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PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BG00011 in Patients With Idiopathic Pulmonary Fibrosis

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1. SYNOPSIS

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BG00011 in Patients With Idiopathic Pulmonary Fibrosis	
Protocol Number:	203PF203	
Version Number:	2	
Name of Study Treatment:	BG00011	
Study Phase:	2b	
Study Indication:	Idiopathic pulmonary fibrosis	
Study Rationale:	This Phase 2b study in subjects with mild to moderate idiopathic pulmonary fibrosis (IPF) who may or may not be receiving background therapies is designed to evaluate the change in forced vital capacity (FVC) after 56 mg of BG00011 is administered subcutaneously (SC) once weekly for 52 weeks. In the previously completed, Phase 2a study (203PF201) in subjects with IPF, BG00011 demonstrated proof of biological activity by altering biomarkers in the lung. Therefore, the current study is being conducted to evaluate the clinical efficacy and safety of BG00011. The primary analysis will be conducted after 52 weeks of placebo-controlled treatment with BG00011.	
Study Objectives and Endpoints:	**Primary Objective**	**Primary Endpoint**
	To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF.	Yearly rate of change in FVC (expressed in mL over 52 weeks) in subjects randomized to BG00011 compared with placebo.
	Secondary Objectives	**Secondary Endpoints**
	To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF as determined by change in percent predicted FVC.	Yearly rate of change in FVC, expressed in percent predicted, over 52 weeks.
	To assess progression-free survival in subjects who receive BG00011	Time to progression, as defined by a composite endpoint, including any of

	compared with placebo.	the following events: Absolute decline of 10% predicted in FVC (FVC percent predicted$_{baseline}$ − FVC percent predicted$_{progression}$ ≥10%). Nonelective hospitalization for respiratory events. Lung transplantation or death.
	To assess the occurrence of IPF exacerbation (using modified diagnostic criteria for acute IPF exacerbation derived from [Collard 2007]) in subjects who receive BG00011 compared with placebo.	Time to first acute exacerbation, measured in days. Proportion of subjects with at least 1 acute exacerbation during the 52 weeks on study. Number of exacerbations during 52 weeks.
	To assess the incidence of absolute decline in FVC ≥10% in subjects who receive BG00011 compared with placebo.	Number of subjects with absolute decline of 10% predicted in FVC (FVC percent predicted$_{baseline}$ − FVC percent predicted$_{progression}$ ≥10%) over 52 weeks.
	To assess the time to death or lung transplantation in subjects who receive BG00011 compared with placebo, and the transplant-free survival rate at Week 26 and Week 52.	Time to death or lung transplantation, measured in days.
	To assess the time to nonelective hospitalizations in subjects who receive BG00011 compared with placebo.	Time to all nonelective hospitalizations and to nonelective respiratory hospitalizations, measured in days.
	To assess additional pulmonary function test (PFT) findings in subjects who receive BG00011 compared with placebo.	Change in absolute and percent predicted FVC from baseline over time. Carbon monoxide diffusion capacity (DL_{CO}) absolute and percent

		predicted changes from baseline over time. Total lung capacity, as measured by plethysmography, absolute and percent predicted changes from baseline over time.
	To assess performance on the 6-Minute Walk Test (6MWT) in subjects who receive BG00011 compared with placebo.	Change from baseline in 6MWT parameters at Weeks 26 and 52.
	To evaluate the safety and tolerability of BG00011.	The incidence, severity, outcome, and relationship to study treatment of adverse events and serious adverse events. Change from baseline in clinical laboratory test results, vital signs, electrocardiogram (ECG), PFT, and high-resolution computed tomography (HRCT) findings. Immunogenicity (antibodies to BG00011).
	To evaluate the serum concentration of BG00011.	Measurement of BG00011 serum concentrations using sparse pharmacokinetic (PK) sample collection at select timepoints during the study.
	Exploratory Objectives and Endpoints are listed in Section 6.	
Study Design:	Phase 2b randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, PK, and tolerability of BG00011 in subjects with IPF.	
Study Location:	Approximately 100 sites in up to 20 countries are planned, including North America, Europe, and Rest of World.	
Number of Planned Subjects:	Approximately 290 subjects will be randomized.	
Study Population:	This study will be conducted in subjects with mild to moderate IPF who may or may not be receiving background therapy (either nintedanib or pirfenidone,	

	though not both). Detailed criteria are described in Section 8.
Treatment Groups:	Subjects will be randomized in a 1:1 ratio to receive BG00011 or placebo: • BG00011 group: Approximately 145 subjects will receive BG00011 56 mg once weekly by SC injection for 52 weeks. • Placebo group: Approximately 145 subjects will receive placebo dosing once weekly by SC injection for 52 weeks. Subjects will be stratified by the concomitant use of background therapy (nintedanib or pirfenidone) with a goal of a 1:1 ratio of BG00011 plus background therapy to BG00011 monotherapy. At least 20% of subjects will not be on background therapy at the time of randomization.
Duration of Treatment and Follow-up:	Study duration for each subject will be approximately 65 weeks, including the following: • 5-week Screening Period • 52-week Placebo-Controlled Treatment Period • 8-week Follow-Up Period

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	6-Minute Walk Test
αvβ6	alpha v beta 6
AE	adverse event
ALAT	Latin American Thoracic Association
ALT	alanine transaminase
anti-HBc	total hepatitis B core antibody
anti-HBs	hepatitis B surface antibody
AUC	area under the concentration-time curve
AUC_{SS}	area under the concentration-time curve at steady state
AST	aspartate transaminase
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
CBC	complete blood count
CRF	case report form
DL_{CO}	carbon monoxide diffusion capacity
DSMB	data safety monitoring board
ECG	electrocardiogram
ERS	European Respiratory Society
FEV_1	forced expiratory volume over 1 second
FVC	forced (expiratory) vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
[redacted]	[redacted]
IA	interim analysis
ICF	informed consent form

Abbreviation	Definition
ICH	International Council for Harmonisation
IFN-γ	interferon-gamma
IgG1	immunoglobulin G subtype 1
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
IRT	interactive response technology
JRS	Japanese Respiratory Society
[redacted]	[redacted]
LAP	latency-associated peptide
[redacted]	[redacted]
LTBP-1	latent transforming growth factor-beta binding protein-1
mAb	monoclonal antibody
MITT	modified intent to treat
[redacted]	[redacted]
mRNA	messenger RNA
NOAEL	no observed adverse effect level
NOEL	no observed effect level
[redacted]	[redacted]
PFT	pulmonary function test
PHI	protected health information
PK	pharmacokinetic(s)
pSMAD2	phosphorylated SMAD2
QLF	quantitative lung fibrotic reticulation score
RGD	arginine-glycine-aspartic acid
RNA	ribonucleic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SP-A	surfactant A
SP-D	surfactant D
[redacted]	[redacted]

Abbreviation	Definition
$t_{1/2}$	half-life
TGF-β	transforming growth factor-beta
[redacted]	[redacted]
T_{max}	time to reach maximum observed concentration
TLC	total lung capacity
[redacted]	[redacted]
UIP	usual interstitial pneumonia
ULN	upper limit of normal
WBC	white blood cell

3. SPONSOR INFORMATION

Biogen MA Inc. (hereafter referred to as "the Sponsor") is the Sponsor of the study.

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For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

4. INTRODUCTION

BG00011 (humanized, immunoglobulin G subtype 1 [IgG1] anti-alpha v beta 6 [αvβ6] monoclonal antibody [mAb]), formerly known as STX-100, is being developed by the Sponsor as a novel therapeutic treatment for patients with idiopathic pulmonary fibrosis (IPF). BG00011 binds to the αvβ6 integrin, which inhibits the integrin from binding to and activating the latent form of transforming growth factor-beta (TGF-β). TGF-β plays a critical role in the initiation and maintenance of fibrosis, and targeted inhibition of the αvβ6/TGF-β pathway may prevent the development of fibrosis, organ scarring, and organ failure. The clinical development plan for BG00011 is designed to demonstrate that blocking αvβ6 and inhibiting the activation of TGF-β in patients with IPF can prevent or reduce the progression of fibrosis, resulting in preservation of pulmonary function.

4.1. Overview of Idiopathic Pulmonary Fibrosis

IPF is a serious, chronic, progressively fatal lung disease involving replacement of normal lung tissue with fibrotic scar tissue. IPF is a rare disease that predominantly affects the middle aged and elderly (after age 60 years; median age at diagnosis: 66 years [Raghu 2014]). The disease is more common in men than women (male predominance approximately 1.3:1) [Raghu 2014]. Patients with IPF typically live for only 3 to 5 years after diagnosis, with a median survival time of approximately 3.5 years from diagnosis [Fernández Pérez 2010; Ley 2011; Raghu 2014]. The 5-year survival rate is 30% to 50% [Raghu 2018],and fewer than 15% of patients live for 10 years or longer [Lynch 2016]. IPF significantly impairs health-related quality of life [Swigris 2005], and the majority of patients also have serious comorbid conditions [Raimundo 2016].

Globally, North America and Europe have the highest incidence and prevalence of IPF [Hutchinson 2015]. The incidence has been increasing steadily worldwide, in part due to an aging population. The annual incidence of IPF is currently between 3 and 9 per 100,000 persons in Europe and North America. In a review of studies published between 1990 and 2011, the prevalence of IPF ranged from 14.0 to 27.9 per 100,000 persons in the United States and from 1.25 to 23.4 per 100,000 persons in Europe [Nalysnyk 2012]. Recent estimates from South Korea suggest the incidence and prevalence of IPF in Asia may be comparable to that of North America and Europe [Lee 2016].

Clinical features of IPF include progressive cough, dyspnea, restrictive ventilatory defect, and progressive fibrosis and destruction of the lung parenchyma [Lynch 2016]. The diagnosis is made in patients with the appropriate clinical features and the histologic pattern of usual interstitial pneumonia (UIP) [based on lung biopsy or high-resolution computed tomography (HRCT)]. Challenging factors for clinical management include older age, comorbid conditions, and acute unpredictable exacerbations. Acute exacerbations of IPF are defined as sudden (typically less than 30 days onset) unexplained worsening of underlying disease, including new radiological infiltrates (based on HRCT) or UIP pattern. The progressive deterioration of lung function results in respiratory failure. The prognosis following acute exacerbation and deterioration of lung function is poor, with 1-year and 5-year survival rates of 56.2% and 18.4%

following acute exacerbation, which is considerably shorter than in IPF patients without acute exacerbation [Song 2011].

The underlying pathophysiology of IPF is unknown. Whatever the inciting event is, it triggers a TGF-β mediated fibrogenic response. As a part of this response, alveolar epithelial cells via the production of signaling mediators, including TGF-β, tumor necrosis factor, endothelin 1, and cytokines, induce proliferation and activation of fibroblasts and myofibroblasts. This leads to secretion of connective tissue matrix molecules, such as collagen, to replace the damaged tissue but also displaces healthy tissue leading to scarring and ultimately organ failure [du Bois 2010].

4.2. Diagnostic Criteria for IPF

The diagnostic criteria for IPF used in this protocol are derived from evidence-based guidelines developed by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) joint task force for the diagnosis and management of IPF [Raghu 2018].

The diagnosis of IPF requires histopathologic and/or radiologic evidence of UIP and exclusion of other causes of idiopathic interstitial pneumonia and interstitial lung diseases (e.g., occupational or environmental exposures, drug toxicities, collagen vascular diseases).

The ATS/ERS/JRS/ALAT joint task force concludes that, in the appropriate clinical setting, the diagnosis of IPF may be ascertained by HRCT alone if the HRCT image fulfills the criteria for "UIP pattern" or a "probable UIP pattern" in subjects >60 years old (i.e., surgical lung biopsy is not required). However, if the HRCT does not show a definitive UIP pattern or a probable UIP pattern in a subject >60 years old, then a surgical lung biopsy is necessary and specific combinations of the HRCT and histopathological criteria are used to determine the diagnosis of IPF (see Table 1).

To be eligible for this study, subjects must meet the HRCT imaging and/or lung histopathological criteria for UIP shown in Table 1 (in addition to the other inclusion and exclusion criteria):

Table 1: Summary of High-Resolution Computed Tomography and Surgical Lung Biopsy Criteria for Diagnosis of IPF

	Surgical Lung Biopsy				
	Not Available	**Histopathology: UIP Pattern**	**Histopathology: Probable UIP Pattern**	**Histopathology: Indeterminate for UIP**	**Histopathology: Alternative Diagnosis**
HRCT: UIP Pattern	ELIGIBLE	ELIGIBLE	ELIGIBLE	ELIGIBLE	NOT ELIGIBLE
HRCT: Probable UIP Pattern	ELIGIBLE[1]	ELIGIBLE	ELIGIBLE	NOT ELIGIBLE	NOT ELIGIBLE
HRCT: Indeterminate UIP Pattern	NOT ELIGIBLE	ELIGIBLE	ELIGIBLE	NOT ELIGIBLE	NOT ELIGIBLE
HRCT: Alternative Diagnosis	NOT ELIGIBLE	NOT ELIGIBLE	NOT ELIGIBLE	NOT ELIGIBLE	NOT ELIGIBLE

HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.
[1]Only subjects who are >60 years old at Screening are eligible.

4.3. Current Therapies for Idiopathic Pulmonary Fibrosis

To date, no therapies have demonstrated efficacy in halting IPF disease progression. Historically, disease-modifying agents for IPF have included nonspecific anti-inflammatory or immunosuppressive agents (i.e., corticosteroids, azathioprine, and cyclophosphamide), which were used in the United States despite the absence of clinical studies to demonstrate their efficacy, with some ultimately demonstrating harm [Raghu 2012].

Two recently approved therapies, pirfenidone (Esbriet®) and nintedanib (Ofev®), have demonstrated a similar ability to slow deterioration in lung function by nearly 50%; however, patients are still faced with death or lung transplantation as the ultimate outcome [Kistler 2014].

Pirfenidone was approved based on the demonstration of a statistically significant benefit on the forced vital capacity (FVC) in subjects with mild to moderate IPF compared with placebo (Genentech Studies PIPF-004, PIPF-006, and PIPF-016 [Esbriet Prescribing Information 2019/SmPC 2019]. The clinical development program included one 52-week and two nearly

identical 72-week clinical studies. The primary endpoint was the change in percent predicted FVC from baseline to study end. Secondary endpoints included the mean change from baseline in FVC and survival. Of the 3 studies, the 52-week study and 1 of the 72-week studies demonstrated that fewer subjects taking pirfenidone had a meaningful decline (10% or greater) in FVC versus placebo (17% versus 32%, respectively), whereas more subjects maintained stable lung function in the 52-week study (23% versus 10%, respectively). In the 52-week study, a significant reduction in the mean decline in FVC was observed in subjects receiving pirfenidone compared with placebo (difference of 193 mL). In one of the two 72-week studies, there was a significant treatment difference of 157 mL; however, there was no significant difference observed in the other 72-week study. There was no statistically significant difference in all-cause mortality between pirfenidone and placebo. Adverse events (AEs) leading to discontinuation of treatment occurred in 14.6% of subjects treated with pirfenidone. Adverse reactions associated with pirfenidone in >10% of subjects versus placebo include, but are not limited to, gastrointestinal disorders and photosensitivity.

Nintedanib was also approved based on the demonstration of a statistically significant benefit on FVC decline in subjects with mild to moderate IPF in three 52-week clinical studies [one Phase 2 study and two identical Phase 3 studies] (Boehringer Ingelheim Studies 1199.30, 1199.32, and 1199.34 [Ofev Prescribing Information 2015/SmPC]). The primary endpoint in all 3 studies was the annual rate of decline in FVC. Secondary endpoints included time to first acute IPF exacerbation, change from baseline in FVC percent predicted, and survival. A statistically significant reduction in the annual rate of decline of FVC was demonstrated in subjects receiving nintedanib compared with subjects receiving placebo, with differences in the 3 studies of 131 mL (Phase 2 study) and 125 and 94 mL (in the 2 Phase 3 studies). The change from baseline in the percent predicted FVC was lower in the group treated with nintedanib. In addition, the time to first acute IPF exacerbation was significantly reduced in subjects receiving nintedanib in 2 of the 3 studies (the Phase 2 and 1 of the Phase 3 studies), but there was no statistically significant difference in all-cause mortality. The most common serious adverse reactions that were reported more frequently with nintedanib treatment than with placebo were bronchitis (1.2% versus 0.8%, respectively) and myocardial infarction (1.5% versus 0.4%, respectively). AEs leading to discontinuation were reported in 21% of the subjects treated with nintedanib. Adverse reactions associated with nintedanib in ≥10% of subjects compared with placebo included gastrointestinal (GI) disorders such as diarrhea (most common), nausea, increased liver enzymes, and abdominal pain.

A study assessing the real-world experience with pirfenidone and nintedanib indicated that while side effects (predominantly GI with both therapies) are common, the side effects are managed in the majority of patients with a treatment discontinuation rate similar to what was observed in the clinical studies [Hughes 2016]. Among patients using pirfenidone, 16% of AEs resulted in a reduction in dose and 20% of AEs resulted in permanent discontinuation. Among subjects using nintedanib, 15% had a reduction in dose and 26% discontinued treatment.

In real-world data, utilization of antifibrotic medications varies considerably by geographic region. In 3 observational studies in the United States, the prevalence of pirfenidone and nintedanib use ranged from 14% to 55% [Viscidi 2017]. In Western Europe, utilization ranged from 29% to 69% [Behr 2015; Pesonen 2017; Sicras-Mainar 2017; Wuyts 2017]. Utilization

appears to be lower in Eastern Europe; among 107 IPF patients in a registry in Poland, 2% had used pirfenidone [Lewandowska 2017]. In a survey of 344 physicians in Latin America, 21% had prescribed pirfenidone to their IPF patients [Torres Villacreses 2017]. In an observational study in Japan, 33% of IPF patients used pirfenidone [Bando 2015].

As the disease continues to progress, lung transplants for appropriate surgical candidates may be considered. However, the 5-year survival rate after lung transplantation ranged from 47% to 53%, based on data from the International Society for Heart and Lung Transplantation and Organ Procurement and Transplantation Network [Kistler 2014]. Considerations regarding the utility of lung transplantation include the limited availability of donor organs, infection, rejection, and the requirement for lifetime immunosuppressive therapy.

Therapies that can halt or reverse disease progression, increase life expectancy, and improve quality of life while demonstrating minimal side effects remain a treatment goal for patients diagnosed with IPF.

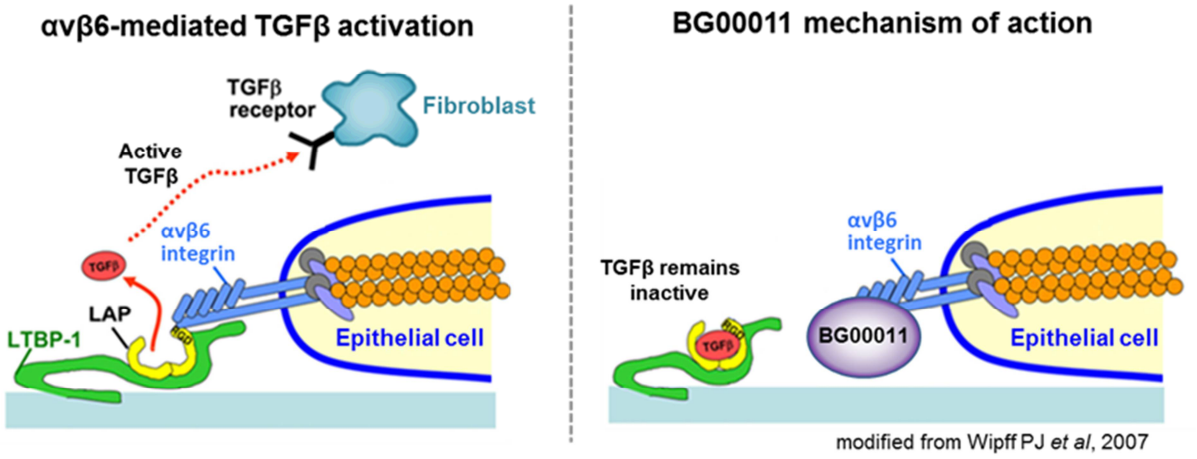
4.4. Profile of Previous Experience With BG00011

4.4.1. Mechanism of Action

TGF-β is a central mediator of fibrogenesis. TGF-β is upregulated and activated in fibrotic diseases, and its signaling results in myofibroblast differentiation and matrix deposition. The αvβ6 integrin is a critical regulator of TGF-β activation. TGF-β is synthesized as a latent precursor protein consisting of latency-associated peptide (LAP) and TGF-β. This complex cannot bind to the TGF-β receptor and is not biologically active. The αvβ6 integrin is expressed at low or undetectable levels in healthy adult tissues but is highly upregulated on epithelial cells during tissue injury and fibrosis. The integrin activates TGF-β by binding to an arginine-glycine-aspartic acid motif within the LAP component of latent TGF-β, leading to the localized activation of the cytokine (Figure 1). BG00011 is a mAb that binds to the αvβ6 integrin and inhibits ligand binding. By blocking the binding of αvβ6 to latent TGF-β, BG00011 prevents αvβ6-mediated TGF-β activation, thereby decreasing TGF-β signaling. Although other mechanisms of TGF-β activation have been identified, studies carried out in αvβ6-deficient mice and with αvβ6-blocking mAbs suggest that αvβ6-mediated activation of TGF-β can prevent the development of fibrosis in the lung, kidney, and liver. Analysis of molecular signatures associated with the progression of fibrosis indicates that the therapeutic impact of the αvβ6-blocking antibodies is mechanistically linked to decreased TGF-β activity.

A key mediator of TGF-β activity is the signal transducer proteins SMAD, which when phosphorylated (phosphorylated SMAD [pSMAD]), regulate the transcriptional activity of TGF-β signaling (Figure 1). Increased pSMAD levels have been positively correlated with lung fibrosis in both the murine bleomycin and radiation models of fibrosis [Chung 2016; Flechsig 2012; Horan 2008]. Given its role in the TGF-β cascade and evidence of correlation with lung fibrosis, pSMAD and several downstream genes were selected as exploratory target engagement biomarkers in nonclinical and the clinical studies with BG00011 in subjects with IPF.

Figure 1: BG00011 Mechanism of Action



αvβ6 = alpha v beta 6; LAP = latency-associated peptide; LTBP-1 = latent transforming growth factor-beta binding protein-1; mAb = monoclonal antibody; RGD = arginine-glycine-aspartic acid; TGF-β = transforming growth factor-beta.
αvβ6 expression is up-regulated on epithelial cells during tissue injury and fibrosis. αvβ6 binds to an RGD motif in the latency-associated peptide region of the latent TGF-β precursor protein, leading to local activation of TGF-β. Anti-αvβ6 mAb interferes with this binding and blocks TGF-β activation.

4.4.2. Nonclinical Experience

Nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies have been performed to support clinical development of BG00011. Inhibition of TGF-β signaling has been shown to be protective in a variety of models of fibrosis, identifying this pathway as an attractive target for therapeutic intervention in IPF. However, given the anti-inflammatory role for TGF-β signaling, appropriate modulation of TGF-β in a tissue specific manner is needed to avoid potentially deleterious systemic effects.

BG00011 is a humanized mAb that cross-reacts with murine, nonhuman primate, and human αvβ6. A murine form of BG00011 (m3G9, previously mu3G9) has demonstrated potent antifibrotic activity in several rodent models of lung, kidney, and liver fibrosis.

4.4.2.1. Pharmacology Models

Nonclinical pharmacology studies to determine the biological activity and safety of BG00011 have been conducted using a murine anti-αvβ6 antibody (m3G9) in mice and BG00011 in cynomolgus monkeys. Several rodent models of fibrosis show increased αvβ6 expression in epithelial cells of the affected tissue, including the lung, kidney, and liver. Efficacy of m3G9 has been demonstrated in models of lung, kidney, and liver fibrosis, as measured by markers of tissue fibrosis, including collagen production and accumulation of α-smooth muscle actin positive fibroblasts [Hahm 2007; Horan 2008; Puthawala 2008].

Key nonclinical studies demonstrating efficacy in lung fibrosis were performed in the bleomycin mouse model, bleomycin-FTY720 mouse model, radiation mouse model, and influenza mouse model. Taken together, the data from these studies indicate that doses of m3G9 at 0.3 and

1.0 mg/kg were consistently associated with improvement in fibrotic response with no significant inflammation in these rodent models of epithelial tissue injury and fibrosis.

In addition, preclinical studies demonstrated that αvβ6 blocking antibody treatment between 0.3 and 1.0 mg/kg led to similar, significant steep reductions of pSMAD in bronchoalveolar lavage (BAL) cells in both mice and cynomolgus monkeys. See the BG00011 Investigator's Brochure for additional information about these studies.

An increased incidence of acute allograft rejection was observed in a monkey kidney transplant study when BG00011 was administered with a standard calcineurin-based immunosuppressive regimen. Therefore, it is recommended that patients with end-stage fibrotic disease requiring organ transplantation do not receive BG00011. Any patient receiving BG00011 who progresses to the point of requiring organ transplantation should immediately discontinue the study treatment.

4.4.2.2. Toxicology Summary

Nonclinical toxicology studies of up to 26 weeks in duration were conducted in the CD-1 mouse and cynomolgus monkey. Murine studies used m3G9, while monkey studies used BG00011. Histologic changes were limited to the lung. These consisted of partially reversed alveolar macrophages, alveolar cellular debris, perivascular lymphoid infiltration, and increases in lung weight in mice and partially reversed alveolar macrophages in monkeys. The no observed adverse effect levels (NOAELs) in the 6-month studies were 1.0 and 10 mg/kg in mice and monkeys, respectively. No carcinogenicity or genotoxicology studies were conducted with BG00011 or m3G9. In the repeat-dose mouse studies with m3G9, low incidences of tumors (such as bronchoalveolar adenoma) were observed sporadically and in a non-dose-related manner. Spontaneous bronchoalveolar lesions have been reported in mouse historical control data. No tumors were noted in monkey studies. Transient elevations of lung tidal and minute volumes were observed in mice. There were no treatment-related changes in pulmonary function, blood pressure, or ECG in monkeys. No neurobehavioral abnormalities were observed, and no histologic changes were found in the central nervous system tissues of mice or monkeys. There were no fertility effects in male and female mice and no teratogenic findings in mice up to the maximum dose of 10 mg/kg. Antidrug antibodies were observed in up to 43% of mice and 25% of monkeys in repeat-dose toxicology studies. For additional information on toxicology studies with BG00011 or m3G9, see the Investigator's Brochure.

