormal laboratory values, if any, are clinically significant (CS) or not clinically significant (NCS), and whether there are associated signs and symptoms. Clinically significant laboratory abnormalities will be reported as AEs.

An abnormal laboratory finding in absence of any other signs or symptoms is not necessarily an AE. 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.

Clinically significant laboratory abnormalities after taking study medication that reflect a meaningful change from the screening value(s) and that require active management are to be considered by the Investigator as AEs (e.g., abnormalities that require study treatment dose modification, discontinuation, more frequent follow-up assessments, etc.).

12 STUDY MONITORING

A site must have had a previous pre-qualification site visit conducted to have a combined pre-qualification site visit and site initiation visit. Following site pre-qualification and/or initiation of the study site, periodic monitoring visits and site closeout visits will be made by FibroGen or its designee. The Investigator must provide direct access to, and allocate sufficient space and time for, the monitor to inspect subject source records, CRFs, queries, collection of local laboratory normal ranges (if applicable), investigational product accountability records, and regulatory documents in accordance with GCP and the ICH E6 guideline.

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 Investigator must also permit the FDA or other applicable regulatory authorities to inspect facilities and records pertaining to this study if so requested. If the Investigator is notified of an inspection pertaining to this study by the FDA or other applicable regulatory authorities, the Investigator must notify FibroGen immediately.

12.1 Data Quality Assurance

The following steps will be taken to ensure that the study is conducted by the study site in compliance with the study protocol, GCP, and other applicable regulatory requirements:

- Investigator meeting and/or Investigator site initiation
- Routine study site monitoring
- Documented study and system training
- CRF and query review against source documents
- Collection of local laboratory normal ranges

The study site may be audited by FibroGen's Quality Assurance department or designee. The Investigator agrees to make available to the auditor all necessary study personnel (including himself/herself), all source documentation, and study subject records related to this trial. The Investigator agrees to follow-up to address and/or correct any audit observations promptly.

12.2 Compliance with Laws and Regulations

This study will be conducted in accordance with the FDA regulations, the ICH E6 guideline for GCP, the Declaration of Helsinki, and applicable local, state, and federal laws, as well as other applicable country laws.

12.3 Audit and Inspection

Authorized representatives of the Sponsor, a regulatory authority, an IEC may visit the investigator site to perform audits or inspections, including source data verification. The Investigator will allow the sponsor auditor, regulatory authority or ethics committee

representative to inspect the drug storage area, study drug stocks, drug accountability records, subject charts 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 should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

12.4 Data Collection and Handling

12.4.1 Source Documents

Source records are original documents, data, and records that are relevant to the clinical trial. The Investigator 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 trial. Source records must be adequate to reconstruct all data transcribed onto the CRFs and resolved queries.

12.4.2 Data Collection, Handling, and Verification

All required data will be entered onto CRFs by authorized site personnel. Data will be entered into a validated, clinical database compliant with 21 CFR Part 11 regulations. The database will be a secured, password-protected system with full audit trail.

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

Adverse events and concomitant medications will be coded using industry standard dictionaries (e.g., Medical Dictionary for Regulatory Activities [MedDRA] and World Health Organization Drug (WHODrug) dictionaries).

The Investigator is responsible for reviewing, verifying, and approving all subject data, i.e., CRFs and queries prior to study completion.

13 HUMAN SUBJECTS

13.1 Ethical Considerations

The study will be conducted in accordance with FDA regulations, the ICH E6 guideline for GCP, the Declaration of Helsinki, any other applicable regulatory requirements, and IRB requirements.

13.2 Communication with the Institutional Review Board

This protocol, the Informed Consent Form, the Investigator's Brochure, and any information to be given to the subject (e.g., subject information sheet, questionnaires) must be submitted to a properly constituted IRB by the Investigator for review and approved by the IRB 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 before the material is used for subject recruitment.

The Investigator is responsible for obtaining reapproval by the IRB annually or more frequently in accordance with the regulatory requirements and policies and procedures established by the IRB. Copies of the Investigator's annual report and other required report to the IRB and copies of the IRB continuance of approval must be furnished to FibroGen. A copy of the signed form FDA 1572 must also accompany the above approval letter provided to FibroGen.

Investigators are also responsible for promptly informing the IRB of any protocol changes or amendments, changes to the Investigator's Brochure, and other safety-related communications from FibroGen. Investigators also are responsible for promptly informing the IRB of protocol deviations/violations, as required by their IRB. Written documentation of IRB approval must be received before the amendment is implemented.