4.4.2.3. Nonclinical Pharmacokinetics

The nonclinical PK disposition profiles of BG00011 and m3G9 were characterized in the cynomolgus monkey and mouse, respectively. Following intravenous (IV) administration of a single dose of BG00011 in cynomolgus monkeys, maximum observed concentration (C_{max}) and area under the concentration time curve (AUC) increased with dose. The mean half-life ($t_{½}$) for both IV and subcutaneous (SC) administration was approximately 4 days. BG00011 was maintained primarily within the vasculature, with a calculated bioavailability of approximately 100%.

Following repeated dosing in monkeys in a 3-month toxicity study, BG00011 (1 to 10 mg/kg SC once weekly) demonstrated dose-proportional exposure, with the $t_{½}$ ranging from 8 to 12 days. In a 6-month toxicity study in monkeys, BG00011 (0.1 to 10 mg/kg SC once weekly) showed a greater-than-dose-proportional increase in exposure, and t½ increased with increasing dose. $t_{½}$ ranged from 1.5 to 10 days. In general, the presence of antidrug antibodies was inversely correlated with BG00011 exposure.

4.4.3. Clinical Experience

As of 28 February 2017, a total of 61 subjects (31 subjects with IPF and 30 healthy volunteers) have received BG00011 in 2 completed clinical studies, Phase 1 Study STX-001 and Phase 2a Study 203PF201. Brief summaries of each of these studies are as follows:

Study STX-001

Study STX-001, a Phase 1 randomized, double-blind, placebo-controlled, single-dose, dose-escalation study, was conducted to evaluate the safety, tolerability, PK, and immunogenicity profile of BG00011 administered SC to healthy volunteers. In this study, 40 subjects were enrolled into 5 ascending-dose cohorts (6 active:2 placebo subjects per cohort) and received a single SC dose of BG00011 (range: 0.003 to 0.3 mg/kg) or placebo (saline injection) and were monitored for 3 months after dosing. BG00011 exposure was dose proportional in the 3 highest dose groups for which serum levels were measurable. The $t_{½}$ of BG00011 was approximately 6 days, with peak serum concentrations observed at 5 days after administration. BG00011 was well tolerated, with no deaths, serious adverse events (SAEs), or premature discontinuations related to an AE. No clinically significant changes were noted for any safety measures including AEs, physical examination, vital signs, or clinical laboratory parameters, including pulmonary function tests (PFTs). AEs occurred in 21 of 30 subjects (70%) who received BG00011 and 8 of 10 subjects (80%) who received placebo. The most common AEs were headache, diarrhea, vomiting, arthropod stings, nasopharyngitis, and nasal congestion.

Study 203PF201

Study 203PF201, a Phase 2a, randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study was conducted to evaluate the safety, tolerability, PK, and effects on biomarkers of BG00011 administered SC to subjects with IPF. Forty-one subjects were enrolled into 5 ascending-dose cohorts ranging from 0.015 to 3.0 mg/kg (planned as 3:1 ratio per cohort). Study treatment was administered as once-weekly SC injections for up to 8 weeks, and each subject was monitored during a follow-up period of 8 to 12 weeks (depending on the dose cohort). Thirty-one subjects received BG00011, and 10 subjects received placebo.

The study was monitored by an independent data safety monitoring board (DSMB) and included safety evaluations that would enable detection of respiratory events (e.g., IPF exacerbation; changes in lung function, including decreases from baseline in FVC by ≥12%, total lung capacity by ≥8%, and diffusing capacity of the lungs for carbon monoxide [DL_{CO}] by ≥15%). Four cohorts completed dosing through 1.0 mg/kg. Prior to the completion of dosing in the fifth and highest dosing cohort (3.0 mg/kg), the study was stopped after meeting the prespecified protocol

stopping criteria, when 2 subjects experienced clinically significant sustained decreases from baseline respiratory status. Following the decision to stop the 3.0 mg/kg cohort and additional discussions with the DSMB, the Sponsor conducted a detailed analysis of the available PK, PD, and safety data from all cohorts and concluded that the potential benefit/risk of BG00011 was acceptable for dosing patients with IPF, with appropriate safety monitoring, at doses not exceeding 1.0 mg/kg. A summary of the PK, PD, and safety data for Study 203PF201 is as follows.

Pharmacokinetic data show that after repeated weekly SC administration, BG00011 exposure increased approximately proportionally to doses ranging from 0.015 to 1.0 mg/kg, but increased greater than proportionally at doses >1.0 mg/kg. After the last dose, the mean terminal $t_{½}$ of BG00011 ranged from 168 to 211 hours across the dose range (approximately 174 hours following repeated administration at doses <3.0 mg/kg). Serum concentrations were relatively sustained throughout the 168-hour sampling period, with the time to reach maximum observed concentration (T_{max}) after the last dose occurring at 24 to 48 hours.

In this study, BG00011 decreased the level of phosphorylated SMAD2 (pSMAD2) in BAL cells starting at the 0.3 mg/kg dose and achieved ≥70% reduction at the 1.0 mg/kg dose. In addition, a substantial decrease in gene expression of several prespecified genes linked to TGF-β signaling was also observed between the 0.3 and 1.0 mg/kg doses. These decreases in pSMAD and gene expression established proof of biology.

A total of 170 AEs were reported in the Phase 2a study. Twenty-seven of 31 subjects (87%) who received BG00011 and 7 of 10 subjects (70%) who received placebo experienced at least 1 AE. The majority of AEs were mild or moderate in severity. The most frequent AEs reported in subjects who received BG00011 were cough, dyspnea, and IPF exacerbation (5 subjects each), hypoxia (4 subjects), fatigue, viral upper respiratory infection, injection site pain, headache, and seasonal allergy (3 subjects each).

Four subjects who received BG00011 experienced SAEs, including atrioventricular block and hypoxemia in a subject in the 0.015 mg/kg cohort, IPF exacerbation in a subject in the 1.0 mg/kg cohort; syncope, Type II second-degree atrioventricular block, fractured mandible, and IPF exacerbation in a subject in the 1.0 mg cohort; and respiratory failure in a subject in the 3.0 mg/kg cohort. None of the SAEs were assessed by the respective Investigators as related to study treatment.

One subject (who experienced syncope, Type II second-degree atrioventricular block, fractured mandible, and IPF exacerbation) died due to the IPF exacerbation after discontinuation from the study.

In summary, multiple SC doses of BG00011 up to 1.0 mg/kg were generally well tolerated in the population of subjects with IPF, with the incidence and severity of AEs, and changes in physical examination, vital signs, or clinical laboratory parameters comparable to those expected in the IPF population. Based on a detailed review of the safety, PK, and PD data for Study 203PF201, the Sponsor considers that the potential benefit/risk of BG00011 is acceptable for dosing in subjects with IPF at doses not exceeding 1.0 mg/kg.

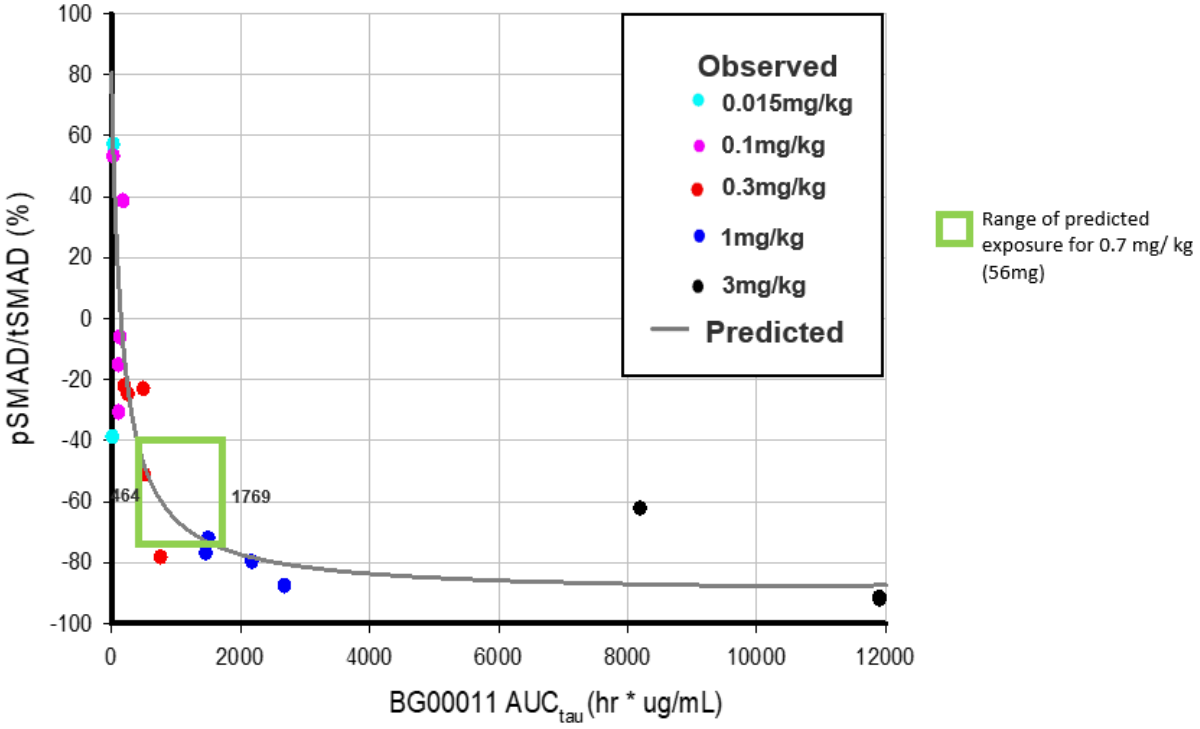
4.5. Study Rationale and Dose Selection

This Phase 2b study is designed to evaluate the treatment effect (change in FVC) of BG00011 administered SC once weekly for 52 doses in subjects with mild to moderate IPF who may or may not be receiving protocol-defined background therapies (i.e., nintedanib or pirfenidone).

As a first-in-class treatment for patients with IPF, the reduction in pSMAD2 levels and gene expression required for clinical efficacy is unknown. Across multiple mouse models of lung fibrosis, αvβ6-blocking antibody treatment with dosing between 0.3 and 1.0 mg/kg leads to significant reductions in pSMAD2 and reduced collagen expression (a marker of fibrosis) without inducing lung inflammation. The steep dose response in pSMAD2 is consistently observed in subjects with IPF (Study 203PF201), in nonhuman primate biomarker studies, and in the rodent models of epithelial injury and fibrotic diseases.

To guide dose selection, an exposure-response analysis was prepared based on reduction in pSMAD2 levels versus BG00011 exposure from observed individual subject data in Study 203PF201 (Figure 2). The area under the concentration time curve at steady state (AUC_{SS}) of the dosing interval after the last dose was used as the exposure variable and the percent change from the baseline level of pSMAD2 was used as the PD response in the assessment of the PK/PD relationship. This curve shows the steep dose response between the 0.3 and 1.0 mg/kg doses.

Figure 2: Plot of BG00011 Exposure and Change in pSMAD2 From Baseline (Study 203PF201)



AUC_{tau} = area under the plasma concentration-time curve for a dosing interval; pSMAD2 = phosphorylated SMAD2.

Note: Two subjects from the 1.0 mg/kg cohort were excluded from the exposure response analysis because they were identified to be outliers (outside 3 standard deviations), without baseline, or below the lower limit of quantitation.

Dose selection for the present study is supported by safety and PK data from the completed single-ascending-dose study in healthy volunteers and the 8-week study in subjects with IPF, along with the 26-week cynomolgus monkey studies, in which an exposure of 31,700 (hr × µg/mL) was identified as the NOAEL. Based on an integrated analysis of safety, PK, and PD, a dose of 0.7 mg/kg (56 mg) of BG00011 was selected to provide the predicted therapeutic exposure that would allow for optimal evaluation of the exposure-response curve with PD responses predicted to have clinical efficacy (median predicted response of 65% [range: 40% to 75%] pSMAD2 reduction) while not exceeding exposures observed at the 1.0 mg/kg dose level and providing an approximate 27-fold margin from the predicted human exposures to the monkey NOAEL.

Since body weight was not identified as a covariate affecting exposure with the currently available data, there is limited pharmacological rationale to use body-weight based dosing over fixed dosing to reduce intersubject variability. In addition, fixed dosing eliminates the need for subjects or caregivers to manually draw doses and mitigates the risk for overdosing or underdosing the desired amount. This finding is also consistent with other PK analyses of therapeutic mAbs [Wang 2009]. An average weight of 80 kg for subjects with IPF, based on

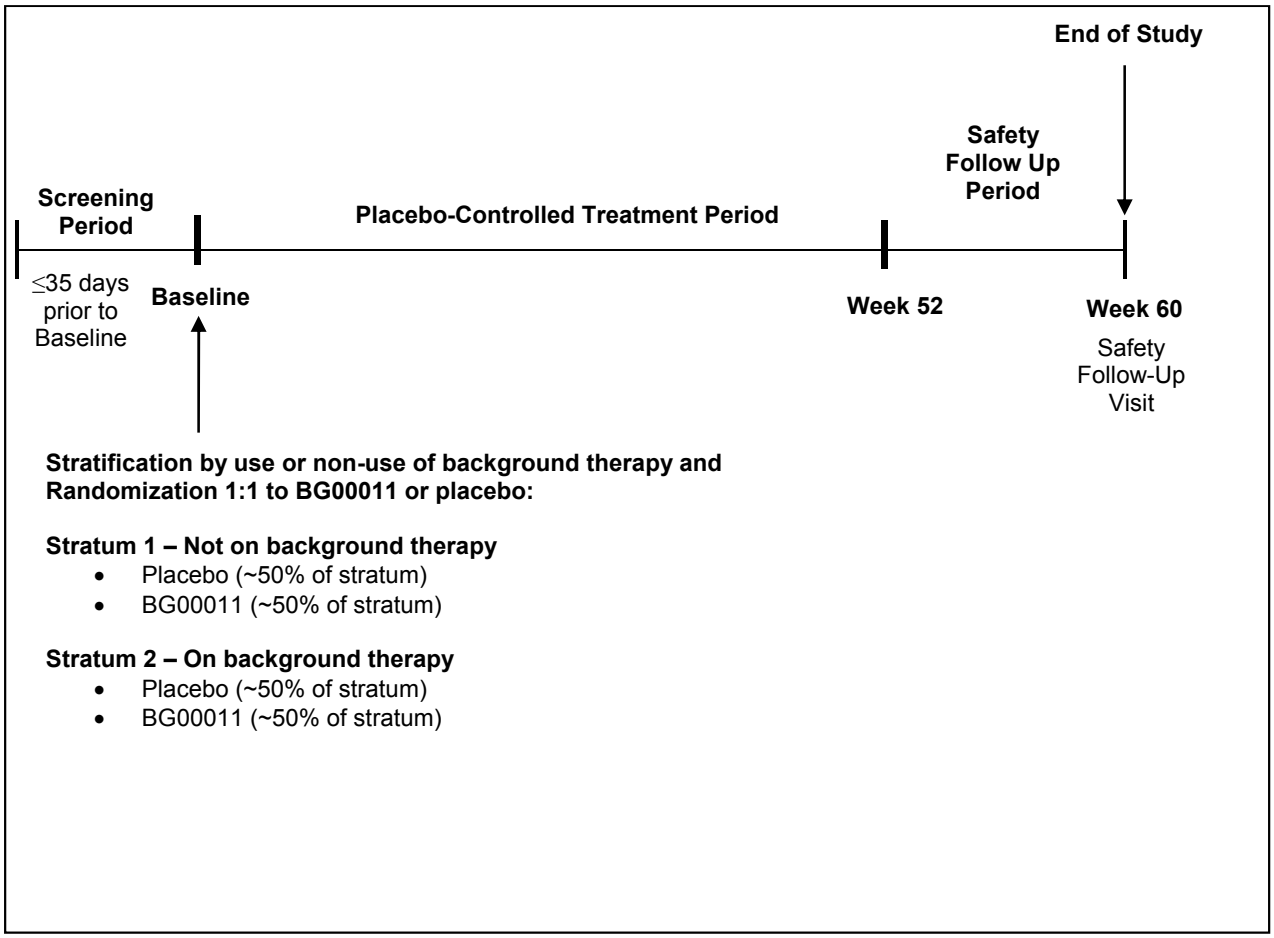
data from prior clinical studies in IPF [Noble 2011; Richeldi 2014], has been used to select the dose of BG00011 56 mg (based on the selection of the target of 0.7 mg/kg dose). Due to limited data in the lower ranges of body weight, subjects will be required to weigh greater than 60 kg to enroll in this Phase 2b study of BG00011.

5. STUDY SCHEMATIC AND STUDY ACTIVITIES

Figure 3 shows a study schematic for Study 203PF203, and Table 2 shows a schedule of study activities.

5.1. Study Schematic

Figure 3: Schematic for Study 203PF203



5.2. Study Activities

Table 2: Schedule of Events

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening**[1]	**Baseline**	**Day 5**[2]	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT**[3]	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
Informed Consent Form	X														
Randomization		X													
Medical History	X	X													
Inclusion/Exclusion Criteria	X	X[4]													
Physical Examination[5]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Body Weight and Height	X								X				X	X	
12-Lead ECG	X	X							X				X	X	X[6]
Vital Signs (temperature, blood pressure, heart rate, respiratory rate)[7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening**[1]	**Baseline**	**Day 5**[2]	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT**[3]	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
Oxygen Saturation[8]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
High Resolution Computed Tomography (HRCT)[9]	X[10]								X[11]				X[11]		X[6]
Spirometry (FVC, FEV_1)	X[12]	X		X	X	X	X	X	X	X	X	X	X		X
Carbon monoxide diffusion capacity (DL_{CO})	X	X		X	X		X		X		X		X		X
Plethysmography		X							X				X		X
6-Minute Walk Test (6MWT)[13]		X							X				X		
[redacted]															

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening**[1]	**Baseline**	**Day 5**[2]	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT**[3]	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
[redacted]															
Serum pregnancy test[14]	X														
HIV, HCV, HBsAg, anti-HBc, anti-HBs Testing	X														
Urine pregnancy test[15]		X		X	X	X	X	X	X	X	X	X	X	X	
Hematology, blood chemistry, and urinalysis	X	X				X			X		X		X	X	X[6]
Serum for BG00011 PK measurement		X[16]	X	X	X	X	X	X	X		X		X	X	
[redacted]															

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening**[1]	**Baseline**	**Day 5**[2]	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT**[3]	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
Serum for anti-BG00011 antibodies		X		X		X			X		X			X	
[redacted]															
Study diary training, administration, and review		X													
Subject completion of study diary[18]		----------Ongoing throughout the study----------													
Administration of study treatment in clinic		X[19]													
Injection training		X	----------Injection retraining to be offered as necessary----------												
Weekly administration of study treatment			To be performed by subject or caregiver once weekly from Week 1 (second dose) through Week 51 (final dose)												
Dispense and/or collect study treatment		X		X	X	X	X	X	X	X	X	X	X		

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening**[1]	**Baseline**	**Day 5**[2]	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT**[3]	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
Compliance/drug accountability				X	X	X	X	X	X	X	X	X	X	X	
Adverse event reporting[20]		**----------Monitor and record throughout Treatment and Follow-Up Periods ----------**													
Serious adverse event reporting	**----------Monitor and record throughout the study ----------**														
Concomitant therapy and procedures recording[21]	**----------Monitor and record throughout the study ----------**														

Abbreviations not already defined in the table: anti-HBc = total hepatitis B core antibody; anti-HBs = hepatitis B surface antibody; EoT = End of Treatment; FEV = forced expiratory volume; FEV_1 = forced expiratory volume over 1 second; FVC = forced vital capacity; HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IPF = idiopathic pulmonary fibrosis; NA = not applicable; PK = pharmacokinetics.

[1] The screening assessments are to occur within 35 days before the Baseline Visit (Day 0).

[2] The Day 5 Visit is for blood collection only (for PK analysis) and may be done in the clinic or at home (by appropriate personnel). Sample collection should occur on Day 5 (not sooner), with a +1 day window allowed (i.e., collection should occur on Day 5 but may occur on Day 6).

[3] If study treatment is permanently discontinued prior to the end of the Treatment Period, an EoT Visit will occur as soon as possible, but within 4 weeks (see Section 10.1 for details). If a subject is withdrawn from the study prior to the end of the Treatment Period, an EoT Visit will occur as soon as possible, but within 4 weeks (see Section 10.2 for details). In either case (discontinuation of treatment or withdrawal from the study) all assessments planned for the Week 52 Visit, except for the HRCT scan, will be performed at the EoT Visit. However, if the EoT Visit falls within the visit window for the Week 26 Visit, the HRCT should be performed.

[4] Entry criteria will be rechecked prior to dosing at the Baseline Visit (Day 0). Investigator to confirm eligibility.

[5] A full physical examination will be performed at the Screening, Baseline, Week 26, and Week 52 Visits, and at the EoT Visit in cases of early withdrawal from the study. At all other study visits, an abbreviated physical examination may be performed (must always include a cardiopulmonary examination and symptom-based examination).

[6] Imaging studies, plethysmography (lung volumes), ECG, or clinical laboratory tests at the IPF Exacerbation Visit will be at the discretion of the Investigator. The optional imaging study at the IPF Exacerbation Visit may be a chest X-ray or HRCT scan.

[7] Blood pressure is to be performed with the subject sitting, after at least 5 minutes at rest. Temperature may be taken by oral or tympanic method.

[8] Using pulse oximeter, oxygen saturation will be measured after the subject has been at rest for at least 5 minutes. The amount of supplemental oxygen the subject is receiving, if any, should be noted.

[9] Noncontrast chest HRCT through the full chest at suspended full inspiration and full expiration will be performed at Screening, Week 26, and Week 52, as detailed in the imaging procedure manual.

[10] A chest HRCT scan performed within 12 months of Screening can be used to determine initial eligibility to enter Screening (to prevent further screening assessments if HRCT does not meet the criteria for IPF). Regardless of whether a historical chest HRCT was submitted, all subjects are required to receive a chest HRCT at Screening. For determination of subject eligibility, all HRCT scans, including the historical and Screening Visit scans, must be consistent with the protocol-defined eligibility of IPF. Eligibility read of the HRCT will be performed by a central radiologist. Historical biopsy data may be provided to support eligibility based on HRCT (see Section 7.2.1).

[11] HRCT will be performed at Weeks 26 and 52 for safety monitoring. Additionally, change from baseline in pulmonary fibrosis will be evaluated by a central radiologist.

[12] Spirometry (before and after bronchodilator use) will be performed to determine eligibility. If the subject qualifies for the study, 1 subsequent spirometry evaluation, without bronchodilator administration, will be performed at the Baseline Visit.

[13] Each test consists of 2 walks.

[14] Serum pregnancy test for women of childbearing potential only. Results must be negative for participation in the study.

[15] Urine pregnancy test for women of childbearing potential only.

[16] Baseline (Day 0) blood samples for PK [redacted] analysis are to be collected before dosing.

[17] Samples can be collected where approved by local regulatory authorities. Subjects must sign a separate consent form.

[18] Documentation of background therapy dosing, including any changes in dose or dosing schedule, should be captured daily in the subject's study diary. Diary entries should be reviewed periodically by study site personnel to ensure compliance and completeness.

[19] Subjects will be observed in the clinic for a minimum of 1 hour following administration of study treatment.

[20] Adverse events are to be captured after the first dose of study treatment through the final study visit. Events that occur prior to dosing should be entered on the Medical History case report form.

[21] All concomitant medications being taken at the time of initial screening (including medications discontinued at that time) through the final study visit are to be recorded on the CRF.

6. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoints**
To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF.	Yearly rate of change in FVC (expressed in mL over 52 weeks) in subjects randomized to BG00011 compared with placebo.
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF as determined by change in percent predicted FVC.	Yearly rate of change in FVC, expressed in percent predicted, over 52 weeks.
To assess progression-free survival in subjects who receive BG00011 compared with placebo.	Time to progression, as defined by a composite endpoint, including any of the following events: • Absolute decline of 10% predicted in FVC (FVC percent predicted$_{baseline}$ – FVC percent predicted$_{progression}$ ≥10%). • Nonelective hospitalization for respiratory events. • Lung transplantation or death.
To assess the occurrence of IPF exacerbation (using modified diagnostic criteria for acute IPF exacerbation derived from [Collard 2007]) in subjects who receive BG00011 compared with placebo.	• Time to first acute exacerbation, measured in days. • Proportion of subjects with at least 1 acute exacerbation during the 52 weeks on study. • Number of exacerbations during 52 weeks.
To assess the incidence of absolute decline in FVC ≥10% in subjects who receive BG00011 compared with placebo.	Number of subjects with absolute decline of 10% predicted in FVC (FVC percent predicted$_{baseline}$ – FVC percent predicted$_{progression}$ ≥10%) over 52 weeks.

To assess the time to death or lung transplantation in subjects who receive BG00011 compared with placebo, and the transplant-free survival rate at Week 26 and Week 52.	Time to death or lung transplantation, measured in days.
To assess the time to nonelective hospitalizations in subjects who receive BG00011 compared with placebo,	Time to all nonelective hospitalizations and to nonelective respiratory hospitalizations, measured in days.
To assess additional PFT findings in subjects who receive BG00011 compared with placebo.	• Change in absolute and percent predicted FVC from baseline over time. • Carbon monoxide diffusion capacity (DL_{CO}), absolute and percent predicted changes from baseline over time. • Total lung capacity, as measured by plethysmography, absolute and percent predicted changes from baseline over time.
To assess performance on the 6MWT in subjects who receive BG00011 compared with placebo.	Change from baseline in 6MWT parameters at Weeks 26 and 52.
To evaluate the safety and tolerability of BG00011.	• The incidence, severity, outcome, and relationship to study treatment of AEs and SAEs. • Change from baseline in clinical laboratory test results, vital signs, ECG, PFT results, and HRCT findings. • Immunogenicity (antibodies to BG00011).
To evaluate the serum concentration of BG00011.	Measurement of BG00011 serum concentrations using sparse PK sample collection at select timepoints during the study.

Exploratory Objectives	Exploratory Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted] • [redacted] • [redacted] • [redacted]
[redacted]	[redacted]
[redacted]	• [redacted] • [redacted] • [redacted]
[redacted]	• [redacted] • [redacted] • [redacted]

[redacted]	• [redacted]

[redacted]

7. STUDY DESIGN

7.1. Study Overview

This is a Phase 2b randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, PK, and tolerability of BG00011 in subjects with IPF. The study will be conducted at approximately 100 sites in up to 20 countries in North America, Europe, and Rest of World. Approximately 290 subjects are planned to be randomized.

To be eligible for the study, subjects must have a diagnosis of IPF consistent with adapted ATS/ERS/JRS/ALAT guidelines (Section 4.2 and Table 1) and meet the eligibility criteria outlined in the protocol. Eligibility for the study will be determined centrally. In addition, features of IPF at Screening must include: FVC ≥50% of predicted value; DL_{CO} (corrected for hemoglobin) ≥30% of predicted value; oxygen saturation ≥90% at rest (receiving ≤2 L/min of supplemental oxygen).

Subjects with IPF who do not meet the criteria for participation in this study under Version 2 of the protocol may be rescreened one time only after discussion between the Principal Investigator and the Sponsor. Subjects with IPF who did not meet the criteria for participation in this study (i.e., a screen failure) under Version 1 of the protocol due to previously adapted ATS 2011 guidelines or hepatitis B criteria, may be screened and rescreened again under Version 2 of the protocol.

Subjects will be stratified by background therapy status (subjects receiving background therapy and subjects not receiving background therapy) and randomized in a 1:1 ratio of BG00011 to placebo (Figure 3). Enrollment will also be monitored to ensure that subjects not receiving background therapy represent at least 20% of each treatment group.

Subjects will receive weekly injections of BG00011 or placebo, as a solution for SC injection in a prefilled syringe, for 52 consecutive weeks (a total of 52 doses). The first dose will be administered at the Baseline (Day 0) Visit. The rest of the doses may be administered independently (e.g., not at the study site) by the subject or the subject's caregiver.

Background therapy for IPF with pirfenidone or nintedanib will be allowed during the study. The subject must be on a stable dose of either medication for at least 8 weeks prior to randomization. The subject is not to be on both medications simultaneously and should not initiate background therapy during the study. In cases where the Investigator feels that background therapy is clinically indicated, this therapy can be started, but the initiation of background therapy during the study will be considered a protocol deviation. While participating in the study, every effort should be made to maintain the subject on a stable dose of background therapy, and dosing should not exceed the labeled maximum dose. However, background therapy dosing may be adjusted or discontinued by the subject's pulmonary care physician. Note that a subject may continue in the study on their assigned study treatment if background therapy is initiated, adjusted, or discontinued. Subjects will maintain a diary to record background therapy dosing and any adjustments made in their therapy.

Assessment of pulmonary function by spirometry (FVC, FEV_1, and FEV_1/FVC) before and after bronchodilator use will be performed at Screening. During the Treatment Period, spirometry evaluation (without bronchodilator use) will be performed at the Baseline Visit and at all Treatment Period visits (excluding Day 5). Other PFTs include DL_{CO} (corrected for Hgb), to be assessed at Screening, Baseline, and Weeks 4, 8, 16, 26, 38, and 52; and total lung capacity and residual volume, to be assessed by full-body plethysmography at Baseline, Week 26, and Week 52. All PFT results will be reviewed centrally.

An independent data safety monitoring board (DSMB) will review the unblinded safety and available PK data throughout the study (at least quarterly) to assess the overall safety profile (see Section 19.2.2 for additional information).

7.2. Study Duration, Study Visits, and Follow-Up

Study duration for an individual subject is approximately 65 weeks, including a Screening Visit up to 5 weeks prior to the first dose of study treatment, a Placebo-Controlled Treatment Period of 52 weeks, and a Safety Follow-Up Visit 8 weeks after the end of the Treatment Period.

7.2.1. Screening

Subjects will undergo screening assessments within 5 weeks (35 days) prior to dosing. Qualifying assessments including medical history, physical examination, vital signs, 12-lead ECG, oxygen saturation, PFTs (before and after bronchodilator administration), HRCT, and clinical laboratory tests including pregnancy testing (women of childbearing potential only), and testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or total hepatitis B core antibody (anti-HBc), hepatitis B surface antibody (anti-HBs) and hepatitis C virus (HCV) antibody will be performed. If the HCV antibody test is positive, hepatitis viral load will be evaluated for active hepatitis C infection.

A chest HRCT scan performed within 12 months of Screening can be used to determine initial eligibility to enter Screening (to prevent further Screening assessments if HRCT does not meet criteria for IPF). Regardless of whether a historical chest HRCT was submitted, all subjects are required to receive a chest HRCT at Screening. For determination of subject eligibility, all HRCT scans, including the historical and Screening Visit scans, must be consistent with the protocol-defined eligibility of IPF. If a historical surgical lung biopsy was performed as part of the subject's initial IPF diagnosis and is available, it must be submitted for central review. Surgical lung biopsies will not be offered as an assessment in this study. The diagnosis of IPF used for eligibility by HRCT and surgical lung biopsy (if available) will be confirmed centrally.

If historical lung biopsy slides are submitted for screening, the central reviewer will return the slides to the site when the review is complete, and the site will return the slides to the original source or provider, as applicable.

Screening assessments (e.g., clinical laboratory assessments or PFTs) for subjects with IPF who do not meet the criteria for participation in this study under Version 2 of the protocol may be rescreened one time only, after discussion between the Principal Investigator and the Sponsor, if

there are questionable results or if abnormalities are felt to be due to inherent variability of the test procedure. Subjects with IPF who did not meet the criteria for participation in this study (i.e., a screen failure) under Version 1 of the protocol due to previously adapted ATS 2011 guidelines or hepatitis B criteria may be screened and rescreened again under Version 2 of the protocol. If a subject must be rescreened for study entry, results from previous screening assessments may be used, as long as the screening windows for those assessments are met and all spirometry data used for subject qualification are derived from a single day. If any PFTs are to be repeated, only the tests that are felt to be questionable should be repeated (i.e., spirometry, DL_{CO}, or plethysmography).

Following confirmation of eligibility on the Screening PFT, subjects will undergo 1 additional set of PFTs without bronchodilator administration to establish their baseline lung function; this assessment will be performed at the Baseline (Day 0) Visit.

Upon fulfilling all of the inclusion criteria and none of the exclusion criteria, subjects will be scheduled to return to the clinic for the Baseline predose evaluations and to ensure that they still qualify for the study.

7.2.2. Placebo-Controlled Treatment Period

The Placebo-Controlled Treatment Period begins with the Baseline (Day 0) Visit and ends with the End of Treatment Visit at Week 52. At the Baseline Visit, the subject's medical history, physical examination, inclusion/exclusion criteria, vital signs, weight and height, oxygen saturation, ECG, and pregnancy status (women of childbearing potential only) will be assessed. Baseline evaluations of PFTs, 6MWT, [redacted] will be obtained. Predose blood samples will be collected for baseline laboratory clinical laboratory tests, [redacted] PK, and antibody assessments. After confirmation of inclusion and exclusion criteria, the subject will be stratified based on use or nonuse of background therapy and then randomized to receive BG00011 56 mg SC or placebo. The subject and/or their caregiver will receive instruction and training on the administration of study treatment, documentation of administration in the study diary, and proper handling of study treatment supplies. The first dose of study treatment will then be administered under the supervision of study site personnel. The subject will be observed for a minimum of 1 hour following the first administration of study treatment. The subject will then be discharged with instructions to return to the study site for Treatment Period visits at Day 5 (for collection of a blood sample for PK analysis only, which may also be done at the subject's residence) and at Weeks 4, 8, 12, 16, 20, 26, 32, 38, 44, and 52 (End of Treatment Visit). See Table 2 for a complete schedule of assessments to be performed at each visit.

7.2.3. Safety Follow-Up Visit

A Safety Follow-Up Visit is to occur 8 weeks after the End of Treatment Visit. Therefore, if the End of Treatment Visit occurs at Week 52, as planned, the Safety Follow-Up Visit will occur at Week 60. See Table 2 for a schedule of assessments to be performed at the Safety Follow-Up Visit.

7.2.4. Study Treatment Discontinuation

If study treatment is discontinued prematurely (i.e., before the subject completes the 52-dose regimen), the subject must return for an End of Treatment Visit as soon as possible but within 4 weeks after discontinuation of treatment. If the End of Treatment Visit occurs in the visit window for the next scheduled visit, then the End of Treatment Visit may be substituted for the scheduled visit. Subjects will then complete all remaining visits as scheduled. See Section 10.1 for additional details about study treatment discontinuation.

7.2.5. Withdrawal From the Study

If a subject is withdrawn from the study, an End of Treatment Visit will be scheduled or performed as soon as possible but within 4 weeks. See Section 10.2 for additional details about withdrawal from the study.

7.2.6. Unscheduled Visit for Acute Exacerbation of IPF

A subject who experiences a worsening of respiratory status at any time during the study should immediately contact their treating physician. The subject should also notify the Investigator (if different than the treating physician) to schedule the IPF Exacerbation Visit as soon as possible so that the Investigator may assess and confirm the IPF exacerbation. Should the subject be unable to come to the clinic for the IPF Exacerbation Visit, the Investigator should attempt to complete the Investigator's determination of IPF exacerbation (see Section 7.2.6.1) as soon as possible.

The IPF Exacerbation Visit should include the following:

- Physical examination
- Vital signs
- Oxygen saturation
- Spirometry
- DL_{CO}
- Imaging studies (chest X-ray or HRCT) if not performed at another facility
- Investigator's determination of IPF exacerbation (see Section 7.2.6.1)

This visit may also include the following at the Investigator's discretion:

- ECG
- Clinical laboratory tests (hematology, blood chemistry, and urinalysis)
- Other tests or evaluations at the discretion of the Investigator

Note: If an IPF exacerbation is suspected at the time of a scheduled visit or is to be evaluated at a scheduled visit, the IPF exacerbation assessments listed above must be performed at the scheduled visit if not already included.

A subject who is evaluated, treated, or hospitalized at a facility other than the study site should contact the study site following that visit to determine if the subject should come in for a stand-alone IPF Exacerbation Visit or have additional IPF exacerbation assessments during a routine, scheduled study visit. In addition, if a subject was hospitalized or had IPF exacerbation assessments at another facility, study site personnel should make every effort to obtain sufficient medical records in order to determine the following:

- Possible triggers or causes of the event.
- The results of relevant tests and assessments, including but not limited to:
  - Detailed radiography reports and copies of images of all radiographic examinations (e.g., chest X-ray or HRCT scan) for submission to the central imaging vendor.
  - Spirometry, body plethysmography (lung volume), and/or DL_{CO} testing reports.
- Descriptions of the severity and duration of the event.
- Details of the medical treatment provided, including relevant medications and other major elements of the clinical management.
- The subject's response to the treatment and clinical status at the time of discharge.

7.2.6.1. Determination of IPF Exacerbation

Based on the results obtained from evaluations at the IPF Exacerbation Visit and/or the records obtained from a visit to another facility (if applicable), the Investigator will determine whether an IPF exacerbation or suspected IPF exacerbation has occurred.

Specific criteria for acute exacerbation of IPF will be determined by the Investigator, using a modified definition of IPF exacerbation derived from the IPF Clinical Research Network (IPFnet) definition of acute exacerbations of IPF in 2007 [Collard 2007], as follows:

- Unexplained worsening or development of dyspnea within 30 days.
- New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit.
- Exclusion of infection per routine clinical practice and microbiological studies.
- Exclusion of alternative causes per routine clinical practice, including the following:
  - left heart failure
  - pulmonary embolism
  - identifiable cause of acute lung injury

The Investigator's determination of IPF exacerbation based on [redacted] (2007 [redacted]) definitions should be documented on the appropriate CRF.

As noted, treatment for an acute exacerbation is at the discretion of the Investigator and medications (such as prednisone) can be freely initiated or increased at the Investigator's discretion.

7.3. Study Stopping Rules

Biogen may terminate this study at any time. The Sponsor will notify Investigators if the study is to be placed on hold, completed, or terminated.

The DSMB will conduct regular reviews of all safety data in an unblinded format. Following each review, the DSMB will provide a recommendation to the Sponsor regarding the appropriateness of continuing the study from a safety perspective, as well as any other recommendations relevant to study conduct and/or subject safety.

The DSMB may recommend discontinuing the study if the event rate in the BG00011 treated arm is 20% higher compared with placebo. The events include, but may not be limited to:

- cumulative number of deaths and/or;
- number of lung transplantations and/or;
- cumulative number of subjects with a confirmed absolute decline of % predicted FVC ≥15 from baseline.

The meeting intervals and the procedures used to provide and assess the data will be described in detail in the DSMB charter.

7.4. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of randomization, or at the timepoint specified in the individual eligibility criterion listed:

1. Ability of the subject or his/her legally authorized representative to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

2. Aged ≥40 years at the time of informed consent.

3. Female subjects must be surgically sterile, postmenopausal (minimum 1 year without menses), or agree to use 1 or more of the following forms of highly effective contraception from the time of signing the informed consent form (ICF) until 3 months after the last injection of study medication: hormonal (i.e., oral, transdermal, implant, or injection); intrauterine device; vasectomized partner (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate); or abstinence. Male subjects must also agree to use 1 or more of the above forms of birth control for either themselves or their partner(s), as appropriate, from the time of signing the ICF until 4 months after the last injection of study medication.

4. IPF diagnosed based on modified ATS/ ERS/JRS/ALAT IPF guideline for diagnosis and management, within 3 years of Screening (see Section 4.2).

5. Combination of HRCT pattern and, if one has been obtained, surgical lung biopsy pattern, as assessed by central reviewers, consistent with diagnosis of IPF (see Section 4.2).

   Note: A chest HRCT performed within 12 months of Screening can be used to determine initial eligibility to enter Screening and must be submitted to the central imaging vendor for eligibility read (to prevent further Screening assessments if HRCT is not consistent with IPF). Regardless of whether a historical chest HRCT was submitted, all subjects are required to receive a chest HRCT at Screening. If a historical HRCT is not available or not submitted, then the HRCT performed at the Screening Visit will be used to determine subject eligibility. For determination of subject eligibility, all HRCT scans, including the historical and Screening Visit scans, must be consistent with the eligibility criteria for IPF. Eligibility read of the HRCT will be performed by a central radiologist.

6. DL_{CO} (corrected for hemoglobin): 30% to 79% predicted of normal at Screening, with no clinically significant deterioration between the Screening Visit and randomization, as determined by the Investigator.

7. FVC ≥50% predicted of normal at Screening, with no clinically significant deterioration between the Screening Visit and randomization, as determined by the Investigator.

8. If a subject is taking nintedanib or pirfenidone, they must be on a stable dose for at least 8 weeks prior to randomization.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of Screening, the time of randomization, or at the timepoint specified in the individual criterion listed:

Lung Function

1. Unable to perform PFTs or undergo HRCT procedure.

2. Peripheral capillary oxygen saturation (SpO_2) <90% at rest (if on oxygen supplementation, must be ≤2 L/min at rest).

3. Findings that are diagnostic of a condition other than UIP based on the combination of surgical lung biopsy (if available), HRCT imaging, transbronchial lung biopsy, or BAL, according to central review of imaging and pathology.

4. Airway obstruction (i.e., prebronchodilator FEV_1/FVC <0.7) or evidence of a bronchodilator response as defined by an absolute increase of ≥12% **and** an increase of ≥200 mL in FEV_1 or FVC, or both, after bronchodilator use, compared with the values before bronchodilator use at Screening.

5. End-stage fibrotic disease likely requiring organ transplantation within 12 months, or if the subject has initiated active evaluation for organ transplantation.

6. The extent of emphysema in the lungs exceeds fibrosis, based on central review of HRCT scans.

7. In the opinion of the Investigator, the subject has experienced significant clinical deterioration between the Screening Visit and randomization.

Medical History

8. Body weight <60 kg at Screening.

9. History of or ongoing malignant disease, including solid tumors and hematologic malignancies, with the exception of basal cell carcinomas, squamous cell carcinomas, and carcinoma in situ of the cervix that have been completely excised and considered cured >2 years prior to Screening.

10. Significant cardiac disease (e.g., New York Heart Association Class 3 or 4; myocardial infarction within the past 6 months; unstable angina; coronary angioplasty or coronary artery bypass graft within the past 6 months; uncontrolled atrial or ventricular cardiac arrhythmias; or pulmonary hypertension requiring pharmacologic treatment).

11. Clinical diagnosis of any connective tissue disease (including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis) or a diagnosis of interstitial pneumonia with autoimmune features as determined by the Investigator applying the recent ERS/ATS research statement [Fischer 2015]. Note: Serological testing is not needed if not clinically indicated.

12. History of organ transplant at any time.

13. Female who is pregnant or breastfeeding.

14. Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) that required hospitalization or was clinically significant in the opinion of the Investigator, within 3 months prior to Screening.

15. Fever (body temperature > 38°C) or symptomatic viral or bacterial infection within 2 weeks prior to the Screening Visit or the Baseline Visit.

16. History or positive test result at Screening for human immunodeficiency virus. Current hepatitis C infection (defined as positive HCV antibody and detectable HCV ribonucleic acid [RNA]). Participants with positive HCV antibody and undetectable HCV RNA are eligible to participate in the study. Current hepatitis B infection (defined as positive for hepatitis B surface antigen [HBsAg] and/or anti-HBc. Participants with immunity to hepatitis B from previous natural infection (defined as negative HBsAg, positive anti-HBc, and positive anti-HBs or vaccination (defined as negative HBsAg, negative anti-HBc, and positive anti-HBs) are eligible to participate in the study.

17. Known hypersensitivity to BG00011 or components of the BG00011 formulation or matching placebo.

18. Active drug or alcohol abuse (as defined by the Investigator) within 3 months prior to Screening.

19. Other disease that may interfere with testing procedures or, in the judgment of the Investigator, may interfere with study participation or may put the patient at risk when participating in this study.

20. Has a disease other than IPF with a life expectancy <2.0 years (Investigator assessment).

21. Other unspecified reasons that, in the opinion of the Investigator or the Sponsor, make the subject unsuitable for enrollment.

Laboratory Parameters

22. Screening values for the following laboratory tests (1 retest within 2 weeks is allowed):
    - Hemoglobin <10 g/dL
    - WBC count $<3.00 \times 10^3/\mu L$
    - Neutrophils $<1.50 \times 10^3/\mu L$
    - Platelets $<80 \times 10^3/\mu L$
    - Total bilirubin >1.5 mg/dL
    - Aspartate transaminase (AST) or alanine transaminase (ALT) >2 × upper limit of normal (ULN)

Medications

23. Currently receiving high-dose corticosteroid, cytotoxic therapy (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), vasodilator therapy for pulmonary hypertension (e.g., bosentan), unapproved (e.g., IFN-γ, penicillamine, cyclosporine, mycophenolate, N-acetylcysteine [may vary by country]) and/or investigational therapy for IPF or administration of such therapeutics within 5 half-lives of the agent prior to initial screening in this study. A current dose of ≤10 mg/day of prednisone or its equivalent is acceptable if the dose is expected to remain stable during the study.

24. Treatment with another investigational drug, investigational device, or approved therapy for investigational use within 5 half-lives of the agent prior to initial screening in this study.

25. Live/attenuated vaccinations within 12 weeks prior to Screening (inactivated influenza vaccine is permitted).

Other

26. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
27. Blood donation (1 unit or more) within 1 month prior to Screening.

28. Male or female planning a pregnancy during the duration of this study. A serum pregnancy test will be performed on all female subjects of childbearing potential.

29. Inability to comply with study requirements.

30. Use of any tobacco product and/or inhaled substance, including but not limited to tobacco or marijuana products, and/or the use of any electronic cigarette or vaping device, within 12 weeks prior to Screening (note that respiratory inhalers for delivery of prescribed medication for pulmonary disease are allowed).

9. SCREENING AND RANDOMIZATION

9.1. Screening

Subjects must provide informed consent before any screening tests are performed (Section 17.3). Participating study sites are required to document all screened candidates initially considered for inclusion in the study.

Screen failures are defined as subjects who sign the ICF but are not subsequently randomized or dosed. If a subject is considered a screen failure, the reasons for exclusion must be documented in the subject's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Subjects with IPF who do not meet the criteria for participation in this study under Version 2 of the protocol may be rescreened one time only after discussion between the Principal Investigator and the Sponsor. Subjects with IPF who did not meet the criteria for participation in this study (i.e., a screen failure) under Version 1 of the protocol due to previously adapted ATS 2011 guidelines or hepatitis B criteria, may be screened and rescreened again under Version 2 of the protocol.

9.2. Randomization

Subjects will be randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2.

Subjects will be assigned a unique identification number that will be used on study-related documents pertaining to the subject. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment or continue in the study.

Randomization will be performed using interactive response technology (IRT). Subjects will be randomized to receive BG00011 or placebo in a 1:1 ratio.

Refer to the Study Reference Guide for details on randomization.

9.3. Blinding Procedures

This is a randomized, double-blinded, placebo-controlled study.

All study staff will be blinded to the subject treatment assignments. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families,

or any member of the study team, either at the study site or at the Sponsor, except the unblinded Pharmacy staff and designated Sponsor personnel.

At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, the Sponsor will provide the randomization codes to Investigators, who then can inform their subjects about the treatment received.

10. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

Study treatment discontinuation is defined as the premature ending of study treatment dosing, i.e., when a subject permanently stops taking the study treatment before the last dose (the Week 51 dose). Reasons for mandatory study treatment discontinuation are listed in Section 10.1.1. The primary reason for study treatment discontinuation must be recorded in the subject's CRF.

Subjects who discontinue study treatment must return for an End of Treatment Visit as soon as possible, but within 4 weeks after discontinuation of treatment. All assessments planned for the Week 52 Visit except the HRCT scan will be performed. If the End of Treatment Visit occurs in the visit window for the next scheduled visit, then the scheduled visit may serve as the End of Treatment Visit, and all assessments for the End of Treatment Visit should occur at that time. Subjects will go on to complete all remaining visits as scheduled, including the Week 52 and Safety Follow-Up Visits (see Table 2 for a list of assessments to occur at the End of Treatment and Safety Follow-Up Visits).

Note: A subject who misses 1 or more doses of study treatment should restart study treatment, receive all remaining doses, and complete all remaining study visits.

See Section 10.2 for information related to the withdrawal of subjects from study.

10.1.1. Reasons for Study Treatment Discontinuation

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject experiences an AE that necessitates permanent discontinuation of study treatment.
- If organ transplantation is planned to occur during the study treatment or Safety Follow-Up Period.
- The subject experiences an urgent medical event that necessitates unblinding of the subject's treatment assignment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.

- The subject withdraws consent to continue study treatment.

10.1.1.1. Safety Criteria for Study Treatment Discontinuation

Liver Chemistry:

Liver chemistry threshold discontinuation criteria have been designed to ensure subject safety and to evaluate liver event etiology during administration of study treatment and during the Follow-Up Period. Study treatment will be discontinued if any of the following criteria are met:

- AST or ALT ≥3 × ULN and total bilirubin level ≥2 × ULN
- AST or ALT ≥5 × ULN: study treatment will be discontinued if the result is confirmed upon retest within 48 hours.
- AST or ALT ≥3 × ULN: study treatment will be discontinued if associated with the appearance or worsening of rash or hepatitis symptoms (i.e., fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash or eosinophilia).

10.2. Withdrawal of Subjects From the Study

Study withdrawal is defined as the premature ending of study visits and assessments. The reasons for mandatory study withdrawal are listed below (Section 10.2.1). Note that discontinuation of study treatment does not require withdrawal from the study if a subject continues to attend clinic visits and complete assessments.

If a subject is withdrawn from the study, an End of Treatment Visit will be scheduled or performed as soon as possible but within 4 weeks. All assessments planned for the Week 52 Visit except the HRCT scan will be performed (see Table 2 for a list of assessments to occur at the End of Treatment Visit).

If a subject is unwilling or unable to attend, at minimum, the End of Treatment Visit, and decides to withdraw consent, the reason for withdrawal will be documented and no further assessments will be obtained.

Subjects who are withdrawn from the study will not be replaced.

10.2.1. Reasons for Withdrawal of Subjects from the Study

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

- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.

10.3. Lost to Follow-Up

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.

- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record.

- If the subject continues to be unreachable, that subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the Directions for Handling and Administration (DHA).

Approximately 290 subjects will be randomized into 2 dose groups as follows:

- Group 1: BG00011 56 mg by SC injection, once weekly for 52 weeks
- Group 2: Placebo by SC injection, once weekly for 52 weeks

The first dose of BG00011 or placebo (study treatment) will be administered at the study site during the Baseline Visit (Day 0). All subsequent doses should be administered by the subject or the subject's caregiver.

11.2. Modification of Dose and/or Treatment Schedule

The dosage and dosing schedule cannot be modified. A window of +2 days is allowed without qualifying as an overdose for non-Baseline Visits; however, subsequent doses should adhere to the dosing schedule initiated at the Baseline Visit.

11.3. Precautions

Subjects will be monitored by study site personnel for at least 1 hour after administration of the first dose of study treatment.

11.4. Compliance

Compliance with study treatment dosing is to be documented by the subject or the subject's caregiver in the electronic study diary and monitored at each study visit by study site personnel.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the time a subject is screened for the study and the final study visit.

11.5.1.1. Allowed Concomitant Therapy

A current dose of ≤10 mg/day of prednisone or its equivalent is acceptable if it has been stable for at least 8 weeks prior to randomization and it is anticipated that the dose will remain stable throughout the subject's enrollment.

During a subject's enrollment, pirfenidone or nintedanib may be taken as background therapy for IPF. The subject must be on a stable dose of either drug for at least 8 weeks prior to randomization. **Both drugs are not to be used simultaneously.** Subjects should not initiate background therapy during the study. In cases where the Investigator feels that background therapy is clinically indicated, this therapy can be started, but the initiation of background therapy during the study will be considered a protocol deviation. Note that a subject may continue in the study on their assigned study treatment if background therapy is initiated, adjusted, or discontinued.