Investigators must also enter the names of the staff that are involved in the study on the Delegation of the Authority form and sign the form (including their responsibilities). This form must be updated when responsibilities of the staff change.

13.3 Informed Consent Form

No study procedure may be implemented prior to obtaining a signed and dated written Informed Consent Form (ICF) from the subject or the subjects legally authorized representative. IRB review and approval are required for the ICF. The final IRB-approved ICF must be provided to FibroGen for regulatory purposes.

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

13.4 Subject Confidentiality

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health information, 45 CFR Parts 160 and 164, and the HIPAA.

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 and HIPAA Authorization Form signed by the subject, or unless permitted or required by law. The subject may request in writing that medical information be given to his/her personal physician.

14 INVESTIGATOR REQUIREMENTS

The Investigator must be medically qualified to directly supervise the conduct of the trial at his or her site. The Investigator agrees to employ qualified staff to participate in the trial. The Investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data/documents.

14.1 Study Medication Accountability

All Study Drug required for completion of this study will be provided by FibroGen. The recipient will acknowledge receipt of the drug by returning the appropriate documentation form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all Study Drug received, dispensed, returned, and disposed of by the study site according to the Study Reference Manual should be recorded using the Drug Inventory Log.

14.2 Disclosure of Data

Data records generated by this study must be available for inspection upon request by representatives of the FDA or other regulatory agencies, national and local health authorities, FibroGen monitors/representatives and collaborators, auditors, and the IRB for each study site.

14.3 Study Files and Retention of Records

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following two categories:

(1) Investigator's Study Files, and (2) Subject Clinical Source Documents.

The Investigator's Study File commonly contains essential documents, which are defined as those documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced. Examples of such essential documents are as follows: the protocol, amendments, CRFs and query forms, IRB approvals correspondence, informed consents, drug records, staff curriculum vitae, laboratory accreditation, authorization forms, and other appropriate documents and correspondence.

Subject clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs) would include (although not be limited to) the following: subject hospitalization records, physician's and nurse's (or other study staff's) notes, appointment book, original laboratory reports, ECGs, x-rays, pathology and special assessment reports, consultant letters, screening and enrollment eligibility documentation, screening and enrollment logs, etc.

The Investigator shall retain records required to be maintained under 21 CFR 312.62(c) for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Investigator shall retain these records until 2 years after the investigation is discontinued and the FDA is notified.

If the Investigator moves or retires, he or she should identify in writing, the designee who will be responsible for record keeping. Archived data may be retained on electronic records or similar medium provided that a back-up exists and a hard copy is obtainable if required. No records will be destroyed without the prior written consent of FibroGen.

15 PUBLICATION POLICY

A detailed explanation of FibroGen’ s publication policy is described in the Clinical Trial Agreement.

16 REFERENCES

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17 APPENDICES

Appendix 1. Schedule of Assessments – Randomized Treatment Phase

Study Period	Screening Period (up to 6 weeks)		Treatment Period																
Visit Number	**1**	**2[a]**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study Days			**Day 1 pre dose**	**Day 1 post dose**																
Study Week (± 3 day window for Week 3 to Week 48)	**Scr 1**	**Scr 2[a]**	**0**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**
Signed and Dated Written Informed Consent	X																			
Inclusion/ Exclusion Criteria	X																			
Demographics	X																			
Medical History	X																			
SGRQ			X					X				X				X				X
Height and Weight[b]	X[b]		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
Complete Physical Exam	X																			X
Focused Physical Exam[c]			X			X		X		X		X		X		X		X		
Pulmonary Function Tests	X[d]		X[e]					X[e]				X[e]				X[e]				X[e]
CBC with Differential	X		X					X				X				X				X
Serum Chemistry	X		X					X				X				X				X
Spot Urine for Urinalysis	X		X					X				X				X				X
Pregnancy Test[f]	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRCT of Chest		X										X								X
12-Lead ECG	X											X								X
Serum and Plasma Biomarkers			X									X								X
Plasma HAHA			X																	
Whole Blood for DNA			X																	
AEs and SAEs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[g]
Concomitant Medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Procedures and Nondrug Therapies	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study Drug infusion[i]			X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Study Period	Screening Period (up to 6 weeks)		Treatment Period																
Visit Number	**1**	**2[a]**	**3**		**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**19**
Study Days			**Day 1 pre dose**	**Day 1 post dose**																
Study Week (± 3 day window for Week 3 to Week 48)	**Scr 1**	**Scr 2[a]**	**0**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**27**	**30**	**33**	**36**	**39**	**42**	**45**	**48**
Subject Disposition			X[j]																	