While participating in the study, every effort should be made to maintain the subject on a stable dose of background therapy. However, background therapy dosing may be adjusted or discontinued by the physician responsible for the subject's pulmonary care, with no dose to exceed the labeled maximum doses. Subjects will maintain a diary to record background therapy dosing and any adjustments made in their background therapy. In the event of an IPF exacerbation meeting the definition described in this protocol, if the Investigator feels that additional therapy (other than pirfenidone or nintedanib) is clinically indicated, this therapy may be started and the medications, doses, and duration of treatment must be documented as concomitant medications. The subject may continue in the study.

Subjects should be instructed to continue the medications that they were receiving at enrollment and to avoid starting any new medications or herbal preparations during the study, since these may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in the medications they are taking.

11.5.1.2. Disallowed Concomitant Therapy

Simultaneous use of pirfenidone and nintedanib.

While participating in this study, subjects should not be receiving chronic high-dose corticosteroid (i.e., >10 mg/day of prednisone or its equivalent), cytotoxic therapy (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), vasodilator therapy for pulmonary hypertension (e.g., bosentan), unapproved (e.g., IFN-γ, penicillamine, cyclosporine, mycophenolate and N-acetylcysteine [may vary by country]), and/or any investigational therapy for IPF or administration of such therapeutics within 5 half-lives of the agent prior to initial screening in this study. Live or attenuated vaccinations within 12 weeks prior to Screening or during the study are not permitted (inactivated influenza vaccine is permitted).

All treatments previously used for clinical management or in previous investigational trials of IPF will be documented on the appropriate CRF.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy, pulmonary rehabilitation) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is screened for the study and final study visit.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If BG00011 is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

12. STUDY TREATMENT MANAGEMENT

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Study site staff should follow the Directions for Handling and Administration, which is located in the pharmacy binder, for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The Directions for Handling and Administration supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects randomized in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment is for one-time use only; do not use any study treatment remaining in the syringe for another subject.

12.1. BG00011

BG00011 drug product is a liquid formulation and supplied in a 1.0 mL syringe (prefilled to 0.8 mL) and is intended for self-administration. The pre-filled syringe contains 56 mg of BG00011 per syringe and is formulated in sodium citrate, methionine, L-arginine, and polysorbate 80 at pH 5.5. The placebo consists of the formulation buffer.

The contents of the BG00011 label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site personnel. Study treatment should not be used after the expiration, expiry, or use-by date.

12.1.1. BG00011 Preparation

The individual preparing BG00011should carefully review the instructions provided in the Directions for Handling and Administration. If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the study treatment, do not use the study treatment. The study treatment in question should be saved at the study site and the problem immediately reported to the Sponsor.

12.1.2. BG00011 Storage

Study treatment (BG00011 and placebo) must be stored in a secure location.

BG00011 prefilled syringes are to be stored at 2°C to 8°C (36°F to 46°F), in a locked refrigerator with limited access. For the most up-to-date storage requirements, follow the instructions provided in the Directions for Handling and Administration.

12.1.3. BG00011 Handling and Disposal

The Investigator must return all used and unused prefilled syringes of BG00011 as instructed by the Sponsor unless approved for onsite destruction.

If any BG00011 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from the Sponsor, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, the Sponsor must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BG00011 Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), amount returned by the subject, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all prefilled syringes both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of BG00011 supplied, dispensed, and subsequently destroyed, lost, or returned to the Sponsor. A written explanation must be provided for any discrepancies.

12.2. Reference Product

The placebo (control agent) to be used in this study is supplied in a 1.0 mL syringe (prefilled to 0.8 mL) and intended for self-administration. The prefilled syringe contains only the buffering solution used for the active drug product (sodium citrate, methionine, L-arginine, and polysorbate 80 at pH 5.5). Labeling, preparation, storage, handling, and disposal instructions for the reference product are identical to those for BG00011.

13. EFFICACY, PHARMACOKINETIC, [redacted] ASSESSMENTS

See Section 5 for the timing of all efficacy, PK, [redacted] assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BG00011.

13.1.1. Pulmonary Function Testing

13.1.1.1. Spirometry

Spirometry testing, including FVC, FEV_1, and FEV_1/FVC, both before and after bronchodilator use, will be performed at Screening. During the Treatment Period, spirometry testing (without bronchodilator use) will be performed at Baseline (Day 0) and at all scheduled study visits except Day 5. The spirometry evaluations performed at the Screening Visit will be used to determine whether the subject qualifies for the study and must be performed within 35 days prior to the first dose of study treatment. At the Baseline Visit, spirometry test results will be obtained prior to the first dose of study treatment. For each subject, spirometry testing should be conducted at approximately the same time of day.

See the Study Reference Guide for full details of spirometry testing procedures.

All spirometry results will be electronically transmitted and confirmed by a central reader. Investigators will receive a report from the central reader.

13.1.1.2. Carbon Monoxide Diffusion Capacity

DL_{CO} measurement will be performed at Screening to determine study eligibility, and at the following study visits: Baseline (Day 0), Week 4, Week 8, Week 16, Week 26, Week 38, and Week 52.

Evaluation of DL_{CO} will be performed by single-breath carbon monoxide diffusing capacity according to ATS/ERS recommendations. See the Study Reference Guide for full details of the DL_{CO} testing procedure.

13.1.1.3. Full-Body Plethysmography

Lung volumes, including total lung capacity and residual volume, will be measured by full-body plethysmography at the following study visits: Baseline (Day 0), Week 26, and Week 52.

See the Study Reference Manual for full details of body plethysmography testing procedures.

13.1.2. High-Resolution Computed Tomography

HRCT scanning will be performed at Screening, Week 26, and Week 52. Noncontrast chest CT through the full chest at suspended full inspiration and full expiration will be performed as detailed in the Imaging Procedure Manual. The HRCT scan performed at Screening will be centrally read, will be used to determine study eligibility, and will establish the predose baseline pattern and extent of disease for comparison with the Week 26 and Week 52 scans.

An independent central radiologist experienced in the evaluation of diffuse lung diseases and blinded to treatment assignment will read all HRCT scans obtained during the study. The central radiologist will evaluate the Screening HRCT to determine eligibility and will also perform qualitative IPF change assessment from Screening and follow-up HRCT scans. [redacted]

See the Imaging Procedure Manual for full details on HRCT scanning procedures.

13.1.3. Acute Exacerbations of IPF

Subjects should be advised of the importance of reporting worsening respiratory status to the Investigator. The subject should also notify the Investigator (if different than the treating physician) to schedule the IPF Exacerbation Visit as soon as possible so that the Investigator may assess and confirm the IPF exacerbation. Should the subject be unable to come to the clinic for the IPF Exacerbation Visit, the Investigator should attempt to complete the Investigator's determination of IPF exacerbation as soon as possible. See Section 7.2.6 for a detailed description of the IPF Exacerbation Visit.

Based on the results obtained from evaluations at the IPF Exacerbation Visit and/or the records obtained from a visit to another facility, using a modified definition of IPF exacerbation derived from IPFnet definition of acute exacerbations of IPF in 2007 [Collard 2007] (see Section 7.2.6.1), the Investigator will determine whether an IPF exacerbation has occurred.

[redacted]

Analyses of IPF exacerbation events, based on [redacted] the modified definition of IPF exacerbation (2007) [redacted] will include the following:

- Time to first acute exacerbation, measured in days.
- Proportion of subjects with at least 1 acute exacerbation during the 52 weeks on study.
- Number of exacerbations during 52 weeks.

See Section 16.2.2.3 and Section 16.2.2.4 for additional details of these analyses.

13.1.4. Respiratory Hospitalizations

All nonelective hospitalizations will be assessed by the Investigator to determine whether the primary cause of the hospitalization was respiratory in nature. The determination of a respiratory hospitalization should be based on a fundamental change in respiratory status that is due either to intrinsic lung disease or to infectious etiology of the lung. The change in respiratory status should not be the result of a secondary effect from another organ or system.

In addition, study site personnel should obtain sufficient medical records to determine the following:

- Possible triggers or causes of the event
- The results of relevant tests and assessments (if performed), including but not limited to:
  - Detailed radiography reports and copies of images of all radiographic examinations (e.g., chest X-ray or HRCT scan) for submission to the central imaging vendor
  - Spirometry, lung volume, and/or DL_{CO} testing reports
  - Echocardiogram
  - Microbiology data
- Descriptions of the severity and duration of the event
- Details of the medical treatment provided, including relevant medications and other major elements of the clinical management
- The subject's response to the treatment and clinical status at the time of discharge.

13.1.5. 6-Minute Walk Test

The 6MWT will be administered at the following study visits: Baseline (Day 0), Week 26, and Week 52. This test, which includes 2 walks, assesses the distance in meters that a subject can walk in 6 minutes, will be conducted according to ATS criteria by study site staff in a suitable location with emergency response supplies available. Detailed criteria for the conduct of the 6MWT, including training requirements for administration of the test, availability of emergency supplies, use of oxygen supplementation during the test, and parameters for starting and stopping the test, are provided in the Study Reference Guide.

[redacted]

[redacted]

[redacted]

[redacted]

13.2. Pharmacokinetic Assessments

Blood samples for PK evaluation will be collected at the following visits: prior to dosing at Baseline (Day 0), Day 5, Week 4, Week 8, Week 12, Week 26, Week 38, Week 52, and Week 60.

The PK data obtained in this Phase 2b study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of BG00011 and to determine measures of individual exposure (such as steady-state trough, time-averaged concentration, or AUC). Model-determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. Results of population PK and exposure-response analyses will be reported separately.

[redacted]

[redacted]

[redacted]

14. SAFETY ASSESSMENTS

Refer to Section 5 for the timing of all safety assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, subjects will be asked to return to the clinic to have the evaluations repeated.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BG00011:

- AE and SAE monitoring and recording
- Lung function

  The assessment of changes in lung function during this study will be performed by comparing the subject's spirometry parameters at Baseline to postbaseline values during the Treatment and Follow-Up Periods. These evaluations will assess both the absolute and the percent predicted changes in FVC. All spirometry tests will be reviewed centrally.

  Expected fluctuations or expected deterioration of the underlying IPF and other pre-existing conditions should not be recorded as an AE except in the following circumstances:

  - Worsening of the disease meets the criteria for an SAE.
  - Action is taken with investigational treatment, such as when treatment is discontinued.
  - Additional treatment is required, such as when concomitant medication is added or changed.
  - In the opinion of the Investigator, an unexpected deterioration from baseline has occurred.
  - The event meets the criteria of an acute exacerbation of IPF or suspected exacerbation of IPF.

  Specific criteria for acute exacerbation of IPF will be determined by the Investigator based on the following 2 definitions:

  Diagnostic Criteria for Acute IPF Exacerbation (2007)

  - Unexplained worsening or development of dyspnea within 30 days.
  - New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit.
  - Exclusion of infection per routine clinical practice and microbiological studies.
  - Exclusion of alternative causes per routine clinical practice, including the following:

- congestive heart failure
- pulmonary embolism
- identifiable cause of acute lung injury

[redacted]

- High-resolution computed tomography

  HRCT scans will be performed during Screening to establish the predose pattern and extent of disease and will serve as the baseline assessment. An independent central radiologist experienced in the evaluation of diffuse lung diseases and blinded to treatment assignment will evaluate the HRCT scans, which will be performed at Screening, Week 26, and Week 52. Every effort will be made to have sequential scans for individual subjects evaluated by the same radiologist.

- Other safety assessments
  - Medical history
  - Concomitant therapy and procedure recording
  - Physical examination
  - Vital signs: oral or tympanic temperature (°C), heart rate (beats/min), respiratory rate (breaths/min), sitting blood pressure (mmHg) after at least 5 minutes' rest
  - Body weight (kg) and height (cm)
  - 12-lead ECG after at least 5 minutes' rest
  - Oxygen saturation (pulse oximetry) after at least 5 minutes' rest
  - Use of supplemental oxygen
  - Study discontinuations (all causes, and due to urgent need for transplantation)
  - Cumulative number of lung transplantations and number of deaths (respiratory and all causes)
  - Cumulative spirometry testing with percent change from baseline and change in percent predicted from baseline calculated at each visit
  - Cumulative number of nonelective hospitalizations

14.2. Laboratory Safety Assessments

All samples will be analyzed using Good Laboratory Practice validated assays.

The following laboratory assessments will be performed to evaluate the safety profile of BG00011:

- Hematology: Complete blood count, including red blood cell count, white blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

- Serum chemistry, including: albumin, alkaline phosphatase, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, chloride, carbon dioxide, creatinine, bilirubin (total and direct), gamma-glutamyl transferase, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, and total protein.

- Urinalysis, including urine protein, glucose, ketones, occult blood, and white blood cells by dipstick, with microscopic examination if indicated.

- At Screening, blood samples for HCV antibody and RNA, HBsAg, anti-HBc, anti-HBs and HIV antibody will be collected to establish eligibility. Appropriate referrals must be made for any active HCV, positive HBsAg, or HIV test that is obtained, according to applicable local laws.

- Serum pregnancy test (Screening).

- Urine pregnancy tests (all visits after Screening).

14.3. Immunogenicity Assessments

The following assessments will be performed to determine the safety of BG00011:

- Collection and analysis of serum samples for the presence and titer of anti-BG00011 antibodies.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject, or their legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

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

Determination of whether an abnormal laboratory value, vital sign result, and/or ECG result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE
- The result requires the subject to receive specific corrective therapy
- The result is considered by the Investigator to be clinically significant

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect
- Is a medically important event

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled preventative health procedure (e.g., colonoscopy) will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2 .
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by the Sponsor according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE (including SAEs) experienced by the subject between the time of first dose of study treatment and the subject's last study visit is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator

will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AE outcome will be recorded on the CRF, as applicable.

Expected fluctuations or expected deterioration of the underlying IPF and other pre-existing conditions should not be recorded as an AE except in the following circumstances:

- Worsening of the disease meets the criteria for an SAE.
- Action is taken with investigational treatment, such as when treatment is discontinued.
- Additional treatment is required, such as when concomitant medication is added or changed.
- In the opinion of the Investigator, an unexpected deterioration from baseline has occurred.
- The event meets the criteria of an acute exacerbation of IPF.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the subject's last study visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to the Sponsor within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported within 24 hours. See the Study Reference Guide's Official Study Contact List for complete contact information.

Subjects will be followed for all SAEs until their last study visit. Thereafter, the event should be reported to the Sponsor only if the Investigator considers the SAE to be related to study treatment.

SAEs that are ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. SAE outcome will be recorded on the CRF, as applicable. Only SAEs that are unresolved will be followed by the Investigator.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify the Sponsor within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

A report ***must be submitted*** to the Sponsor regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, a completed SAE form must be sent to the Sponsor; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or the Sponsor to be related to the study treatment administered.

Appropriate personnel at the Sponsor will unblind SUSARs for the purpose of regulatory reporting. The Sponsor will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. The Sponsor will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 3 months after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject from first dose of study treatment up to 3 months after the last dose by faxing or emailing the appropriate form to the Sponsor within 24 hours of the study site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The

Investigator or study site staff must report the outcome of the pregnancy to the Sponsor. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as SAEs if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. A window of +2 days is allowed without qualifying as an overdose for non-Baseline Visits; however, subsequent doses should adhere to the dosing schedule initiated at the Baseline Visit. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to the Sponsor within 24 hours of the site becoming aware of the overdose. An overdose must be reported to the Sponsor even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to the Sponsor. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact the Sponsor to discuss such situations.

15.5. Contraception Requirements

All women of childbearing potential and all men must practice highly effective contraception during the study. Women in the study (and/or their partner) must continue highly effective contraception and must not donate eggs for 3 months after stopping study treatment. Men in the study (and/or their partner) must continue effective contraception and must not donate sperm for 4 months after stopping study treatment.

For the purposes of this study, women who do not meet one of the following criteria are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
    - 12 continuous months of natural (spontaneous) amenorrhea without an alternative medical cause.
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as use of 1 of the following:

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted progestogen-only hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For males:

- Vasectomy (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).
- Sex with a woman who uses the methods described for females if she is of childbearing potential.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies in female subjects and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax or email it to the Sponsor within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to the Sponsor within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

15.6.2. The Sponsor

The Sponsor's responsibilities include the following:

- Before a site can enroll any subjects, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- The Sponsor is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy

16.2.1. Analysis Population

The modified intent-to-treat (MITT) population, defined as all subjects who are randomized and receive at least 1 dose of study treatment, will be used for the efficacy analyses unless otherwise specified. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

The per-protocol (PP) population, defined as all subjects who are randomized and without major protocol violations, will be used for sensitivity analysis for the primary endpoint.

Subgroup analysis (e.g., background therapy strata as subgroup) will be done for the primary endpoint and some of the secondary endpoints. The details will be specified in the SAP.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include number of subjects randomized, number of subjects with data, and percentage of subjects with data in each category. Statistical testing for efficacy endpoints will be made between subjects treated with BG00011 and with placebo.

All statistical tests will be 2-sided.

16.2.2.2. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the MITT population with a baseline and at least 1 postbaseline FVC measurement.

The primary efficacy outcome variable is the yearly rate of change in FVC (actual value, expressed in mL, over 52 weeks). The primary endpoint will be analyzed using a random coefficients linear regression model, with an absolute change in FVC as the outcome variable

assuming linear decline in lung function over time. The model includes random coefficients for intercept and slope (time), and fixed-effect terms for treatment, randomization stratum (background therapy), age, and baseline FVC. Interaction terms in the model will be the interaction between treatment and time, and the interaction between pirfenidone or nintedanib and time.

Every effort should be made to reduce the amount of missing data. In the analysis of the primary endpoint, missing data will be assumed to be missing at random. An unstructured variance-covariance structure will be used to model the within-patient measurements variability. If it fails to converge, an AR(1) structure will be used. The variance-covariance matrix, modeled to estimate the interindividual variability, is considered to have a variance components structure. Because the statistical model assumes a linear decline in lung function over time and, hence, implicitly imputes missing data based on individual's estimated rate of worsening of lung function prior to treatment discontinuation, similar to linear extrapolation. If a subject who was not on background therapy at randomization initiates treatment with background therapy during the study, the subject's data collected after the initiation of background therapy will be excluded from the primary analysis. However, a sensitivity analysis that includes the excluded data will be performed.

Support analyses for the primary endpoint includes:

1. Analysis using multiple imputation with pattern mixture models will be carried out. Details of sensitivity analysis and assumptions for different pattern will be described in the statistical analysis plan (SAP).

2. A mixed model of repeated measures model will be used to compare the difference between the 2 treatment groups in FVC change at 52 weeks and other scheduled visits. An unstructured variance-covariance structure will be used in this model. If the model fails to converge, an AR(1) structure will be used.

3. Rate of decline in percent predicted FVC at 52 weeks will be analyzed by the same method as FVC actual value.

A model including the interaction between treatment and background therapy strata will be used to explore the treatment effects within each subgroup.

16.2.2.3. Analysis of the Secondary Endpoints

Time to progression will be presented using Kaplan-Meier curves, a stratified log-rank test will be used to compare the 2 treatment groups using randomization stratum as the stratification factor. The proportion of subjects who progressed in each arm will be summarized. Each component of progression will be summarized descriptively. If a subject who was not on background therapy at randomization initiates treatment with background therapy during the study, the subject will be censored at the time of new background therapy initiation.

Other time-to-event types of endpoints, e.g., time to first acute exacerbation, time to death or lung transplant, nonelective hospitalization (due to respiratory causes and due to all causes), and

survival rate (death from all causes and death due to respiratory causes) at 26 weeks and 52 weeks will be analyzed similarly.

The number of subjects experiencing an absolute decline of 10% predicted in FVC will be analyzed using a logistic regression model, adjusting for the randomization stratification factor, patient age, and baseline FVC.

Other pulmonary function endpoints and the 6MWT at 52 weeks will be analyzed similarly to the primary endpoint. For other visits, an analysis of covariance model adjusting the randomization stratification factor, age, and FVC at Baseline will be used to compare the treatment groups. The cumulative distribution of subjects by change in absolute and percent predicted FVC from Baseline to Week 52 will be presented in graph form.

Details of the analyses, including the handling of missing data, will be described in a SAP.

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for serum PK analyses is defined as all subjects in the MITT population who have at least 1 measurable BG00011 concentration in serum.

16.3.2. Methods of Analysis

Samples for measuring serum concentrations of BG00011 will be collected as specified in Section 5.2. BG00011 concentrations in serum will be summarized using descriptive statistics at the scheduled PK sample collection visits.

This study will collect only sparse PK samples; thus, the serum concentration data will be summarized descriptively by visit. No noncompartmental or compartmental methods will be

used to analyze the PK data for presentation in the clinical study report. Details of the PK analysis will be described in the SAP.

Mean serum concentrations of BG00011 will be plotted versus time on both a linear and a logarithmic scale. No dose-proportionality assessments will be conducted because of the sparse PK data sampling.

Atypical drug concentrations (e.g., very low or very high) will be excluded from the analysis, if no apparent explanation exists. Concentration observations will also be removed from the data set if corresponding dosing or sampling times are missing or cannot be reconstructed.

Concentration values below the limit of quantification will be removed from analysis. All deletions of data points will be appropriately documented.

[redacted]

16.6. Safety

16.6.1. Analysis Population

The safety population is defined as all subjects who receive at least 1 dose of study treatment.

16.6.2. Methods of Analysis

16.6.2.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. All analyses of AEs will be based on the principle of treatment emergence. An AE is considered to be treatment emergent if it has an onset date on or after the date of first dosing, or if it was present prior to the first dose and subsequently worsened. The incidence of all AEs will be presented by system organ class and preferred term by treatment group. In addition, the incidence of all AEs will be presented by severity and by relationship to study treatment.

16.6.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry, and urinalysis evaluations. Analyses of clinically significant abnormalities, shifts from baseline to postbaseline relative to the normal range, as well as changes from baseline by visit will be presented by treatment group.

16.6.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities, which will be defined in more detail in the SAP. The incidence of clinically relevant abnormalities in vital signs will be summarized by treatment group.

16.6.2.4. Electrocardiograms

The analysis of ECG data will focus on clinically relevant abnormalities, which will be defined in more detail in the SAP. ECG changes from baseline may be summarized using descriptive statistics and presented by dose group, overall active treatment group, and visit.

16.6.2.5. Physical Examinations

Abnormal findings during physical examinations will be recorded as AEs and will be reflected in the summary of AEs.

16.7. Immunogenicity Data

16.7.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects who were randomized and received at least 1 dose of study treatment and who have at least 1 postdose immunogenicity sample evaluated for anti-BG00011 antibodies.

16.7.2. Methods of Analysis

The incidence of anti-BG00011 antibodies will be summarized by treatment group over time.

16.8. Interim Analyses

After the last subjects complete the treatment period (up to Week 52), an interim database lock may occur and an interim analysis (IA) of efficacy and safety data may be conducted. All Investigators, study site personnel, and subjects will remain blinded to treatment assignments until after the end of the study. If this IA occurs, members of the Sponsor study team not in direct contact with the study sites will have access to the study data after all subjects complete all Week 52 assessments. Members of the Sponsor study team who become unblinded to the data for this IA will have no further contact with study sites until after the final database lock.

16.9. Sample Size Considerations

The sample size calculation is based on the annual declining rate in FVC (mL/year). With 145 subjects randomized per arm, and assuming a 15% dropout rate over a 1-year treatment period, the study has approximately 80% power to show that the BG00011 treatment arms differentiate from the arm without BG00011 at a 2-sided 15% α level, given a treatment effect of 82.5 mL/year with a common standard deviation of 280 mL. The calculation is based on the assumption that the FVC decline rate in subjects receiving placebo and no background therapy is 220 mL/year, and in subjects receiving background but no BG00011 therapy it is assumed to be 110 mL/year. A 60% reduction in the FVC decline rate in the subjects receiving placebo would be a treatment effect of 132 mL/year. A 30% reduction in the FVC decline rate in subjects receiving background therapy would be a treatment effect of 33 mL/year. With the assumption that 50% of each type of subject are randomized in the study, the combined treatment effect is approximately 82.5 mL/year. The 15% dropout rate for this study was estimated based on prior experience for the placebo arms in the Phase 3 studies for nintedanib and pirfenidone [King 2014; Richeldi 2014].

17. ETHICAL REQUIREMENTS

The Sponsor, any designee, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The investigator is responsible for endorsing all data on completed CRFs electronically, prior to any Interim lock or Database lock.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study.

If the Investigator makes any changes to the ICF, the Sponsor must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to the Sponsor. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and the Sponsor.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

The Sponsor must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee and the Sponsor.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee) and the data will be used during analysis of study results. (See Section 17.4.)

A copy of the signed and dated ICFs must be given to the subject or the subject's legally authorized representative. The original signed and dated ICFs will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, subjects' race will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or pharmacokinetic profile of the study treatment. Subjects' race is required for the calculation of the percent predicted equations used in pulmonary function testing.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. The Sponsor, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in the Sponsor) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

The Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by the Sponsor. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate.

During and/or after completion of the study, quality assurance officers named by the Sponsor or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes.

During these visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to the Sponsor or designee in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, monitoring, and management of SAE reports, and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool configured by the CRO and hosted by the electronic data capture vendor.

Electronic Clinical Outcome Assessment (eCOA) data will be entered by the subject, the subject's caregiver, and/or study site staff on a device developed and supported by the eCOA vendor. Site staff will monitor data via a secure Web portal developed and supported by the eCOA vendor.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by the Sponsor to store samples collected from subjects in this study for [redacted] drug concentrations, and anti-BG00011 antibodies in whole blood, plasma, and serum. These samples may be analyzed by a central laboratory or a third-party laboratory, as applicable. A central laboratory will also perform the safety laboratory tests noted in the Schedule of Events (Table 2): blood chemistry, hematology, urinalysis, serum pregnancy, HBsAg, anti-HBc, anti-HBs, HCV, and HIV panels.

A local laboratory may be used by the study site to analyze repeat tests if needed.

19.1.5. Central Facility for Other Assessments

A central vendor has been selected by the Sponsor to read and interpret all HRCT scans for this study.

A central vendor has been selected by the Sponsor to read and interpret lung function assessment data.

A central vendor has been selected by the Sponsor to read and interpret ECG data.

19.2. Study Committees

19.2.1. Advisory Committee

Advisory committees will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committees will be blinded to subject treatment assignments.

19.2.2. Data Safety Monitoring Board

An independent DSMB will be established to assess the overall safety profile throughout the conduct of the study. A DSMB charter will be developed to guide the overall governance plan for the DSMB in alignment with the Safety Monitoring Plan. The DSMB will review the unblinded safety (including but not limited to AEs, clinical laboratory data, ECGs, pulmonary function testing, and imaging data) and available PK data on an ongoing basis until the last subject completes dosing. The meeting intervals and the procedures used to provide and assess the data will be described in detail in the DSMB charter. Upon review of the data, the DSMB may recommend that the Sponsor discontinue the study, modify the study conduct, or continue the study with no changes.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records. In addition, the Investigator must notify the Sponsor of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

The Sponsor will designate one of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by the Sponsor.

The Sponsor will follow all applicable local regulations pertaining to study report signatories.

20. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BG00011 in Patients With Idiopathic Pulmonary Fibrosis," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

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PROTOCOL NUMBER: 203PF203 / NCT03573505

PHASE OF DEVELOPMENT: 2b

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BG00011 in Patients With Idiopathic Pulmonary Fibrosis

EUDRA CT NUMBER: 2017-003158-18

DATE: 20 November 2017
Version 1
Final

SPONSOR SIGNATURE PAGE

Protocol 203PF203 was approved by:

[redacted] 21 November 2017

[redacted], MD, PhD Date

[redacted]

Biogen

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1. SYNOPSIS

Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BG00011 in Patients With Idiopathic Pulmonary Fibrosis	
Protocol Number:	203PF203	
Version Number:	1	
Name of Study Treatment:	BG00011	
Study Phase:	2b	
Study Indication:	Idiopathic pulmonary fibrosis	
Study Rationale:	This Phase 2b study in subjects with mild to moderate idiopathic pulmonary fibrosis (IPF) who may or may not be receiving background therapies is designed to evaluate the change in forced vital capacity (FVC) after 56 mg of BG00011 is administered subcutaneously (SC) once weekly for 52 weeks. In the previously completed, Phase 2a study (203PF201) in subjects with IPF, BG00011 demonstrated proof of biological activity by altering biomarkers in the lung. Therefore, the current study is being conducted to evaluate the clinical efficacy and safety of BG00011. The primary analysis will be conducted after 52 weeks of placebo-controlled treatment with BG00011.	
Study Objectives and Endpoints:	**Primary Objective**	**Primary Endpoint**
	To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF.	Yearly rate of change in FVC (expressed in mL over 52 weeks) in subjects randomized to BG00011 compared with placebo.
	Secondary Objectives	**Secondary Endpoints**
	To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF as determined by change in percent predicted FVC.	Yearly rate of change in FVC, expressed in percent predicted, over 52 weeks.
	To assess progression-free survival in subjects who receive BG00011	Time to progression, as defined by a composite endpoint, including any of

	compared with placebo.	the following events: Absolute decline of 10% predicted in FVC (FVC percent predicted$_{baseline}$ − FVC percent predicted$_{progression}$ ≥10%). Nonelective hospitalization for respiratory events. Lung transplantation or death.
	To assess the occurrence of IPF exacerbation (using modified diagnostic criteria for acute IPF exacerbation derived from [Collard 2007]) in subjects who receive BG00011 compared with placebo.	Time to first acute exacerbation, measured in days. Proportion of subjects with at least 1 acute exacerbation during the 52 weeks on study. Number of exacerbations during 52 weeks.
	To assess the incidence of absolute decline in FVC ≥10% in subjects who receive BG00011 compared with placebo.	Number of subjects with absolute decline of 10% predicted in FVC (FVC percent predicted$_{baseline}$ − FVC percent predicted$_{progression}$ ≥10%) over 52 weeks.
	To assess the time to death or lung transplantation in subjects who receive BG00011 compared with placebo, and the transplant-free survival rate at Week 26 and Week 52.	Time to death or lung transplantation, measured in days.
	To assess the time to nonelective hospitalizations in subjects who receive BG00011 compared with placebo.	Time to all nonelective hospitalizations and to nonelective respiratory hospitalizations, measured in days.
	To assess additional pulmonary function test (PFT) findings in subjects who receive BG00011 compared with placebo.	Change in absolute and percent predicted FVC from baseline over time. Carbon monoxide diffusion capacity (DL_{CO}) absolute and percent

		predicted changes from baseline over time. Total lung capacity, as measured by plethysmography, absolute and percent predicted changes from baseline over time.
	To assess performance on the 6-Minute Walk Test (6MWT) in subjects who receive BG00011 compared with placebo.	Change from baseline in 6MWT parameters at Weeks 26 and 52.
	To evaluate the safety and tolerability of BG00011.	The incidence, severity, outcome, and relationship to study treatment of adverse events and serious adverse events. Change from baseline in clinical laboratory test results, vital signs, electrocardiogram (ECG), PFT, and high-resolution computed tomography (HRCT) findings. Immunogenicity (antibodies to BG00011).
	To evaluate the serum concentration of BG00011.	Measurement of BG00011 serum concentrations using sparse pharmacokinetic (PK) sample collection at select timepoints during the study.
	Exploratory Objectives and Endpoints are listed in Section 6.	
Study Design:	Phase 2b randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, PK, and tolerability of BG00011 in subjects with IPF.	
Study Location:	Approximately 100 sites in up to 20 countries are planned, including North America, Europe, and Rest of World.	
Number of Planned Subjects:	Approximately 290 subjects will be randomized.	
Study Population:	This study will be conducted in subjects with mild to moderate IPF who may or may not be receiving background therapy (either nintedanib or pirfenidone,	

	though not both). Detailed criteria are described in Section 8.
Treatment Groups:	Subjects will be randomized in a 1:1 ratio to receive BG00011 or placebo: • BG00011 group: Approximately 145 subjects will receive BG00011 56 mg once weekly by SC injection for 52 weeks. • Placebo group: Approximately 145 subjects will receive placebo dosing once weekly by SC injection for 52 weeks. Subjects will be stratified by the concomitant use of background therapy (nintedanib or pirfenidone) with a goal of a 1:1 ratio of BG00011 monotherapy to BG00011 plus background therapy. Hence, it is intended that approximately 50% of subjects in each treatment group will be on background therapy and approximately 50% of subjects in each group will not be on background therapy at the time of randomization.
Duration of Treatment and Follow-up:	Study duration for each subject will be approximately 65 weeks, including the following: • 5-week Screening Period • 52-week Placebo-Controlled Treatment Period • 8-week Follow-Up Period

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
6MWT	6-Minute Walk Test
αvβ6	alpha v beta 6
AE	adverse event
ALAT	Latin American Thoracic Association
ALT	alanine transaminase
AUC	area under the concentration-time curve
AUC_{SS}	area under the concentration-time curve at steady state
AST	aspartate transaminase
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
CBC	complete blood count
CRF	case report form
DL_{CO}	carbon monoxide diffusion capacity
DSMB	data safety monitoring board
ECG	electrocardiogram
ERS	European Respiratory Society
FEV_1	forced expiratory volume over 1 second
FVC	forced (expiratory) vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HCV	hepatitis C antibody
HIV	human immunodeficiency virus
HRCT	high-resolution computed tomography
HRQoL	health-related quality of life
ICF	informed consent form
ICH	International Council for Harmonisation
IFN-γ	interferon-gamma

Abbreviation	Definition
IgG1	immunoglobulin G subtype 1
ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
IRT	interactive response technology
JRS	Japanese Respiratory Society
[redacted]	[redacted]
LAP	latency-associated peptide
[redacted]	[redacted]
LTBP-1	latent transforming growth factor-beta binding protein-1
mAb	monoclonal antibody
[redacted]	[redacted]
mRNA	messenger RNA
NOAEL	no observed adverse effect level
NOEL	no observed effect level
[redacted]	[redacted]
PFT	pulmonary function test
PHI	protected health information
PK	pharmacokinetic(s)
pSMAD2	phosphorylated SMAD2
QLF	quantitative lung fibrotic reticulation score
RGD	arginine-glycine-aspartic acid
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SP-A	surfactant A
SP-D	surfactant D
[redacted]	[redacted]
$t_{1/2}$	half-life
TGF-β	transforming growth factor-beta
[redacted]	[redacted]
T_{max}	time to reach maximum observed concentration

Abbreviation	Definition
TLC	total lung capacity
[redacted]	[redacted]
UIP	usual interstitial pneumonia
WBC	white blood cell

3. SPONSOR INFORMATION

Biogen MA Inc. (hereafter referred to as Biogen) is the Sponsor of the study.

Biogen MA Inc.	Biogen Idec Research Limited
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Cambridge, MA 02142	70 Norden Road
United States	Maidenhead, Berkshire
	SL6 4AY
	United Kingdom

For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study Reference Guide's Official Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

4. INTRODUCTION

BG00011 (humanized, immunoglobulin G subtype 1 [IgG1] anti-alpha v beta 6 [αvβ6] monoclonal antibody [mAb]), formerly known as STX-100, is being developed by Biogen as a novel therapeutic treatment for patients with idiopathic pulmonary fibrosis (IPF). BG00011 binds to the αvβ6 integrin, which inhibits the integrin from binding to and activating the latent form of transforming growth factor-beta (TGF-β). TGF-β plays a critical role in the initiation and maintenance of fibrosis, and targeted inhibition of the αvβ6/TGF-β pathway may prevent the development of fibrosis, organ scarring, and organ failure. The clinical development plan for BG00011 is designed to demonstrate that blocking αvβ6 and inhibiting the activation of TGF-β in patients with IPF can prevent or reduce the progression of fibrosis, resulting in preservation of pulmonary function.

4.1. Overview of Idiopathic Pulmonary Fibrosis

IPF is a serious, chronic, progressively fatal lung disease involving replacement of normal lung tissue with fibrotic scar tissue. IPF is a rare disease that predominantly affects the middle aged and elderly (after age 60 years; median age at diagnosis: 66 years [Raghu 2014]). The disease is more common in men than women (male predominance approximately 1.3:1) [Raghu 2014]. Patients with IPF typically live for only 3 to 5 years after diagnosis, with a median survival time of approximately 3.5 years from diagnosis [Fernández Pérez 2010; Ley 2011; Raghu 2014]. The 5-year survival rate is 30% to 50% [Raghu 2011],and fewer than 15% of patients live for 10 years or longer [Lynch 2016]. IPF significantly impairs health-related quality of life [Swigris 2005], and the majority of patients also have serious comorbid conditions [Raimundo 2016].

Globally, North America and Europe have the highest incidence and prevalence of IPF [Hutchinson 2015]. The incidence has been increasing steadily worldwide, in part due to an aging population. The annual incidence of IPF is currently between 3 and 9 per 100,000 persons in Europe and North America. In a review of studies published between 1990 and 2011, the prevalence of IPF ranged from 14.0 to 27.9 per 100,000 persons in the United States and from 1.25 to 23.4 per 100,000 persons in Europe [Nalysnyk 2012]. Recent estimates from South Korea suggest the incidence and prevalence of IPF in Asia may be comparable to that of North America and Europe [Lee 2016].

Clinical features of IPF include progressive cough, dyspnea, restrictive ventilatory defect, and progressive fibrosis and destruction of the lung parenchyma [Lynch 2016]. The diagnosis is made in patients with the appropriate clinical features and the histologic pattern of usual interstitial pneumonia (UIP) [based on lung biopsy or high-resolution computed tomography (HRCT)]. Challenging factors for clinical management include older age, comorbid conditions, and acute unpredictable exacerbations. Acute exacerbations of IPF are defined as sudden (typically less than 30 days onset) unexplained worsening of underlying disease, including new radiological infiltrates (based on HRCT) or UIP pattern. The progressive deterioration of lung function results in respiratory failure. The prognosis following acute exacerbation and

deterioration of lung function is poor, with 1-year and 5-year survival rates of 56.2% and 18.4% following acute exacerbation, which is considerably shorter than in IPF patients without acute exacerbation [Song 2011].

The underlying pathophysiology of IPF is unknown. Whatever the inciting event is, it triggers a TGF-β mediated fibrogenic response. As a part of this response, alveolar epithelial cells via the production of signaling mediators, including TGF-β, tumor necrosis factor, endothelin 1, and cytokines, induce proliferation and activation of fibroblasts and myofibroblasts. This leads to secretion of connective tissue matrix molecules, such as collagen, to replace the damaged tissue but also displaces healthy tissue leading to scarring and ultimately organ failure [du Bois 2010].

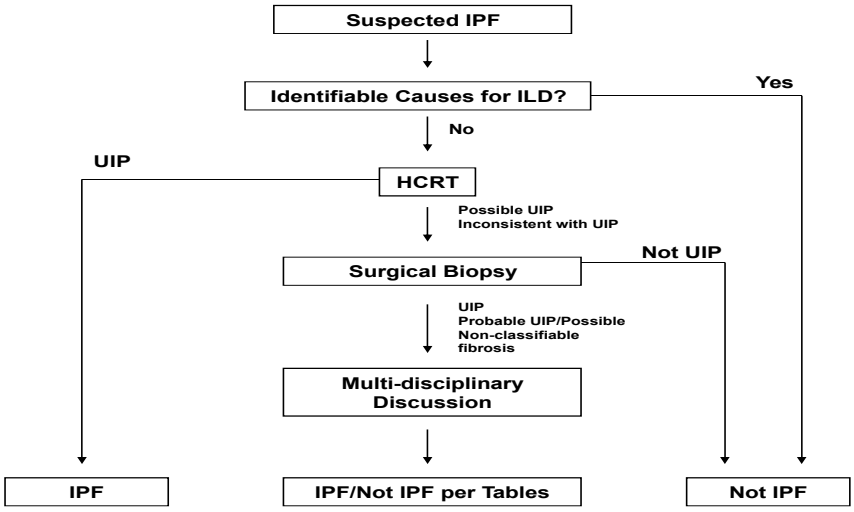
4.2. Diagnostic Criteria for IPF

The diagnostic criteria for IPF used in this protocol are derived from evidence-based guidelines developed by the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association (ATS/ERS/JRS/ALAT) joint task force for the diagnosis and management of IPF (originally presented May 17, 2010 at the ATS Conference, New Orleans, LA) [Raghu 2011].

The diagnosis of IPF requires histopathologic and/or radiologic evidence of UIP and exclusion of other causes of idiopathic interstitial pneumonia and interstitial lung diseases (e.g., occupational or environmental exposures, drug toxicities, collagen vascular diseases).

The ATS/ERS/JRS/ALAT joint task force concludes that, in the appropriate clinical setting, the diagnosis of IPF may be ascertained by HRCT alone if the HRCT image fulfills the criteria for "UIP pattern" (i.e., surgical lung biopsy is not required). However, if the HRCT does not show a definitive UIP pattern, then a surgical lung biopsy is necessary and specific combinations of the HRCT and histopathological criteria are used to determine the diagnosis of IPF (see Figure 1 and Table 1).

Figure 1: Diagnostic Algorithm for IPF (Adapted from the ATS/ERS/JRA/ALAT Guidelines)



ATS/ERS/JRA/ALAT = American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.

To be eligible for this study, subjects must meet the HRCT imaging and/or lung histopathological criteria for UIP shown in Table 1 (in addition to the other inclusion and exclusion criteria):

Table 1: Summary of High-Resolution Computed Tomography and Surgical Lung Biopsy Criteria for Diagnosis of IPF

	Surgical Lung Biopsy				
	Not Available	**Histopathology: UIP Pattern**	**Histopathology: Probable UIP Pattern**	**Histopathology: Possible UIP/ Nonclassifiable Fibrosis Pattern**	**Histopathology: Not UIP Pattern**
HRCT: UIP Pattern	ELIGIBLE	ELIGIBLE (IPF diagnosed)	ELIGIBLE (IPF diagnosed)	ELIGIBLE (IPF diagnosed)	NOT Eligible (No diagnosis of IPF)
HRCT: Possible UIP Pattern	NOT Eligible	ELIGIBLE (IPF diagnosed)	ELIGIBLE (IPF diagnosed)	NOT Eligible (Probable IPF)	NOT Eligible (No diagnosis of IPF)
HRCT: Inconsistent with UIP Pattern	NOT Eligible	NOT Eligible (Possible IPF)	NOT Eligible (No diagnosis of IPF)	NOT Eligible (No diagnosis of IPF)	NOT Eligible (No diagnosis of IPF)

HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis; UIP = usual interstitial pneumonia.
Note: Combined findings of HRCT and surgical biopsy that the guidelines classify as "Possible IPF" or as "Probable IPF" are **not** eligible for this study.

4.3. Current Therapies for Idiopathic Pulmonary Fibrosis

To date, no therapies have demonstrated efficacy in halting IPF disease progression. Historically, disease-modifying agents for IPF have included nonspecific anti-inflammatory or immunosuppressive agents (i.e., corticosteroids, azathioprine, and cyclophosphamide), which were used in the United States despite the absence of clinical studies to demonstrate their efficacy, with some ultimately demonstrating harm [Raghu 2012].

Two recently approved therapies, pirfenidone (Esbriet®) and nintedanib (Ofev®), have demonstrated a similar ability to slow deterioration in lung function by nearly 50%; however, patients are still faced with death or lung transplantation as the ultimate outcome [Kistler 2014].

Pirfenidone was approved based on the demonstration of a statistically significant benefit on the forced vital capacity (FVC) in subjects with mild to moderate IPF compared with placebo (Genentech Studies PIPF-004, PIPF-006, and PIPF-016 [Esbriet Prescribing Information 2015/SmPC]). The clinical development program included one 52-week and two nearly

identical 72-week clinical studies. The primary endpoint was the change in percent predicted FVC from baseline to study end. Secondary endpoints included the mean change from baseline in FVC and survival. Of the 3 studies, the 52-week study and 1 of the 72-week studies demonstrated that fewer subjects taking pirfenidone had a meaningful decline (10% or greater) in FVC versus placebo (17% versus 32%, respectively), whereas more subjects maintained stable lung function in the 52-week study (23% versus 10%, respectively). In the 52-week study, a significant reduction in the mean decline in FVC was observed in subjects receiving pirfenidone compared with placebo (difference of 193 mL). In one of the two 72-week studies, there was a significant treatment difference of 157 mL; however, there was no significant difference observed in the other 72-week study. There was no statistically significant difference in all-cause mortality between pirfenidone and placebo. Adverse events (AEs) leading to discontinuation of treatment occurred in 14.6% of subjects treated with pirfenidone. Adverse reactions associated with pirfenidone in >10% of subjects versus placebo include, but are not limited to, gastrointestinal disorders and photosensitivity.

Nintedanib was also approved based on the demonstration of a statistically significant benefit on FVC decline in subjects with mild to moderate IPF in three 52-week clinical studies [one Phase 2 study and two identical Phase 3 studies] (Boehringer Ingelheim Studies 1199.30, 1199.32, and 1199.34 [Ofev Prescribing Information 2015/SmPC]). The primary endpoint in all 3 studies was the annual rate of decline in FVC. Secondary endpoints included time to first acute IPF exacerbation, change from baseline in FVC percent predicted, and survival. A statistically significant reduction in the annual rate of decline of FVC was demonstrated in subjects receiving nintedanib compared with subjects receiving placebo, with differences in the 3 studies of 131 mL (Phase 2 study) and 125 and 94 mL (in the 2 Phase 3 studies). The change from baseline in the percent predicted FVC was lower in the group treated with nintedanib. In addition, the time to first acute IPF exacerbation was significantly reduced in subjects receiving nintedanib in 2 of the 3 studies (the Phase 2 and 1 of the Phase 3 studies), but there was no statistically significant difference in all-cause mortality. The most common serious adverse reactions that were reported more frequently with nintedanib treatment than with placebo were bronchitis (1.2% versus 0.8%, respectively) and myocardial infarction (1.5% versus 0.4%, respectively). AEs leading to discontinuation were reported in 21% of the subjects treated with nintedanib. Adverse reactions associated with nintedanib in ≥10% of subjects compared with placebo included gastrointestinal (GI) disorders such as diarrhea (most common), nausea, increased liver enzymes, and abdominal pain.

A study assessing the real-world experience with pirfenidone and nintedanib indicated that while side effects (predominantly GI with both therapies) are common, the side effects are managed in the majority of patients with a treatment discontinuation rate similar to what was observed in the clinical studies [Hughes 2016]. Among patients using pirfenidone, 16% of AEs resulted in a reduction in dose and 20% of AEs resulted in permanent discontinuation. Among subjects using nintedanib, 15% had a reduction in dose and 26% discontinued treatment.

In real-world data, utilization of antifibrotic medications varies considerably by geographic region. In 3 observational studies in the United States, the prevalence of pirfenidone and nintedanib use ranged from 14% to 55% [Viscidi 2017]. In Western Europe, utilization ranged

from 29% to 69% [Behr 2015; Pesonen 2017; Sicras-Mainar 2017; Wuyts 2017]. Utilization appears to be lower in Eastern Europe; among 107 IPF patients in a registry in Poland, 2% had used pirfenidone [Lewandowska 2017]. In a survey of 344 physicians in Latin America, 21% had prescribed pirfenidone to their IPF patients [Torres Villacreses 2017]. In an observational study in Japan, 33% of IPF patients used pirfenidone [Bando 2015].

As the disease continues to progress, lung transplants for appropriate surgical candidates may be considered. However, the 5-year survival rate after lung transplantation ranged from 47% to 53%, based on data from the International Society for Heart and Lung Transplantation and Organ Procurement and Transplantation Network [Kistler 2014]. Considerations regarding the utility of lung transplantation include the limited availability of donor organs, infection, rejection, and the requirement for lifetime immunosuppressive therapy.

Therapies that can halt or reverse disease progression, increase life expectancy, and improve quality of life while demonstrating minimal side effects remain a treatment goal for patients diagnosed with IPF.

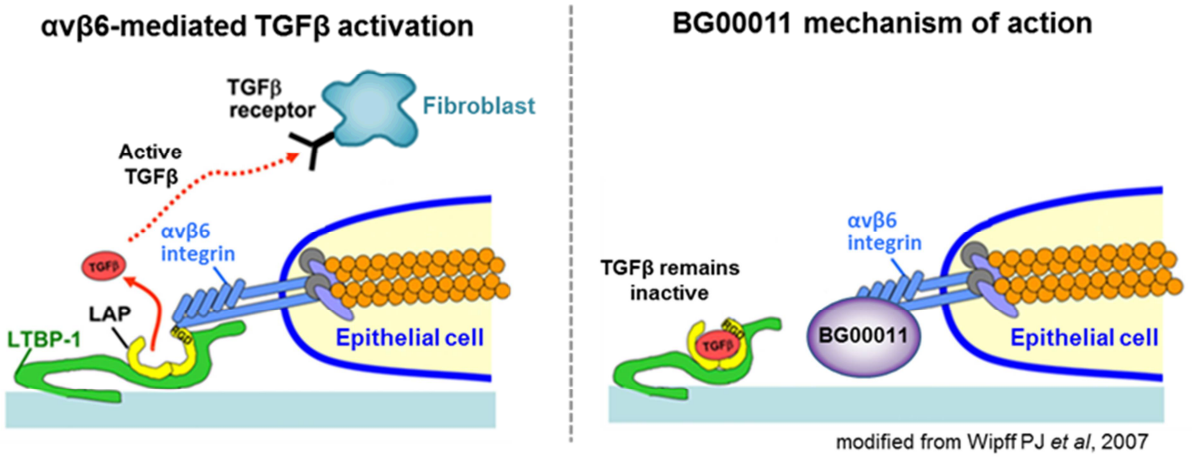
4.4. Profile of Previous Experience With BG00011

4.4.1. Mechanism of Action

TGF-β is a central mediator of fibrogenesis. TGF-β is upregulated and activated in fibrotic diseases, and its signaling results in myofibroblast differentiation and matrix deposition. The αvβ6 integrin is a critical regulator of TGF-β activation. TGF-β is synthesized as a latent precursor protein consisting of latency-associated peptide (LAP) and TGF-β. This complex cannot bind to the TGF-β receptor and is not biologically active. The αvβ6 integrin is expressed at low or undetectable levels in healthy adult tissues but is highly upregulated on epithelial cells during tissue injury and fibrosis. The integrin activates TGF-β by binding to an arginine-glycine-aspartic acid motif within the LAP component of latent TGF-β, leading to the localized activation of the cytokine (Figure 2). BG00011 is a mAb that binds to the αvβ6 integrin and inhibits ligand binding. By blocking the binding of αvβ6 to latent TGF-β, BG00011 prevents αvβ6-mediated TGF-β activation, thereby decreasing TGF-β signaling. Although other mechanisms of TGF-β activation have been identified, studies carried out in αvβ6-deficient mice and with αvβ6-blocking mAbs suggest that αvβ6-mediated activation of TGF-β can prevent the development of fibrosis in the lung, kidney, and liver. Analysis of molecular signatures associated with the progression of fibrosis indicates that the therapeutic impact of the αvβ6-blocking antibodies is mechanistically linked to decreased TGF-β activity.

A key mediator of TGF-β activity is the signal transducer proteins SMAD, which when phosphorylated (phosphorylated SMAD [pSMAD]), regulate the transcriptional activity of TGF-β signaling (Figure 2). Increased pSMAD levels have been positively correlated with lung fibrosis in both the murine bleomycin and radiation models of fibrosis [Chung 2016; Flechsig 2012; Horan 2008]. Given its role in the TGF-β cascade and evidence of correlation with lung fibrosis, pSMAD and several downstream genes were selected as exploratory target engagement biomarkers in nonclinical and the clinical studies with BG00011 in subjects with IPF.

Figure 2: BG00011 Mechanism of Action



αvβ6 = alpha v beta 6; LAP = latency-associated peptide; LTBP-1 = latent transforming growth factor-beta binding protein-1; mAb = monoclonal antibody; RGD = arginine-glycine-aspartic acid; TGF-β = transforming growth factor-beta.
αvβ6 expression is up-regulated on epithelial cells during tissue injury and fibrosis. αvβ6 binds to an RGD motif in the latency-associated peptide region of the latent TGF-β precursor protein, leading to local activation of TGF-β. Anti-αvβ6 mAb interferes with this binding and blocks TGF-β activation.