Abbreviations: AE = adverse event; CBC = complete blood count; DLCO = diffusing capacity of the lungs for carbon monoxide; ECG = electrocardiogram; EX = extended (treatment); HAHA = human anti-human antibody; HCG = human chorionic gonadotropin; HRCT = high resolution computed tomography; SAE = serious adverse event; Scr = screening visit; SGRQ = Saint George's Respiratory Questionnaire

a Screening Visit 2 may be combined with Screening Visit 1.

b Height will be measured only once at Screening Visit 1. Weight will be measured every 12 weeks to determine dose for the subsequent 12-week interval.

c Including chest auscultation

d Spirometry (DLCO at first screening test only).

e Spirometry

f Pregnancy tests (performed at Screening Visit 1, pre-dose Day 1, and pre-dose at other times) for women of childbearing potential only: serum pregnancy test at Screening Visit 1; urine pregnancy tests at other visits. A positive urine pregnancy test must be confirmed by serum HCG.

g See Section 11.3.1 for follow-up of AEs.

h Refer to Section 4.6.1 for prohibited concomitant medications.

i Vital signs (blood pressure, pulse, respiration rate, and temperature) must be recorded prior to each FG-3019 infusion. Intra-infusion and post-infusion assessments will be performed according to Section 6.3.

j Subjects who do not complete all visits in the Treatment Period will be encouraged to return for the assessments listed in Appendix 3.

Appendix 2. Schedule of Assessments – Extended Treatment Phase

Study Period	**Treatment Period[a]**																
Visit Number	**1-EX**	**2-EX**	**3-EX**	**4-EX**	**5-EX**	**6-EX**	**7-EX**	**8-EX**	**9-EX**	**10-EX**	**11-EX**	**12EX**	**13-EX**	**14-EX**	**15-EX**	**16-EX**	**17-EX**
Study Week (± 3 d window for Week 3-EX to Week 48-EX)	**0- (Day 1-EX)**	**3-EX**	**6-EX**	**9-EX**	**12-EX**	**15-EX**	**18-EX**	**21-EX**	**24-EX**	**27-EX**	**30-EX**	**33-EX**	**36-EX**	**39-EX**	**42-EX**	**45-EX**	**48-EX**
SGRQ					X				X				X				X
Weight[b]	X				X				X				X				X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Complete Physical Exam																	X
Focused Physical Exam[c]			X		X		X		X		X		X		X		
Spirometry					X[d]				X[d]				X[d]				X[d]
CBC with Differential					X				X				X				X
Serum Chemistry					X				X				X				X
Spot Urine for Urinalysis					X				X				X				X
Pregnancy Test[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
HRCT of Chest									X								X
12-Lead ECG									X								X
Serum and Plasma Biomarkers									X								X
AEs and SAEs[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Procedures and Nondrug Therapies	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
FG-3019 Infusion[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subject Disposition	X[i]																
FOOTNOTES ARE ON THE FOLLOWING PAGE																	

Abbreviations: AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; EX = extended (treatment); FVC = forced vital capacity; HAHA = human anti-human antibody; HCG = human chorionic gonadotropin; HRCT = high resolution computed tomography; SAE = serious adverse event; SGRQ = Saint George's Respiratory Questionnaire.

a The total duration of the study for subjects is indeterminate because subjects in the extension period may continue treatment until they meet stopping criteria (Section 4.2.3). Subjects who complete 48 weeks of treatment extension may continue treatment according to this table (beginning in Week 1Ex).

b Weight will be measured every 12 weeks to determine dose for the subsequent 12-week interval.

c Including chest auscultation

d Spirometry

e Pregnancy tests (performed pre-dose Day 1-EX and at other times) for women of childbearing potential only: urine pregnancy tests at all Extended Treatment Period visits. A positive urine pregnancy test must be confirmed by serum HCG.

f See Section 11.3.1 for follow-up of AEs.

g Refer to Section 4.6.1 for prohibited concomitant medications.

h Vital signs (blood pressure, pulse, respiration rate, and temperature) must be recorded prior to each FG-3019 infusion. Intra-infusion and post-infusion assessments will be performed according to Section 6.3.

i Subjects who do not complete all visits in the Treatment Period will be encouraged to return for the assessments listed in Appendix 3.