4.4.2. Nonclinical Experience

Nonclinical pharmacology, pharmacokinetic (PK), and toxicology studies have been performed to support clinical development of BG00011. Inhibition of TGF-β signaling has been shown to be protective in a variety of models of fibrosis, identifying this pathway as an attractive target for therapeutic intervention in IPF. However, given the anti-inflammatory role for TGF-β signaling, appropriate modulation of TGF-β in a tissue specific manner is needed to avoid potentially deleterious systemic effects.

BG00011 is a humanized mAb that cross-reacts with murine, nonhuman primate, and human αvβ6. A murine form of BG00011 (m3G9, previously mu3G9) has demonstrated potent antifibrotic activity in several rodent models of lung, kidney, and liver fibrosis.

4.4.2.1. Pharmacology Models

Nonclinical pharmacology studies to determine the biological activity and safety of BG00011 have been conducted using a murine anti-αvβ6 antibody (m3G9) in mice and BG00011 in cynomolgus monkeys. Several rodent models of fibrosis show increased αvβ6 expression in epithelial cells of the affected tissue, including the lung, kidney, and liver. Efficacy of m3G9 has been demonstrated in models of lung, kidney, and liver fibrosis, as measured by markers of tissue fibrosis, including collagen production and accumulation of α-smooth muscle actin positive fibroblasts [Hahm 2007; Horan 2008; Puthawala 2008].

Key nonclinical studies demonstrating efficacy in lung fibrosis were performed in the bleomycin mouse model, bleomycin-FTY720 mouse model, radiation mouse model, and influenza mouse model. Taken together, the data from these studies indicate that doses of m3G9 at 0.3 and

1.0 mg/kg were consistently associated with improvement in fibrotic response with no significant inflammation in these rodent models of epithelial tissue injury and fibrosis.

In addition, preclinical studies demonstrated that αvβ6 blocking antibody treatment between 0.3 and 1.0 mg/kg led to similar, significant steep reductions of pSMAD in bronchoalveolar lavage (BAL) cells in both mice and cynomolgus monkeys. See the BG00011 Investigator's Brochure for additional information about these studies.

An increased incidence of acute allograft rejection was observed in a monkey kidney transplant study when BG00011 was administered with a standard calcineurin-based immunosuppressive regimen. Therefore, it is recommended that patients with end-stage fibrotic disease requiring organ transplantation do not receive BG00011. Any patient receiving BG00011 who progresses to the point of requiring organ transplantation should immediately discontinue the study treatment.

4.4.2.2. Toxicology Summary

Nonclinical toxicology studies of up to 26 weeks in duration were conducted in the CD-1 mouse and cynomolgus monkey. Murine studies used m3G9, while monkey studies used BG00011. Histologic changes were limited to the lung. These consisted of partially reversed alveolar macrophages, alveolar cellular debris, perivascular lymphoid infiltration, and increases in lung weight in mice and partially reversed alveolar macrophages in monkeys. The no observed adverse effect levels (NOAELs) in the 6-month studies were 1.0 and 10 mg/kg in mice and monkeys, respectively. No carcinogenicity or genotoxicology studies were conducted with BG00011 or m3G9. In the repeat-dose mouse studies with m3G9, low incidences of tumors (such as bronchoalveolar adenoma) were observed sporadically and in a non-dose-related manner. Spontaneous bronchoalveolar lesions have been reported in mouse historical control data. No tumors were noted in monkey studies. Transient elevations of lung tidal and minute volumes were observed in mice. There were no treatment-related changes in pulmonary function, blood pressure, or ECG in monkeys. No neurobehavioral abnormalities were observed, and no histologic changes were found in the central nervous system tissues of mice or monkeys. There were no fertility effects in male and female mice and no teratogenic findings in mice up to the maximum dose of 10 mg/kg. Antidrug antibodies were observed in up to 43% of mice and 25% of monkeys in repeat-dose toxicology studies. For additional information on toxicology studies with BG00011 or m3G9, see the Investigator's Brochure.

4.4.2.3. Nonclinical Pharmacokinetics

The nonclinical PK disposition profiles of BG00011 and m3G9 were characterized in the cynomolgus monkey and mouse, respectively. Following intravenous (IV) administration of a single dose of BG00011 in cynomolgus monkeys, maximum observed concentration (C_{max}) and area under the concentration time curve (AUC) increased with dose. The mean half-life ($t_{½}$) for both IV and subcutaneous (SC) administration was approximately 4 days. BG00011 was maintained primarily within the vasculature, with a calculated bioavailability of approximately 100%.

Following repeated dosing in monkeys in a 3-month toxicity study, BG00011 (1 to 10 mg/kg SC once weekly) demonstrated dose-proportional exposure, with the $t_{½}$ ranging from 8 to 12 days. In a 6-month toxicity study in monkeys, BG00011 (0.1 to 10 mg/kg SC once weekly) showed a greater-than-dose-proportional increase in exposure, and t½ increased with increasing dose. $t_{½}$ ranged from 1.5 to 10 days. In general, the presence of antidrug antibodies was inversely correlated with BG00011 exposure.

4.4.3. Clinical Experience

As of 28 February 2017, a total of 61 subjects (31 subjects with IPF and 30 healthy volunteers) have received BG00011 in 2 completed clinical studies, Phase 1 Study STX-001 and Phase 2a Study 203PF201. Brief summaries of each of these studies are as follows:

Study STX-001

Study STX-001, a Phase 1 randomized, double-blind, placebo-controlled, single-dose, dose-escalation study, was conducted to evaluate the safety, tolerability, PK, and immunogenicity profile of BG00011 administered SC to healthy volunteers. In this study, 40 subjects were enrolled into 5 ascending-dose cohorts (6 active:2 placebo subjects per cohort) and received a single SC dose of BG00011 (range: 0.003 to 0.3 mg/kg) or placebo (saline injection) and were monitored for 3 months after dosing. BG00011 exposure was dose proportional in the 3 highest dose groups for which serum levels were measurable. The $t_{½}$ of BG00011 was approximately 6 days, with peak serum concentrations observed at 5 days after administration. BG00011 was well tolerated, with no deaths, serious adverse events (SAEs), or premature discontinuations related to an AE. No clinically significant changes were noted for any safety measures including AEs, physical examination, vital signs, or clinical laboratory parameters, including pulmonary function tests (PFTs). AEs occurred in 21 of 30 subjects (70%) who received BG00011 and 8 of 10 subjects (80%) who received placebo. The most common AEs were headache, diarrhea, vomiting, arthropod stings, nasopharyngitis, and nasal congestion.

Study 203PF201

Study 203PF201, a Phase 2a, randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study was conducted to evaluate the safety, tolerability, PK, and effects on biomarkers of BG00011 administered SC to subjects with IPF. Forty-one subjects were enrolled into 5 ascending-dose cohorts ranging from 0.015 to 3.0 mg/kg (planned as 3:1 ratio per cohort). Study treatment was administered as once-weekly SC injections for up to 8 weeks, and each subject was monitored during a follow-up period of 8 to 12 weeks (depending on the dose cohort). Thirty-one subjects received BG00011, and 10 subjects received placebo.

The study was monitored by an independent data safety monitoring board (DSMB) and included safety evaluations that would enable detection of respiratory events (e.g., IPF exacerbation; changes in lung function, including decreases from baseline in FVC by ≥12%, total lung capacity by ≥8%, and diffusing capacity of the lungs for carbon monoxide [DL_{CO}] by ≥15%). Four cohorts completed dosing through 1.0 mg/kg. Prior to the completion of dosing in the fifth and highest dosing cohort (3.0 mg/kg), the study was stopped after meeting the prespecified protocol stopping

criteria, when 2 subjects experienced clinically significant sustained decreases from baseline respiratory status. Following the decision to stop the 3.0 mg/kg cohort and additional discussions with the DSMB, Biogen conducted a detailed analysis of the available PK, PD, and safety data from all cohorts and concluded that the potential benefit/risk of BG00011 was acceptable for dosing patients with IPF, with appropriate safety monitoring, at doses not exceeding 1.0 mg/kg. A summary of the PK, PD, and safety data for Study 203PF201 is as follows.

Pharmacokinetic data show that after repeated weekly SC administration, BG00011 exposure increased approximately proportionally to doses ranging from 0.015 to 1.0 mg/kg, but increased greater than proportionally at doses >1.0 mg/kg. After the last dose, the mean terminal $t_{½}$ of BG00011 ranged from 168 to 211 hours across the dose range (approximately 174 hours following repeated administration at doses <3.0 mg/kg). Serum concentrations were relatively sustained throughout the 168-hour sampling period, with the time to reach maximum observed concentration (T_{max}) after the last dose occurring at 24 to 48 hours.

In this study, BG00011 decreased the level of phosphorylated SMAD2 (pSMAD2) in BAL cells starting at the 0.3 mg/kg dose and achieved ≥70% reduction at the 1.0 mg/kg dose. In addition, a substantial decrease in gene expression of several prespecified genes linked to TGF-β signaling was also observed between the 0.3 and 1.0 mg/kg doses. These decreases in pSMAD and gene expression established proof of biology.

A total of 170 AEs were reported in the Phase 2a study. Twenty-seven of 31 subjects (87%) who received BG00011 and 7 of 10 subjects (70%) who received placebo experienced at least 1 AE. The majority of AEs were mild or moderate in severity. The most frequent AEs reported in subjects who received BG00011 were cough, dyspnea, and IPF exacerbation (5 subjects each), hypoxia (4 subjects), fatigue, viral upper respiratory infection, injection site pain, headache, and seasonal allergy (3 subjects each).

Four subjects who received BG00011 experienced SAEs, including atrioventricular block and hypoxemia in a subject in the 0.015 mg/kg cohort, IPF exacerbation in a subject in the 1.0 mg/kg cohort; syncope, Type II second-degree atrioventricular block, fractured mandible, and IPF exacerbation in a subject in the 1.0 mg cohort; and respiratory failure in a subject in the 3.0 mg/kg cohort. None of the SAEs were assessed by the respective Investigators as related to study treatment.

One subject (who experienced syncope, Type II second-degree atrioventricular block, fractured mandible, and IPF exacerbation) died due to the IPF exacerbation after discontinuation from the study.

In summary, multiple SC doses of BG00011 up to 1.0 mg/kg were generally well tolerated in the population of subjects with IPF, with the incidence and severity of AEs, and changes in physical examination, vital signs, or clinical laboratory parameters comparable to those expected in the IPF population. Based on a detailed review of the safety, PK, and PD data for Study 203PF201, Biogen considers that the potential benefit/risk of BG00011 is acceptable for dosing in subjects with IPF at doses not exceeding 1.0 mg/kg.

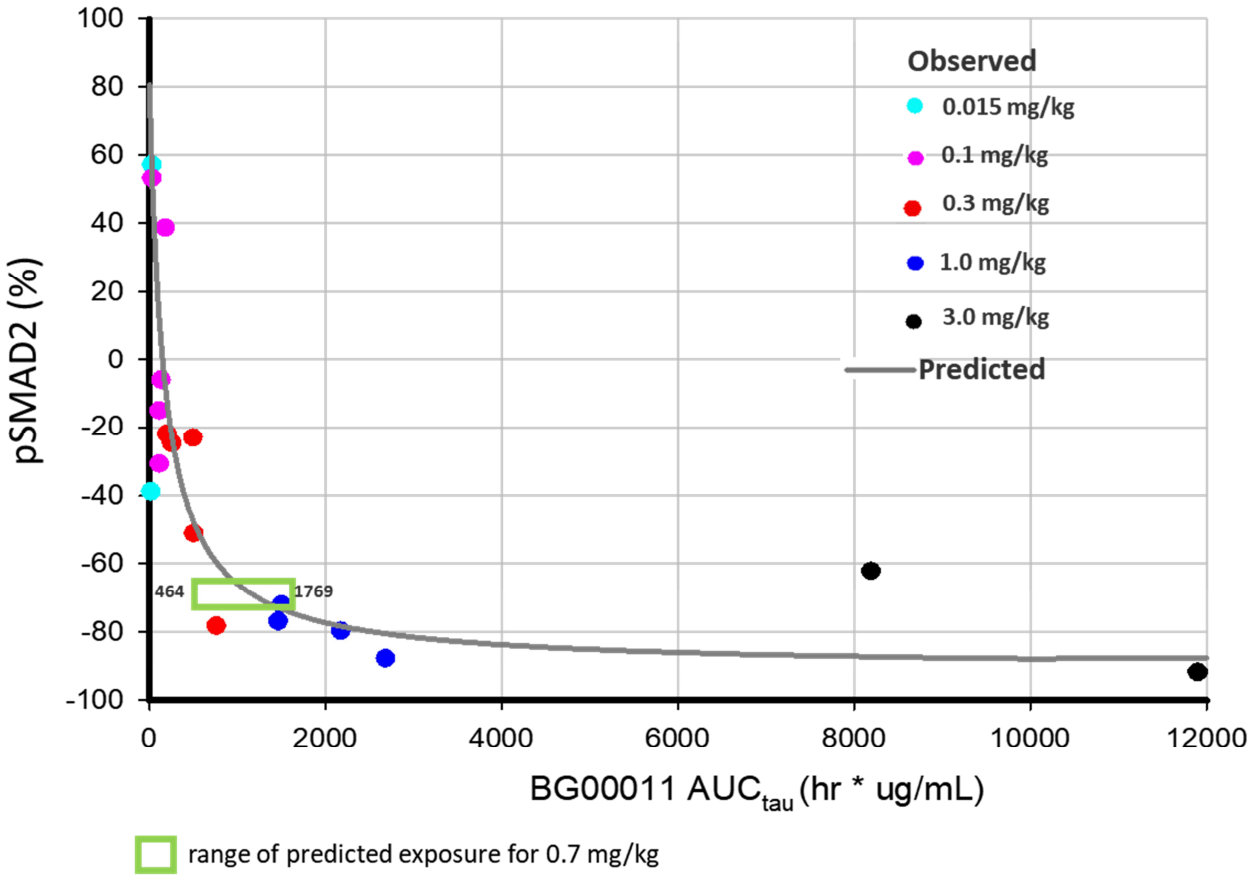
4.5. Study Rationale and Dose Selection

This Phase 2b study is designed to evaluate the treatment effect (change in FVC) of BG00011 administered SC once weekly for 52 doses in subjects with mild to moderate IPF who may or may not be receiving protocol-defined background therapies (i.e., nintedanib or pirfenidone).

As a first-in-class treatment for patients with IPF, the reduction in pSMAD2 levels and gene expression required for clinical efficacy is unknown. Across multiple mouse models of lung fibrosis, αvβ6-blocking antibody treatment with dosing between 0.3 and 1.0 mg/kg leads to significant reductions in pSMAD2 and reduced collagen expression (a marker of fibrosis) without inducing lung inflammation. The steep dose response in pSMAD2 is consistently observed in subjects with IPF (Study 203PF201), in nonhuman primate biomarker studies, and in the rodent models of epithelial injury and fibrotic diseases.

To guide dose selection, an exposure-response analysis was prepared based on reduction in pSMAD2 levels versus BG00011 exposure from observed individual subject data in Study 203PF201 (Figure 3). The area under the concentration time curve at steady state (AUC_{SS}) of the dosing interval after the last dose was used as the exposure variable and the percent change from the baseline level of pSMAD2 was used as the PD response in the assessment of the PK/PD relationship. This curve shows the steep dose response between the 0.3 and 1.0 mg/kg doses.

Figure 3: Plot of BG00011 Exposure and Change in pSMAD2 From Baseline (Study 203PF201)



AUC_{tau} = area under the plasma concentration-time curve for a dosing interval; pSMAD2 = phosphorylated SMAD2.

Note: Two subjects from the 1.0 mg/kg cohort were excluded from the exposure response analysis because they were identified to be outliers (outside 3 standard deviations), without baseline, or below the lower limit of quantitation.

Dose selection for the present study is supported by safety and PK data from the completed single-ascending-dose study in healthy volunteers and the 8-week study in subjects with IPF, along with the 26-week cynomolgus monkey studies, in which an exposure of 31,700 (hr × µg/mL) was identified as the NOAEL. Based on an integrated analysis of safety, PK, and PD, a dose of 0.7 mg/kg (56 mg) of BG00011 was selected to provide the predicted therapeutic exposure that would allow for optimal evaluation of the exposure-response curve with PD responses predicted to have clinical efficacy (median predicted response of 65% [range: 40% to 75%] pSMAD2 reduction) while not exceeding exposures observed at the 1.0 mg/kg dose level and providing an approximate 27-fold margin from the predicted human exposures to the monkey NOAEL.

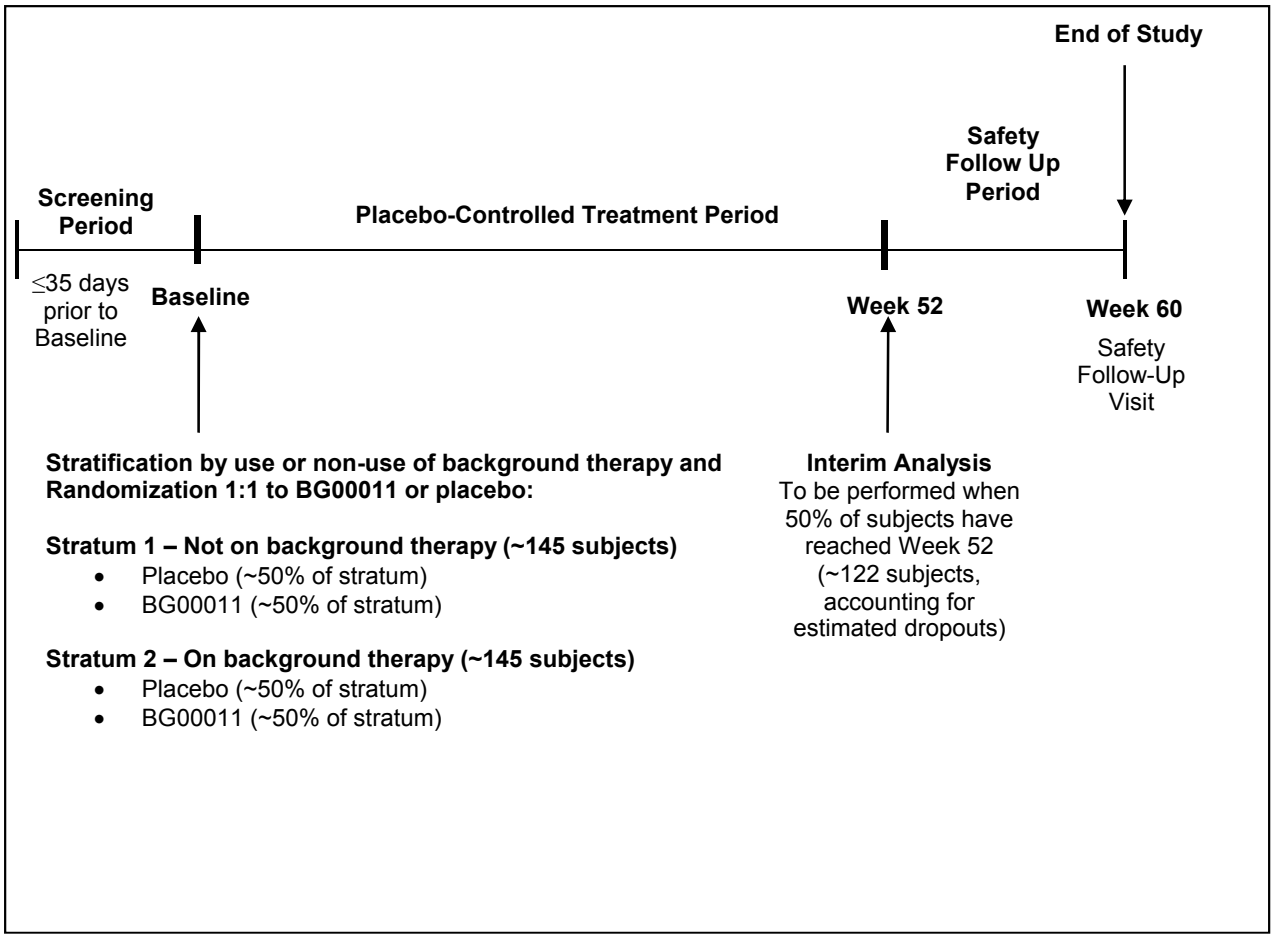
Since body weight was not identified as a covariate affecting exposure with the currently available data, there is limited pharmacological rationale to use body-weight based dosing over fixed dosing to reduce intersubject variability. In addition, fixed dosing eliminates the need for subjects or caregivers to manually draw doses and mitigates the risk for overdosing or underdosing the desired amount. This finding is also consistent with other PK analyses of therapeutic mAbs [Wang 2009]. An average weight of 80 kg for subjects with IPF, based on data from prior clinical studies in IPF [Noble 2011; Richeldi 2014], has been used to select the dose of BG00011 56 mg (based on the selection of the target of 0.7 mg/kg dose). Due to limited data in the lower ranges of body weight, subjects will be required to weigh greater than 60 kg to enroll in this Phase 2b study of BG00011.

5. STUDY SCHEMATIC AND STUDY ACTIVITIES

Figure 4 shows a study schematic for Study 203PF203, and Table 2 shows a schedule of study activities.

5.1. Study Schematic

Figure 4: Schematic for Study 203PF203



5.2. Study Activities

Table 2: Schedule of Events

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening[1]**	**Baseline**	**Day 5[2]**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT[3]**	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
Informed Consent Form	X														
Randomization		X													
Medical History	X	X													
Inclusion/Exclusion Criteria	X	X[4]													
Physical Examination[5]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Body Weight and Height	X								X				X	X	
12-Lead ECG	X	X							X				X	X	X[6]
Vital Signs (temperature, blood pressure, heart rate, respiratory rate)[7]	X	X		X	X	X	X	X	X	X	X	X	X	X	X

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening[1]**	**Baseline**	**Day 5[2]**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT[3]**	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
Oxygen Saturation[8]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
High Resolution Computed Tomography (HRCT)[9]	X[10]								X[11]				X[11]		X[6]
Spirometry (FVC, FEV_1)	X[12]	X		X	X	X	X	X	X	X	X	X	X		X
Carbon monoxide diffusion capacity (DL_{CO})	X	X		X	X		X		X		X		X		X
Plethysmography		X							X				X		X[6]
6-Minute Walk Test (6MWT)		X							X				X		
[redacted]															

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening[1]**	**Baseline**	**Day 5[2]**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT[3]**	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
[redacted]															
Serum pregnancy test[13]	X														
HIV, HCV, HBsAg, HBcAb Testing	X														
Urine pregnancy test[14]		X		X	X	X	X	X	X	X	X	X	X	X	
Hematology, blood chemistry, and urinalysis	X	X				X			X		X		X	X	X[6]
Serum for BG00011 PK measurement		X[15]	X	X	X	X	X	X	X		X		X	X	
[redacted]															
Serum for anti-BG00011 antibodies		X		X		X			X		X			X	
[redacted]															

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening[1]**	**Baseline**	**Day 5[2]**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT[3]**	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
Study diary training, administration, and review		X													
Subject completion of study diary[17]		----------Ongoing throughout the study----------													
Administration of study treatment in clinic		X[18]													
Injection training		X	----------Injection retraining to be offered as necessary----------												
Weekly administration of study treatment			To be performed by subject or caregiver once weekly from Week 1 (second dose) through Week 51 (final dose)												
Dispense and/or collect study treatment		X		X	X	X	X	X	X	X	X	X	X		
Compliance/drug accountability				X	X	X	X	X	X	X	X	X	X	X	
Adverse event reporting[19]		**----------Monitor and record throughout Treatment and Follow-Up Periods ----------**													

Period	**Screening Period**	**Placebo-Controlled Treatment Period**												**Safety Follow-Up**	**Unscheduled**
Study Visit	**Screening[1]**	**Baseline**	**Day 5[2]**	**Week 4**	**Week 8**	**Week 12**	**Week 16**	**Week 20**	**Week 26**	**Week 32**	**Week 38**	**Week 44**	**Week 52/ EoT[3]**	**Week 60**	**IPF Exacerbation**
Study Day	**≤35 days prior to Baseline**	**0**	**5**	**28**	**56**	**84**	**112**	**140**	**182**	**224**	**266**	**308**	**364**	**420**	**NA**
Visit Window (Days)	**NA**	**NA**	**+1**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**NA**
Serious adverse event reporting	**----------Monitor and record throughout the study ----------**														
Concomitant therapy and procedures recording[20]	**----------Monitor and record throughout the study ----------**														

Abbreviations not already defined in the table: EoT = End of Treatment; FEV = forced expiratory volume; FEV_1 = forced expiratory volume over 1 second; FVC = forced vital capacity; HBsAg = hepatitis B surface antigen; HBcAb = hepatitis B core antibody; HCV = hepatitis C antibody; HIV = human immunodeficiency virus; IPF = idiopathic pulmonary fibrosis; NA = not applicable; PK = pharmacokinetics.

[1] The Screening Visit is to occur within 35 days before the Baseline Visit (Day 0).

[2] The Day 5 Visit is for blood collection only (for PK analysis) and may be done in the clinic or at home (by appropriate personnel). Sample collection should occur on Day 5 (not sooner), with a +1 day window allowed (i.e., collection should occur on Day 5 but may occur on Day 6).

[3] If study treatment is permanently discontinued prior to the end of the Treatment Period, an EoT Visit will occur as soon as possible, but within 4 weeks (see Section 10.1 for details). If a subject is withdrawn from the study prior to the end of the Treatment Period, an EoT Visit will occur as soon as possible, but within 4 weeks (see Section 10.2 for details). In either case (discontinuation of treatment or withdrawal from the study) all assessments planned for the Week 52 Visit, except for the HRCT scan, will be performed at the EoT Visit. However, if the EoT Visit falls within the visit window for the Week 26 Visit, the HRCT should be performed.

[4] Entry criteria will be rechecked prior to dosing at the Baseline Visit (Day 0). Investigator to confirm eligibility.

[5] A full physical examination will be performed at the Screening, Baseline, Week 26, and Week 52 Visits, and at the EoT Visit in cases of early withdrawal from the study. At all other study visits, an abbreviated physical examination may be performed (must always include a cardiopulmonary examination and symptom-based examination).

[6] Imaging studies, plethysmography (lung volumes), ECG, or clinical laboratory tests at the IPF Exacerbation Visit will be at the discretion of the Investigator. The optional imaging study at the IPF Exacerbation Visit may be a chest X-ray or HRCT scan.

[7] Blood pressure is to be performed with the subject sitting, after at least 5 minutes at rest.

[8] Using pulse oximeter, oxygen saturation will be measured after the subject has been at rest for at least 5 minutes. The amount of supplemental oxygen the subject is receiving, if any, should be noted.

[9] Noncontrast chest HRCT through the full chest at suspended full inspiration and full expiration will be performed at Screening, Week 26, and Week 52, as detailed in the imaging procedure manual.

[10] A chest HRCT scan performed within 12 months of Screening can be used to determine initial eligibility to enter Screening (to prevent further screening assessments if HRCT does not meet the criteria for IPF). Regardless of whether a historical chest HRCT was submitted, all subjects are required to receive a chest HRCT at Screening. For determination of subject eligibility, all HRCT scans, including the historical and Screening Visit scans, must be consistent with the diagnosis of IPF. Eligibility read of the HRCT will be performed by a central radiologist. Historical biopsy data may be provided to support eligibility based on HRCT (see Section 7.2.1).
[11] HRCT will be performed at Weeks 26 and 52 for safety monitoring. Additionally, change from baseline in pulmonary fibrosis will be evaluated by a central radiologist.
[12] Spirometry (before and after bronchodilator use) will be performed to determine eligibility. If the subject qualifies for the study, 1 subsequent spirometry evaluation, without bronchodilator administration, will be performed at the Baseline Visit.
[13] Serum pregnancy test for women of childbearing potential only. Results must be negative for participation in the study.
[14] Urine pregnancy test for women of childbearing potential only.
[15] [redacted]
Documentation of background therapy dosing, including any changes in dose or dosing schedule, should be captured daily in the subject's study diary. Diary entries should be reviewed periodically by study site personnel to ensure compliance and completeness.
[18] Subjects will be observed in the clinic for a minimum of 1 hour following administration of study treatment.
[19] Adverse events are to be captured after the first dose of study treatment through the final study visit. Events that occur prior to dosing should be entered on the Medical History case report form.
[20] All concomitant medications being taken at the time of initial screening (including medications discontinued at that time) through the final study visit are to be recorded on the CRF.

6. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	**Primary Endpoints**
To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF.	Yearly rate of change in FVC (expressed in mL over 52 weeks) in subjects randomized to BG00011 compared with placebo.
Secondary Objectives	**Secondary Endpoints**
To evaluate the efficacy of BG00011 compared with placebo in subjects with IPF as determined by change in percent predicted FVC.	Yearly rate of change in FVC, expressed in percent predicted, over 52 weeks.
To assess progression-free survival in subjects who receive BG00011 compared with placebo.	Time to progression, as defined by a composite endpoint, including any of the following events: • Absolute decline of 10% predicted in FVC (FVC percent predicted$_{baseline}$ – FVC percent predicted$_{progression}$ ≥10%). • Nonelective hospitalization for respiratory events. • Lung transplantation or death.
To assess the occurrence of IPF exacerbation (using modified diagnostic criteria for acute IPF exacerbation derived from [Collard 2007]) in subjects who receive BG00011 compared with placebo.	• Time to first acute exacerbation, measured in days. • Proportion of subjects with at least 1 acute exacerbation during the 52 weeks on study. • Number of exacerbations during 52 weeks.
To assess the incidence of absolute decline in FVC ≥10% in subjects who receive BG00011 compared with placebo.	Number of subjects with absolute decline of 10% predicted in FVC (FVC percent predicted$_{baseline}$ – FVC percent predicted$_{progression}$ ≥10%) over 52 weeks.

To assess the time to death or lung transplantation in subjects who receive BG00011 compared with placebo, and the transplant-free survival rate at Week 26 and Week 52.	Time to death or lung transplantation, measured in days.
To assess the time to nonelective hospitalizations in subjects who receive BG00011 compared with placebo,	Time to all nonelective hospitalizations and to nonelective respiratory hospitalizations, measured in days.
To assess additional PFT findings in subjects who receive BG00011 compared with placebo.	• Change in absolute and percent predicted FVC from baseline over time. • Carbon monoxide diffusion capacity (DL_{CO}), absolute and percent predicted changes from baseline over time. • Total lung capacity, as measured by plethysmography, absolute and percent predicted changes from baseline over time.
To assess performance on the 6MWT in subjects who receive BG00011 compared with placebo.	Change from baseline in 6MWT parameters at Weeks 26 and 52.
To evaluate the safety and tolerability of BG00011.	• The incidence, severity, outcome, and relationship to study treatment of AEs and SAEs. • Change from baseline in clinical laboratory test results, vital signs, ECG, PFT results, and HRCT findings. • Immunogenicity (antibodies to BG00011).
To evaluate the serum concentration of BG00011.	Measurement of BG00011 serum concentrations using sparse PK sample collection at select timepoints during the study.
Exploratory Objectives	**Exploratory Endpoints**
[redacted]	[redacted]

7. STUDY DESIGN

7.1. Study Overview

This is a Phase 2b randomized, double-blind, placebo-controlled study designed to evaluate the efficacy, safety, PK, and tolerability of BG00011 in subjects with IPF. The study will be conducted at approximately 100 sites in up to 20 countries in North America, Europe, and Rest of World. Approximately 290 subjects are planned to be randomized.

To be eligible for the study, subjects must have a diagnosis of IPF consistent with current ATS/ERS/JRS/ALAT guidelines (Section 4.2, Table 1, and Figure 1). Eligibility for the study will be determined centrally. In addition, features of IPF at Screening must include: FVC ≥50% of predicted value; DL_{CO} (corrected for hemoglobin) ≥30% of predicted value; oxygen saturation ≥90% at rest (receiving ≤2 L/min of supplemental oxygen). Subjects with IPF who do not otherwise qualify for study eligibility may be rescreened once at the discretion of the Principal Investigator.

Subjects will be stratified by background therapy status (subjects receiving background therapy and subjects not receiving background therapy) and randomized in a 1:1 ratio of BG00011 to placebo (Figure 4). Enrollment will also be monitored to ensure that subjects receiving background therapy represent approximately 50% of each treatment group.

Subjects will receive weekly injections of BG00011 or placebo, as a solution for SC injection in a prefilled syringe, for 52 consecutive weeks (a total of 52 doses). The first dose will be administered at the Baseline (Day 0) Visit. The rest of the doses may be administered independently (e.g., not at the study site) by the subject or the subject's caregiver.

Background therapy for IPF with pirfenidone or nintedanib will be allowed during the study. The subject must be on a stable dose of either medication for at least 8 weeks prior to randomization. The subject is not to be on both medications simultaneously and should not initiate background therapy during the study. In cases where the Investigator feels that background therapy is clinically indicated, this therapy can be started, but the initiation of background therapy during the study will be considered a protocol deviation. While participating in the study, every effort should be made to maintain the subject on a stable dose of background therapy, and dosing should not exceed the labeled maximum dose. However, background therapy dosing may be adjusted or discontinued by the subject's pulmonary care physician. The subject may continue in the study if background therapy is discontinued. Subjects will maintain a diary to record background therapy dosing and any adjustments made in their therapy.

Assessment of pulmonary function by spirometry (FVC, FEV_1, and FEV_1/FVC) before and after bronchodilator use will be performed at Screening. During the Treatment Period, spirometry evaluation (without bronchodilator use) will be performed at the Baseline Visit and at all Treatment Period visits (excluding Day 5). Other PFTs include DL_{CO} (corrected for Hgb), to be

assessed at Screening, Baseline, and Weeks 4, 8, 16, 26, 38, and 52; and total lung capacity and residual volume, to be assessed by full-body plethysmography at Baseline, Week 26, and Week 52. All PFT results will be reviewed centrally.

An independent data safety monitoring board (DSMB) will review the unblinded safety and available PK data throughout the study (at least quarterly) to assess the overall safety profile (see Section 19.2.2 for additional information).

7.2. Study Duration, Study Visits, and Follow-Up

Study duration for an individual subject is approximately 65 weeks, including a Screening Visit up to 5 weeks prior to the first dose of study treatment, a Placebo-Controlled Treatment Period of 52 weeks, and a Safety Follow-Up Visit 8 weeks after the end of the Treatment Period.

7.2.1. Screening

Subjects will undergo screening assessments within 5 weeks (35 days) prior to dosing. Qualifying assessments including medical history, physical examination, vital signs, 12-lead ECG, oxygen saturation, PFTs (before and after bronchodilator administration), HRCT, and clinical laboratory tests including pregnancy testing (women of childbearing potential only), and testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg) or hepatitis B core antibody (HBcAb), and hepatitis C (HCV) antibody will be performed. If the HCV antibody test is positive, hepatitis viral load will be evaluated for active hepatitis C infection.

A chest HRCT scan performed within 12 months of Screening can be used to determine initial eligibility to enter Screening (to prevent further Screening assessments if HRCT does not meet criteria for IPF). Regardless of whether a historical chest HRCT was submitted, all subjects are required to receive a chest HRCT at Screening. For determination of subject eligibility, all HRCT scans, including the historical and Screening Visit scans, must be consistent with the diagnosis of IPF. If a historical surgical lung biopsy was obtained as part of the subject's initial IPF diagnosis, it must be submitted for central review. Surgical lung biopsies will not be offered as an assessment in this study. The diagnosis of IPF used for eligibility by HRCT and surgical lung biopsy (if obtained) will be confirmed centrally.

Screening assessments (e.g., clinical laboratory assessments or PFTs) may be repeated one time at the discretion of the Investigator if there are questionable results or if abnormalities are felt to be due to inherent variability of the test procedure. If a subject must be rescreened for study entry, results from previous screening assessments may be used, as long as the screening windows for those assessments are met and all spirometry data used for subject qualification are derived from a single day. If any PFTs are to be repeated, only the tests that are felt to be questionable should be repeated (i.e., spirometry, DL_{CO}, or plethysmography).

Following confirmation of eligibility on the Screening PFT, subjects will undergo 1 additional set of PFTs without bronchodilator administration to establish their baseline lung function; this assessment will be performed at the Baseline (Day 0) Visit.

Upon fulfilling all of the inclusion criteria and none of the exclusion criteria, subjects will be scheduled to return to the clinic for the Baseline predose evaluations and to ensure that they still qualify for the study.

7.2.2. Placebo-Controlled Treatment Period

The Placebo-Controlled Treatment Period begins with the Baseline (Day 0) Visit and ends with the End of Treatment Visit at Week 52. At the Baseline Visit, the subject's medical history, physical examination, inclusion/exclusion criteria, vital signs, weight and height, oxygen saturation, ECG, and pregnancy status (women of childbearing potential only) will be assessed. Baseline evaluations of PFTs, 6MWT, [redacted] will be obtained. Predose blood samples will be collected for baseline laboratory clinical laboratory tests, [redacted] PK, and antibody assessments. After confirmation of inclusion and exclusion criteria, the subject will be stratified based on use or nonuse of background therapy and then randomized to receive BG00011 56 mg SC or placebo. The subject and/or their caregiver will receive instruction and training on the administration of study treatment, documentation of administration in the study diary, and proper handling of study treatment supplies. The first dose of study treatment will then be administered under the supervision of study site personnel. The subject will be observed for a minimum of 1 hour following the first administration of study treatment. The subject will then be discharged with instructions to return to the study site for Treatment Period visits at Day 5 (for collection of a blood sample for PK analysis only, which may also be done at the subject's residence) and at Weeks 4, 8, 12, 16, 20, 26, 32, 38, 44, and 52 (End of Treatment Visit). See Table 2 for a complete schedule of assessments to be performed at each visit.

7.2.3. Safety Follow-Up Visit

A Safety Follow-Up Visit is to occur 8 weeks after the End of Treatment Visit. Therefore, if the End of Treatment Visit occurs at Week 52, as planned, the Safety Follow-Up Visit will occur at Week 60. See Table 2 for a schedule of assessments to be performed at the Safety Follow-Up Visit.

7.2.4. Study Treatment Discontinuation

If study treatment is discontinued prematurely (i.e., before the subject completes the 52-dose regimen), the subject must return for an End of Treatment Visit as soon as possible but within 4 weeks after discontinuation of treatment. If the End of Treatment Visit occurs in the visit window for the next scheduled visit, then the End of Treatment Visit may be substituted for the scheduled visit. Subjects will then complete all remaining visits as scheduled. See Section 10.1 for additional details about study treatment discontinuation.

7.2.5. Withdrawal From the Study

If a subject is withdrawn from the study, an End of Treatment Visit will be scheduled or performed as soon as possible but within 4 weeks. See Section 10.2 for additional details about withdrawal from the study.

7.2.6. Unscheduled Visit for Acute Exacerbation of IPF

A subject who experiences a worsening of respiratory status at any time during the study should immediately contact their treating physician. The subject should also notify the Investigator (if different than the treating physician) to determine the need for an IPF Exacerbation Visit.

The IPF Exacerbation Visit should include the following:

- Physical examination
- Vital signs
- Oxygen saturation
- Spirometry
- DL_{CO}
- Imaging studies (chest X-ray or HRCT) if not performed at another facility
- Investigator's determination of IPF exacerbation (see Section 7.2.6.1)

This visit may also include the following:

- ECG
- Clinical laboratory tests at the discretion of the Investigator
- Other tests or evaluations at the discretion of the Investigator

Note: If an IPF exacerbation is suspected at the time of a scheduled visit or is to be evaluated at a scheduled visit, the IPF exacerbation assessments listed above should be included in the scheduled visit if not already included.

A subject who is evaluated, treated, or hospitalized at a facility other than the study site should contact the study site following that visit to determine the need for an IPF Exacerbation Visit. The site assessments at the IPF Exacerbation Visit following an evaluation, treatment, or hospitalization at another facility are the same as those performed at the study site. In addition, study site personnel should obtain sufficient medical records in order to determine the following:

- Possible triggers or causes of the event.
- The results of relevant tests and assessments, including but not limited to:
  - Detailed radiography reports and copies of images of all radiographic examinations (e.g., chest X-ray or HRCT scan) for submission to the central imaging vendor.
  - Spirometry, lung volume, and/or DL_{CO} testing reports.
- Descriptions of the severity and duration of the event.
- Details of the medical treatment provided, including relevant medications and other major elements of the clinical management.
- The subject's response to the treatment and clinical status at the time of discharge.

7.2.6.1. Determination of IPF Exacerbation

Based on the results obtained from evaluations at the IPF Exacerbation Visit and/or the records obtained from a visit to another facility, the Investigator will determine whether an IPF exacerbation or suspected IPF exacerbation has occurred.

Specific criteria for acute exacerbation of IPF will be determined by the Investigator, using a modified definition of IPF exacerbation derived from the IPF Clinical Research Network (IPFnet) definition of acute exacerbations of IPF in 2007 [Collard 2007], as follows:

- Unexplained worsening or development of dyspnea within 30 days.
- New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit.
- Exclusion of infection per routine clinical practice and microbiological studies.
- Exclusion of alternative causes per routine clinical practice, including the following:
  - left heart failure
  - pulmonary embolism
  - identifiable cause of acute lung injury

[redacted]

The Investigator's determination of IPF exacerbation based on [redacted] (2007 [redacted]) definitions should be documented on the appropriate CRF.

As noted, treatment for an acute exacerbation is at the discretion of the Investigator and medications (such as prednisone) can be freely initiated or increased at the Investigator's discretion.

7.3. Study Stopping Rules

Biogen may terminate this study at any time. Biogen will notify Investigators if the study is to be placed on hold, completed, or terminated.

The DSMB will conduct regular reviews of all safety data in an unblinded format. Following each review, the DSMB will provide a recommendation to Biogen regarding the appropriateness of continuing the study from a safety perspective, as well as any other recommendations relevant to study conduct and/or subject safety.

The DSMB may recommend discontinuing the study if the event rate in the BG00011 treated arm is 20% higher compared with placebo. The events include, but may not be limited to:

- cumulative number of deaths and/or;
- number of lung transplantations and/or;
- cumulative number of subjects with a confirmed absolute decline of % predicted FVC ≥15 from baseline.

The meeting intervals and the procedures used to provide and assess the data will be described in detail in the DSMB charter.

7.4. End of Study

The end of study is last subject, last visit.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of randomization, or at the timepoint specified in the individual eligibility criterion listed:

1. Ability of the subject or his/her legally authorized representative to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

2. Aged ≥40 years at the time of informed consent.

3. Female subjects must be surgically sterile, postmenopausal (minimum 1 year without menses), or agree to use 1 or more of the following forms of highly effective contraception from the time of signing the informed consent form (ICF) until 3 months after the last injection of study medication: hormonal (i.e., oral, transdermal, implant, or injection); intrauterine device; vasectomized partner (with appropriate postvasectomy documentation of the absence of sperm in the ejaculate); or abstinence. Male subjects must also agree to use 1 or more of the above forms of birth control for either themselves or their partner(s), as appropriate, from the time of signing the ICF until 4 months after the last injection of study medication.

4. IPF diagnosed based on modified ATS/ ERS/JRS/ALAT IPF guideline for diagnosis and management, within 3 years of Screening (see Section 4.2).

5. Combination of HRCT pattern and, if one has been obtained, surgical lung biopsy pattern, as assessed by central reviewers, consistent with diagnosis of IPF (see Section 4.2).

   Note: A chest HRCT performed within 12 months of Screening can be used to determine initial eligibility to enter Screening and must be submitted to the central imaging vendor for eligibility read (to prevent further Screening assessments if HRCT is not consistent with IPF). Regardless of whether a historical chest HRCT was submitted, all subjects are required to receive a chest HRCT at Screening. If a historical HRCT is not available or not submitted, then the HRCT performed at the Screening Visit will be used to determine subject eligibility. For determination of subject eligibility, all HRCT scans, including the historical and Screening Visit scans, must be consistent with the eligibility criteria for IPF. Eligibility read of the HRCT will be performed by a central radiologist.

6. DL_{CO} (corrected for hemoglobin): 30% to 79% predicted of normal at Screening, with no clinically significant deterioration between the Screening Visit and randomization, as determined by the Investigator.

7. FVC ≥50% predicted of normal at Screening, with no clinically significant deterioration between the Screening Visit and randomization, as determined by the Investigator.

8. If a subject is taking nintedanib or pirfenidone, they must be on a stable dose for at least 8 weeks prior to randomization.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of Screening, the time of randomization, or at the timepoint specified in the individual criterion listed:

Lung Function

1. Unable to perform PFTs or undergo HRCT procedure.

2. Peripheral capillary oxygen saturation (SpO_2) <90% at rest (if on oxygen supplementation, must be ≤2 L/min at rest).

3. Findings that are diagnostic of a condition other than UIP based on the combination of surgical lung biopsy (if available), HRCT imaging, transbronchial lung biopsy, or BAL, according to central review of imaging and pathology.

4. Airway obstruction (i.e., prebronchodilator FEV_1/FVC <0.7) or evidence of a bronchodilator response as defined by an absolute increase of ≥12% **and** an increase of ≥200 mL in FEV_1 or FVC, or both, after bronchodilator use, compared with the values before bronchodilator use at Screening.

5. End-stage fibrotic disease likely requiring organ transplantation within 12 months, or if the subject has initiated active evaluation for organ transplantation.

6. The extent of emphysema in the lungs exceeds fibrosis, based on central review of HRCT scans.

7. In the opinion of the Investigator, the subject has experienced significant clinical deterioration between the Screening Visit and randomization.

Medical History

8. Body weight <60 kg at Screening.

9. History of or ongoing malignant disease, including solid tumors and hematologic malignancies, with the exception of basal cell carcinomas, squamous cell carcinomas, and carcinoma in situ of the cervix that have been completely excised and considered cured >2 years prior to Screening.

10. Significant cardiac disease (e.g., New York Heart Association Class 3 or 4; myocardial infarction within the past 6 months; unstable angina; coronary angioplasty or coronary artery bypass graft within the past 6 months; uncontrolled atrial or ventricular cardiac arrhythmias; or pulmonary hypertension requiring pharmacologic treatment).

11. Clinical diagnosis of any connective tissue disease (including but not limited to scleroderma, polymyositis/dermatomyositis, systemic lupus erythematosus, and rheumatoid arthritis) or a diagnosis of interstitial pneumonia with autoimmune features as determined by the Investigator applying the recent ERS/ATS research statement [Fischer 2015]. Note: Serological testing is not needed if not clinically indicated.

12. History of organ transplant at any time.

13. Female who is pregnant or breastfeeding.

14. Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) that required hospitalization or was clinically significant in the opinion of the Investigator, within 3 months prior to Screening.

15. Fever (body temperature > 38°C) or symptomatic viral or bacterial infection within 2 weeks prior to the Screening Visit or the Baseline Visit.

16. History or positive test result at Screening for HIV. Positive test result at Screening for hepatitis B virus (defined as positive for HBsAg or HBcAb). Current active HCV infection, determined by HCV RNA above the limit of detection. In subjects with positive HCV antibody titer, active HCV will be detected using HCV RNA test.

17. Known hypersensitivity to BG00011 or components of the BG00011 formulation or matching placebo.

18. Active drug or alcohol abuse (as defined by the Investigator) within 3 months prior to Screening.

19. Other disease that may interfere with testing procedures or, in the judgment of the Investigator, may interfere with study participation or may put the patient at risk when participating in this study.

20. Has a disease other than IPF with a life expectancy <2.0 years (Investigator assessment).

21. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

Laboratory Parameters

22. Screening values for the following laboratory tests (1 retest within 2 weeks is allowed):
    - Hemoglobin <10 g/dL

- WBC count <3.00 x 10^3/μL
- Neutrophils <1.50 x 10^3/μL
- Platelets <80 x 10^3/μL
- Total bilirubin >1.5 mg/dL
- AST and ALT >2.0 times upper limit of normal

Medications

23. Currently receiving high-dose corticosteroid, cytotoxic therapy (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), vasodilator therapy for pulmonary hypertension (e.g., bosentan), unapproved (e.g., IFN-γ, penicillamine, cyclosporine, mycophenolate, N-acetylcysteine [may vary by country]) and/or investigational therapy for IPF or administration of such therapeutics within 5 half-lives of the agent prior to initial screening in this study. A current dose of ≤10 mg/day of prednisone or its equivalent is acceptable if the dose is expected to remain stable during the study.

24. Treatment with another investigational drug, investigational device, or approved therapy for investigational use within 5 half-lives of the agent prior to initial screening in this study.

25. Live/attenuated vaccinations within 12 weeks prior to Screening (inactivated influenza vaccine is permitted).

Other

26. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
27. Blood donation (1 unit or more) within 1 month prior to Screening.

28. Male or female planning a pregnancy during the duration of this study. A serum pregnancy test will be performed on all female subjects of childbearing potential.

29. Inability to comply with study requirements.

30. Use of any tobacco or "electronic cigarette" product within 12 weeks prior to Screening.

9. SCREENING AND RANDOMIZATION

9.1. Screening

Subjects must provide informed consent before any screening tests are performed (Section 17.3). Participating study sites are required to document all screened candidates initially considered for inclusion in the study.

Screen failures are defined as subjects who sign the ICF but are not subsequently randomized or dosed. If a subject is considered a screen failure, the reasons for exclusion must be documented in the subject's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Subjects with IPF who do not meet the criteria for participation in this study (i.e., a screen failure) may be rescreened one time only, at the discretion of the Principal Investigator.

9.2. Randomization

Subjects will be randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2.

Subjects will be assigned a unique identification number that will be used on study-related documents pertaining to the subject. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment or continue in the study.

Randomization will be performed using interactive response technology (IRT). Subjects will be randomized to receive BG00011 or placebo in a 1:1 ratio.

Refer to the Study Reference Guide for details on randomization.

9.3. Blinding Procedures

This is a randomized, double-blinded, placebo-controlled study.

All study staff will be blinded to the subject treatment assignments. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the study team, either at the study site or at Biogen, except the unblinded Pharmacy staff and designated Biogen personnel.

At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, Biogen will provide the randomization codes to Investigators, who then can inform their subjects about the treatment received.

10. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

Study treatment discontinuation is defined as the premature ending of study treatment dosing, i.e., when a subject permanently stops taking the study treatment before the last dose (the Week 51 dose). Reasons for mandatory study treatment discontinuation are listed in Section 10.1.1. The primary reason for study treatment discontinuation must be recorded in the subject's CRF.

Subjects who discontinue study treatment must return for an End of Treatment Visit as soon as possible, but within 4 weeks after discontinuation of treatment. All assessments planned for the Week 52 Visit except the HRCT scan will be performed. If the End of Treatment Visit occurs in the visit window for the next scheduled visit, then the scheduled visit may serve as the End of Treatment Visit, and all assessments for the End of Treatment Visit should occur at that time. Subjects will go on to complete all remaining visits as scheduled, including the Week 52 and Safety Follow-Up Visits (see Table 2 for a list of assessments to occur at the End of Treatment and Safety Follow-Up Visits).

Note: A subject who misses 1 or more doses of study treatment should restart study treatment, receive all remaining doses, and complete all remaining study visits.

See Section 10.2 for information related to the withdrawal of subjects from study.

10.1.1. Reasons for Study Treatment Discontinuation

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject experiences an AE that necessitates permanent discontinuation of study treatment.
- The subject experiences an urgent medical event that necessitates unblinding of the subject's treatment assignment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.
- The subject withdraws consent to continue study treatment.

10.2. Withdrawal of Subjects From the Study

Study withdrawal is defined as the premature ending of study visits and assessments. The reasons for mandatory study withdrawal are listed below (Section 10.2.1). Note that discontinuation of study treatment does not require withdrawal from the study if a subject continues to attend clinic visits and complete assessments.

If a subject is withdrawn from the study, an End of Treatment Visit will be scheduled or performed as soon as possible but within 4 weeks. All assessments planned for the Week 52 Visit except the HRCT scan will be performed (see Table 2 for a list of assessments to occur at the End of Treatment Visit).

If a subject is unwilling or unable to attend, at minimum, the End of Treatment Visit, and decides to withdraw consent, the reason for withdrawal will be documented and no further assessments will be obtained.