Appendix 3. Schedule of Assessments – Early Termination/End of Treatment and Follow-up Visit

Assessment	Early Termination/End of Treatment[a]	End of Study
1. SGRQ	X[b]	
2. Vital Signs	X[b]	X
3. Complete Physical Exam	X[b]	
4. Spirometry	X[b,c]	
5. CBC with Differential	X[b]	
6. Serum Chemistry	X[b]	
7. Spot Urine for Urinalysis	X[b]	
8. Pregnancy Test[d]	X[b]	X
9. HRCT of Chest	X[b]	
10. 12-Lead ECG	X[b]	
11. Serum and Plasma Biomarkers	X[b]	
12. Plasma HAHA		X
13. AEs and SAEs[e]	X[b,e]	X[b,e]
14. Concomitant Medications[f]	X[b]	X
15. Procedures and Nondrug Therapies	X[b]	X
16. Subject Disposition	X	X

Abbreviations: AE = adverse event; CBC = complete blood count; ECG = electrocardiogram; HAHA = human anti-human antibody; HCG = human chorionic gonadotropin; HRCT = high resolution computed tomography; PFT = pulmonary function test; SAE = serious adverse event; SGRQ = Saint George's Respiratory Questionnaire.

a End of treatment, including due to withdrawal/progression evaluation preferably 3 weeks after last dose of study drug for all subjects who have received more than 4 doses of FG-3019. The End of Study, final safety assessment should be 4 weeks after last dose of study drug. Study windows are ± 3 days

b Subjects who completed the withdrawal/progression evaluations at Week 48 or for early withdrawal do not need to repeat them. Study endpoint evaluations do not require repetition if performed within 8 weeks, HRCT does not require repetition if performed within 4 months, and safety assessments, such as clinical laboratory tests, do not require repetition if performed within 2 weeks.

c Spirometry .

d Pregnancy tests for women of childbearing potential only: urine pregnancy tests at all Extended Treatment Period visits. A positive urine pregnancy test must be confirmed by serum HCG.

e See Sections 4.7 and 11.3.1 for follow-up of AEs.

f Refer to Section 4.6.1 for prohibited concomitant medications.

Appendix 4. HRCT Criteria and Histopathological Criteria for UIP Pattern*

HRCT Criteria for UIP Pattern

UIP Pattern (All Four Features)

- Subpleural, basal predominance
- Reticular abnormality
- Honeycombing with or without traction bronchiectasis
- Absence of features listed (below) as Inconsistent with UIP Pattern

Possible UIP Pattern (All Three Features)

- Subpleural, basal predominance
- Reticular abnormality
- Absence of features listed (below) as Inconsistent with UIP Pattern

Inconsistent with UIP Pattern (Any of the Seven Features)

- Upper or mid-lung predominance
- Peribronchovascular predominance
- Extensive ground glass abnormality (extent > reticular abnormality)
- Profuse micronodules (bilateral, predominately upper lobes)
- Discrete cysts (multiple, bilateral away from areas of honeycombing)
- Diffuse mosaic attenuation/air trapping (bilateral, in three or more lobes)
- Consolidation in bronchopulmonary segment(s)/lobe(s)

Histopathological Criteria for UIP Pattern

UIP Pattern (All Four Criteria)

- Evidence of marked fibrosis/architectural distortion, ± honeycombing in a predominantly subpleural/paraseptal distribution
- Presence of patchy involvement of lung parenchyma by fibrosis
- Presence of fibroblast foci
- Absence of features against a diagnosis of UIP suggesting an alternate diagnosis (hyaline membranes, organizing pneumonia, granulomas, marked interstitial inflammatory cell infiltrate away from honeycombing, predominant airway centered changes, other features suggestive of an alternate diagnosis)

*Raghu, 2011

Appendix 5. 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 TLC scan. RV scans are not required for the quantitative image analysis data being collected for this study. Effective dose estimates provided: (For this study, visits occur at Baseline, 6 months, 1 year, 18 months and 2 years (i.e. 5 studies).

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) (5 studies)	10.7 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 AAPM 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