Subjects who are withdrawn from the study will not be replaced.

10.2.1. Reasons for Withdrawal of Subjects from the Study

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

- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.

10.3. Lost to Follow-Up

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record.
- If the subject continues to be unreachable, that subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the Directions for Handling and Administration (DHA).

Approximately 290 subjects will be randomized into 2 dose groups as follows:

- Group 1: BG00011 56 mg by SC injection, once weekly for 52 weeks
- Group 2: Placebo by SC injection, once weekly for 52 weeks

The first dose of BG00011 or placebo (study treatment) will be administered at the study site during the Baseline Visit (Day 0). All subsequent doses should be administered by the subject or the subject's caregiver.

11.2. Modification of Dose and/or Treatment Schedule

The dosage and dosing schedule cannot be modified.

11.3. Precautions

Subjects will be monitored by study site personnel for at least 1 hour after administration of the first dose of study treatment.

11.4. Compliance

Compliance with study treatment dosing is to be documented by the subject or the subject's caregiver in the electronic study diary and monitored at each study visit by study site personnel.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance administered between the time a subject is screened for the study and the final study visit.

11.5.1.1. Allowed Concomitant Therapy

A current dose of ≤10 mg/day of prednisone or its equivalent is acceptable if it has been stable for at least 8 weeks prior to randomization and it is anticipated that the dose will remain stable throughout the subject's enrollment.

During a subject's enrollment, pirfenidone or nintedanib may be taken as background therapy for IPF. The subject must be on a stable dose of either drug for at least 8 weeks prior to

randomization. **Both drugs are not to be used simultaneously.** Subjects should not initiate background therapy during the study.

While participating in the study, every effort should be made to maintain the subject on a stable dose of background therapy. However, background therapy dosing may be adjusted or discontinued by the physician responsible for the subject's pulmonary care, with no dose to exceed the labeled maximum doses. The subject may continue in the study if background therapy is discontinued. Subjects will maintain a diary to record background therapy dosing and any adjustments made in their background therapy.

In the event of an IPF exacerbation meeting the definition described in this protocol, if the Investigator feels that additional therapy (other than pirfenidone or nintedanib) is clinically indicated, this therapy may be started and the medications, doses, and duration of treatment must be documented as concomitant medications. The subject may continue in the study.

Subjects should be instructed to continue the medications that they were receiving at enrollment and to avoid starting any new medications or herbal preparations during the study, since these may confound the results of the study. However, medically indicated medication or treatment should not be withheld. Subjects should inform the Investigator of any changes in the medications they are taking.

11.5.1.2. Disallowed Concomitant Therapy

Simultaneous use of pirfenidone and nintedanib.

Subjects should not be receiving chronic high-dose corticosteroid (i.e., >10 mg/day of prednisone or its equivalent), cytotoxic therapy (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), vasodilator therapy for pulmonary hypertension (e.g., bosentan), unapproved (e.g., IFN-γ, penicillamine, cyclosporine, mycophenolate [may vary by country]), and/or any investigational therapy while participating in this study, nor can they have received such therapies within 5 half-lives of the agent prior to initial screening. Live or attenuated vaccinations within 12 weeks prior to Screening or during the study are not permitted (inactivated influenza vaccine is permitted).

All treatments previously used for clinical management or in previous investigational trials of IPF will be documented on the appropriate CRF.

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy, pulmonary rehabilitation) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the time the subject is screened for the study and final study visit.

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If BG00011 is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

12. STUDY TREATMENT MANAGEMENT

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Study site staff should follow the Directions for Handling and Administration, which is located in the pharmacy binder, for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The Directions for Handling and Administration supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects randomized in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment is for one-time use only; do not use any study treatment remaining in the syringe for another subject.

12.1. BG00011

BG00011 drug product is a liquid formulation and supplied in a 1.0 mL syringe (prefilled to 0.8 mL) and is intended for self-administration. The pre-filled syringe contains 56 mg of BG00011 per syringe and is formulated in sodium citrate, methionine, L-arginine, and polysorbate 80 at pH 5.5. The placebo consists of the formulation buffer.

The contents of the BG00011 label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site personnel. Study treatment should not be used after the expiration, expiry, or use-by date.

12.1.1. BG00011 Preparation

The individual preparing BG00011should carefully review the instructions provided in the Directions for Handling and Administration. If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the study treatment, do not use the study treatment. The study treatment in question should be saved at the study site and the problem immediately reported to Biogen.

12.1.2. BG00011 Storage

Study treatment (BG00011 and placebo) must be stored in a secure location.

BG00011 prefilled syringes are to be stored at 2°C to 8°C (36°F to 46°F), in a locked refrigerator with limited access. For the most up-to-date storage requirements, follow the instructions provided in the Directions for Handling and Administration.

12.1.3. BG00011 Handling and Disposal

The Investigator must return all used and unused prefilled syringes of BG00011 as instructed by Biogen unless approved for onsite destruction.

If any BG00011 supplies are to be destroyed at the study site, the institution or appropriate site personnel must obtain prior approval from Biogen, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. BG00011 Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), amount returned by the subject, and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all prefilled syringes both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of BG00011 supplied, dispensed, and subsequently destroyed, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Reference Product

The placebo (control agent) to be used in this study is supplied in a 1.0 mL syringe (prefilled to 0.8 mL) and intended for self-administration. The prefilled syringe contains only the buffering solution used for the active drug product (sodium citrate, methionine, L-arginine, and polysorbate 80 at pH 5.5). Labeling, preparation, storage, handling, and disposal instructions for the reference product are identical to those for BG00011.

13. EFFICACY, PHARMACOKINETIC, [redacted] ASSESSMENTS

See Section 5 for the timing of all efficacy, PK, [redacted] assessments.

13.1. Clinical Efficacy Assessments

The following clinical assessments will be performed to evaluate the efficacy of BG00011.

13.1.1. Pulmonary Function Testing

13.1.1.1. Spirometry

Spirometry testing, including FVC, FEV_1, and FEV_1/FVC, both before and after bronchodilator use, will be performed at Screening. During the Treatment Period, spirometry testing (without bronchodilator use) will be performed at Baseline (Day 0) and at all scheduled study visits except Day 5. The spirometry evaluations performed at the Screening Visit will be used to determine whether the subject qualifies for the study and must be performed within 35 days prior to the first dose of study treatment. At the Baseline Visit, spirometry test results will be obtained prior to the first dose of study treatment. For each subject, spirometry testing should be conducted at approximately the same time of day.

See the Study Reference Guide for full details of spirometry testing procedures.

All spirometry results will be electronically transmitted and confirmed by a central reader. Investigators will receive a report from the central reader.

13.1.1.2. Carbon Monoxide Diffusion Capacity

DL_{CO} measurement will be performed at Screening to determine study eligibility, and at the following study visits: Baseline (Day 0), Week 4, Week 8, Week 16, Week 26, Week 38, and Week 52.

Evaluation of DL_{CO} will be performed by single-breath carbon monoxide diffusing capacity according to ATS/ERS recommendations. See the Study Reference Guide for full details of the DL_{CO} testing procedure.

13.1.1.3. Full-Body Plethysmography

Lung volumes, including total lung capacity and residual volume, will be measured by full-body plethysmography at the following study visits: Baseline (Day 0), Week 26, and Week 52.

See the Study Reference Manual for full details of body plethysmography testing procedures.

13.1.2. High-Resolution Computed Tomography

HRCT scanning will be performed at Screening, Week 26, and Week 52. Noncontrast chest CT through the full chest at suspended full inspiration and full expiration will be performed as detailed in the Imaging Procedure Manual. The HRCT scan performed at Screening will be centrally read, will be used to determine study eligibility, and will establish the predose baseline pattern and extent of disease for comparison with the Week 26 and Week 52 scans.

An independent central radiologist experienced in the evaluation of diffuse lung diseases and blinded to treatment assignment will read all HRCT scans obtained during the study. The central radiologist will evaluate the Screening HRCT to determine eligibility and will also perform qualitative IPF change assessment from Screening and follow-up HRCT scans. [redacted]

See the Imaging Procedure Manual for full details on HRCT scanning procedures.

13.1.3. Acute Exacerbations of IPF

Subjects should be advised of the importance of reporting worsening respiratory status to the Investigator. The Investigator will determine whether the subject should come to the study site for an IPF Exacerbation Visit. See Section 7.2.6 for a detailed description of the IPF Exacerbation Visit.

Based on the results obtained from evaluations at the IPF Exacerbation Visit and/or the records obtained from a visit to another facility, using a modified definition of IPF exacerbation derived from IPFnet definition of acute exacerbations of IPF in 2007 [Collard 2007](see Section 7.2.6.1), the Investigator will determine whether an IPF exacerbation has occurred.

[redacted]

Analyses of IPF exacerbation events, based on [redacted] the modified definition of IPF exacerbation (2007) [redacted], will include the following:

- Time to first acute exacerbation, measured in days.
- Proportion of subjects with at least 1 acute exacerbation during the 52 weeks on study.
- Number of exacerbations during 52 weeks.

See Section 16.2.2.3 and Section 16.2.2.4 for additional details of these analyses.

13.1.4. Respiratory Hospitalizations

All nonelective hospitalizations will be assessed by the Investigator to determine whether the primary cause of the hospitalization was respiratory in nature. The determination of a respiratory hospitalization should be based on a fundamental change in respiratory status that is due either to intrinsic lung disease or to infectious etiology of the lung. The change in respiratory status should not be the result of a secondary effect from another organ or system.

In addition, study site personnel should obtain sufficient medical records to determine the following:

- Possible triggers or causes of the event
- The results of relevant tests and assessments (if performed), including but not limited to:
  - Detailed radiography reports and copies of images of all radiographic examinations (e.g. chest X-ray or HRCT scan) for submission to the central imaging vendor
  - Spirometry, lung volume, and/or DL_{CO} testing reports
  - Echocardiogram
  - Microbiology data
- Descriptions of the severity and duration of the event
- Details of the medical treatment provided, including relevant medications and other major elements of the clinical management
- The subject's response to the treatment and clinical status at the time of discharge.

13.1.5. 6-Minute Walk Test

The 6MWT will be administered at the following study visits: Baseline (Day 0), Week 26, and Week 52. This test, which assesses the distance in meters that a subject can walk in 6 minutes, will be conducted according to ATS criteria by study site staff in a suitable location with emergency response supplies available. Detailed criteria for the conduct of the 6MWT, including training requirements for administration of the test, availability of emergency supplies, use of oxygen supplementation during the test, and parameters for starting and stopping the test, are provided in the Study Reference Guide.

[redacted]

[redacted]

13.2. Pharmacokinetic Assessments

Blood samples for PK evaluation will be collected at the following visits: prior to dosing at Baseline (Day 0), Day 5, Week 4, Week 8, Week 12, Week 26, Week 38, Week 52, and Week 60.

The PK data obtained in this Phase 2b study will be combined with data from other studies in the clinical development program to develop a population PK model. This model will be used to evaluate the effects of intrinsic and extrinsic covariates on the PK of BG00011 and to determine measures of individual exposure (such as steady-state trough, time-averaged concentration, or AUC). Model-determined exposures will be used for exposure-response analyses of selected efficacy and safety endpoints. Results of population PK and exposure-response analyses will be reported separately.

[redacted]

[redacted]

14. SAFETY ASSESSMENTS

Refer to Section 5 for the timing of all safety assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, subjects will be asked to return to the clinic to have the evaluations repeated.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BG00011:

- AE and SAE monitoring and recording
- Lung function

  The assessment of changes in lung function during this study will be performed by comparing the subject's spirometry parameters at Baseline to postbaseline values during the Treatment and Follow-Up Periods. These evaluations will assess both the absolute and the percent predicted changes in FVC. All spirometry tests will be reviewed centrally.

  Expected fluctuations or expected deterioration of the underlying IPF and other pre-existing conditions should not be recorded as an AE except in the following circumstances:

  - Worsening of the disease meets the criteria for an SAE.
  - Action is taken with investigational treatment, such as when treatment is discontinued.
  - Additional treatment is required, such as when concomitant medication is added or changed.
  - In the opinion of the Investigator, an unexpected deterioration from baseline has occurred.
  - The event meets the criteria of an acute exacerbation of IPF or suspected exacerbation of IPF.

  Specific criteria for acute exacerbation of IPF will be determined by the Investigator based on the following 2 definitions:

  Diagnostic Criteria for Acute IPF Exacerbation (2007)

  - Unexplained worsening or development of dyspnea within 30 days.
  - New diffuse pulmonary infiltrates on chest X-ray, and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities) since last visit.
  - Exclusion of infection per routine clinical practice and microbiological studies.
  - Exclusion of alternative causes per routine clinical practice, including the following:

- congestive heart failure
- pulmonary embolism
- identifiable cause of acute lung injury

[redacted]

- High-resolution computed tomography

  HRCT scans will be performed during Screening to establish the predose pattern and extent of disease and will serve as the baseline assessment. An independent central radiologist experienced in the evaluation of diffuse lung diseases and blinded to treatment assignment will evaluate the HRCT scans, which will be performed at Screening, Week 26, and Week 52. Every effort will be made to have sequential scans for individual subjects evaluated by the same radiologist.

- Other safety assessments
  - Medical history
  - Concomitant therapy and procedure recording
  - Physical examination
  - Vital signs: oral temperature (°C), heart rate (beats/min), respiratory rate (breaths/min), sitting blood pressure (mmHg) after at least 5 minutes' rest
  - Body weight (kg) and height (cm)
  - 12-lead ECG after at least 5 minutes' rest
  - Oxygen saturation (pulse oximetry) after at least 5 minutes' rest
  - Use of supplemental oxygen
  - Study discontinuations (all causes, and due to urgent need for transplantation)
  - Cumulative number of lung transplantations and number of deaths (respiratory and all causes)
  - Cumulative spirometry testing with percent change from baseline and change in percent predicted from baseline calculated at each visit
  - Cumulative number of nonelective hospitalizations

14.2. Laboratory Safety Assessments

All samples will be analyzed using Good Laboratory Practice validated assays.

The following laboratory assessments will be performed to evaluate the safety profile of BG00011:

- Hematology: Complete blood count, including red blood cell count, white blood cell count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.

- Serum chemistry, including: albumin, alkaline phosphatase, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, blood urea nitrogen, calcium, chloride, carbon dioxide, creatinine, bilirubin (total and direct), gamma-glutamyl transferase, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, and total protein.

- Urinalysis, including urine protein, glucose, ketones, occult blood, and white blood cells by dipstick, with microscopic examination if indicated.

- At Screening, blood samples for HCV antibody and RNA, HBsAg, HBcAb, and HIV antibody will be collected to establish eligibility. Appropriate referrals must be made for any active HCV, positive HBsAg, or HIV test that is obtained, according to applicable local laws.

- Serum pregnancy test (Screening).

- Urine pregnancy tests (all visits after Screening).

14.3. Immunogenicity Assessments

The following assessments will be performed to determine the safety of BG00011:

- Collection and analysis of serum samples for the presence and titer of anti-BG00011 antibodies.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject, or their legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

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

Determination of whether an abnormal laboratory value, vital sign result, and/or ECG result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE
- The result requires the subject to receive specific corrective therapy
- The result is considered by the Investigator to be clinically significant

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect
- Is a medically important event

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled preventative health procedure (e.g., colonoscopy) will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
    - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2 .
- The relationship of the event to study treatment as defined in Section 15.2.2
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment.

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE (including SAEs) experienced by the subject between the time of first dose of study treatment and the subject's last study visit is to be recorded on the CRF, regardless of the

severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AE outcome will be recorded on the CRF, as applicable.

Expected fluctuations or expected deterioration of the underlying IPF and other pre-existing conditions should not be recorded as an AE except in the following circumstances:

- Worsening of the disease meets the criteria for an SAE.
- Action is taken with investigational treatment, such as when treatment is discontinued.
- Additional treatment is required, such as when concomitant medication is added or changed.
- In the opinion of the Investigator, an unexpected deterioration from baseline has occurred.
- The event meets the criteria of an acute exacerbation of IPF.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the subject's last study visit is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported within 24 hours. See the Study Reference Guide's Official Study Contact List for complete contact information.

Subjects will be followed for all SAEs until their last study visit. Thereafter, the event should be reported to Biogen only if the Investigator considers the SAE to be related to study treatment.

SAEs that are ongoing when the subject completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. SAE outcome will be recorded on the CRF, as applicable. Only SAEs that are unresolved will be followed by the Investigator.

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs

A report ***must be submitted*** to Biogen regardless of the following:

- Whether or not the subject has undergone study-related procedures
- Whether or not the subject has received study treatment
- The severity of the event
- The relationship of the event to study treatment

To report initial or follow-up information on an SAE, a completed SAE form must be sent to Biogen; refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Biogen. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

Appropriate personnel at Biogen will unblind SUSARs for the purpose of regulatory reporting. Biogen will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen will submit SUSARs to Investigators in a blinded fashion.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 3 months after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject from first dose of study treatment up to 3 months after the last dose by faxing or emailing the appropriate form to Biogen within 24 hours of the study site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The

Investigator or study site staff must report the outcome of the pregnancy to Biogen. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as SAEs if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to Biogen within 24 hours of the site becoming aware of the overdose. An overdose must be reported to Biogen even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to Biogen. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator should contact the study's Medical Director. Refer to the Study Reference Guide's Official Study Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen to discuss such situations.

15.5. Contraception Requirements

All women of childbearing potential and all men must practice highly effective contraception during the study. Women in the study (and/or their partner) must continue highly effective contraception and must not donate eggs for 3 months after stopping study treatment. Men in the study (and/or their partner) must continue effective contraception and must not donate sperm for 4 months after stopping study treatment.

For the purposes of this study, women who do not meet one of the following criteria are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
    - 12 continuous months of natural (spontaneous) amenorrhea without an alternative medical cause.
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as use of 1 of the following:

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted progestogen-only hormonal methods of contraception.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For males:

- Vasectomy (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).
- Sex with a woman who uses the methods described for females if she is of childbearing potential.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical trial. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies in female subjects and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax or email it to Biogen within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before a site can enroll any subjects, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objectives of the study and the endpoints to be analyzed are listed in Section 6.

16.1. Demography and Baseline Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy

16.2.1. Analysis Population

The intent-to-treat (ITT) population, defined as all subjects who are randomized and receive at least 1 dose of study treatment, will be used for the efficacy analyses unless otherwise specified. For each endpoint, additional conditions may apply to the definition of the population for the analysis. Subjects will be analyzed in the groups to which they were randomized.

The per-protocol (PP) population, defined as all subjects who are randomized and without major protocol violations, will be used for sensitivity analysis for the primary endpoint.

Subgroup analysis (e.g., background therapy strata as subgroup) will be done for the primary endpoint and some of the secondary endpoints. The details will be specified in the SAP.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, standard deviation, median, and range. For categorical endpoints, this will generally include number of subjects randomized, number of subjects with data, and percentage of subjects with data in each category. Statistical testing for efficacy endpoints will be made between subjects treated with BG00011 and with placebo.

All statistical tests will be 2-sided.

16.2.2.2. Analysis of the Primary Endpoint

The population for the primary endpoint analysis will be subjects in the ITT population with a baseline and at least 1 postbaseline FVC measurement.

The primary efficacy outcome variable is the yearly rate of change in FVC (actual value, expressed in mL, over 52 weeks). The primary endpoint will be analyzed using a random coefficients linear regression model, with an absolute change in FVC as the outcome variable

assuming linear decline in lung function over time. The model includes random coefficients for intercept and slope (time), and fixed-effect terms for treatment, randomization stratum (background therapy), age, and baseline FVC. Interaction terms in the model will be the interaction between treatment and time, and the interaction between pirfenidone or nintedanib and time.

Every effort should be made to reduce the amount of missing data. In the analysis of the primary endpoint, missing data will be assumed to be missing at random. An unstructured variance-covariance structure will be used to model the within-patient measurements variability. If it fails to converge, an AR(1) structure will be used. The variance-covariance matrix, modeled to estimate the interindividual variability, is considered to have a variance components structure. Because the statistical model assumes a linear decline in lung function over time and, hence, implicitly imputes missing data based on individual's estimated rate of worsening of lung function prior to treatment discontinuation, similar to linear extrapolation. If a subject who was not on background therapy at randomization initiates treatment with background therapy during the study, the subject's data collected after the initiation of background therapy will be excluded from the primary analysis. However, a sensitivity analysis that includes the excluded data will be performed.

Support analyses for the primary endpoint includes:

1. Analysis using multiple imputation with pattern mixture models will be carried out. Details of sensitivity analysis and assumptions for different pattern will be described in the statistical analysis plan (SAP).

2. A mixed model of repeated measures model will be used to compare the difference between the 2 treatment groups in FVC change at 52 weeks and other scheduled visits. An unstructured variance-covariance structure will be used in this model. If the model fails to converge, an AR(1) structure will be used.

3. Rate of decline in percent predicted FVC at 52 weeks will be analyzed by the same method as FVC actual value.

A model including the interaction between treatment and background therapy strata will be used to explore the treatment effects within each subgroup.

16.2.2.3. Analysis of the Secondary Endpoints

Time to progression will be presented using Kaplan-Meier curves, a stratified log-rank test will be used to compare the 2 treatment groups using randomization stratum as the stratification factor. The proportion of subjects who progressed in each arm will be summarized. Each component of progression will be summarized descriptively. If a subject who was not on background therapy at randomization initiates treatment with background therapy during the study, the subject will be censored at the time of new background therapy initiation.

Other time-to-event types of endpoints, e.g., time to first acute exacerbation, time to death or lung transplant, nonelective hospitalization (due to respiratory causes and due to all causes), and

survival rate (death from all causes and death due to respiratory causes) at 26 weeks and 52 weeks will be analyzed similarly.

The number of subjects experiencing an absolute decline of 10% predicted in FVC will be analyzed using a logistic regression model, adjusting for the randomization stratification factor, patient age, and baseline FVC.

Other pulmonary function endpoints and the 6MWT at 52 weeks will be analyzed similarly to the primary endpoint. For other visits, an analysis of covariance model adjusting the randomization stratification factor, age, and FVC at Baseline will be used to compare the treatment groups. The cumulative distribution of subjects by change in absolute and percent predicted FVC from Baseline to Week 52 will be presented in graph form.

Details of the analyses, including the handling of missing data, will be described in a SAP.

16.3. Pharmacokinetics

16.3.1. Analysis Population

The population for serum PK analyses is defined as all subjects in the ITT population who have at least 1 measurable BG00011 concentration in serum.

16.3.2. Methods of Analysis

Samples for measuring serum concentrations of BG00011 will be collected as specified in Section 5.2. BG00011 concentrations in serum will be summarized using descriptive statistics at the scheduled PK sample collection visits.

This study will collect only sparse PK samples; thus, the serum concentration data will be summarized descriptively by visit. No noncompartmental or compartmental methods will be

used to analyze the PK data for presentation in the clinical study report. Details of the PK analysis will be described in the SAP.

Mean serum concentrations of BG00011 will be plotted versus time on both a linear and a logarithmic scale. No dose-proportionality assessments will be conducted because of the sparse PK data sampling.

Atypical drug concentrations (e.g., very low or very high) will be excluded from the analysis, if no apparent explanation exists. Concentration observations will also be removed from the data set if corresponding dosing or sampling times are missing or cannot be reconstructed.

Concentration values below the limit of quantification will be removed from analysis. All deletions of data points will be appropriately documented.

[redacted]

16.6. Safety

16.6.1. Analysis Population

The safety population is defined as all subjects who receive at least 1 dose of study treatment.

16.6.2. Methods of Analysis

16.6.2.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities. All analyses of AEs will be based on the principle of treatment emergence. An AE is considered to be treatment emergent if it has an onset date on or after the date of first dosing, or if it was present prior to the first dose and subsequently worsened. The incidence of all AEs will be presented by system organ class and preferred term by treatment group. In addition, the incidence of all AEs will be presented by severity and by relationship to study treatment.

16.6.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry, and urinalysis evaluations. Analyses of clinically significant abnormalities, shifts from baseline to postbaseline relative to the normal range, as well as changes from baseline by visit will be presented by treatment group.

16.6.2.3. Vital Signs

The analysis of vital signs will focus on clinically relevant abnormalities, which will be defined in more detail in the SAP. The incidence of clinically relevant abnormalities in vital signs will be summarized by treatment group.

16.6.2.4. Electrocardiograms

The analysis of ECG data will focus on clinically relevant abnormalities, which will be defined in more detail in the SAP. ECG changes from baseline may be summarized using descriptive statistics and presented by dose group, overall active treatment group, and visit.

16.6.2.5. Physical Examinations

Abnormal findings during physical examinations will be recorded as AEs and will be reflected in the summary of AEs.

16.7. Immunogenicity Data

16.7.1. Analysis Population

The analysis population for immunogenicity is defined as all subjects who were randomized and received at least 1 dose of study treatment and who have at least 1 postdose immunogenicity sample evaluated for anti-BG00011 antibodies.

16.7.2. Methods of Analysis

The incidence of anti-BG00011 antibodies will be summarized by treatment group over time.

16.8. Interim Analyses

An interim analysis will be performed for internal decision making (i.e., Phase 3 planning) when approximately 50% of study subjects have completed the Week 52 Visit. Data from subjects who have completed the Week 26 Visit or later visits, or have completed the End of Treatment Visit, will be included in this analysis. The actual timing of the interim analysis might be adjusted depending on the enrollment of each randomization stratum to ensure there is adequate information to enable decision making. This analysis will be carried out by an unblinded internal team (the blinding of the study will be maintained to the subjects, study sites, and study operation team). No Type I error adjustments will be made. Details of the interim analysis will be described in the SAP.

16.9. Sample Size Considerations

The sample size calculation is based on the annual declining rate in FVC (mL/year). With 145 subjects randomized per arm, and assuming a 15% dropout rate over a 1-year treatment period, the study has approximately 80% power to show that the BG00011 treatment arms differentiate from the arm without BG00011 at a 2-sided 15% α level, given a treatment effect of 82.5 mL/year with a common standard deviation of 280 mL. The calculation is based on the assumption that the FVC decline rate in subjects receiving placebo and no background therapy is 220 mL/year, and in subjects receiving background but no BG00011 therapy it is assumed to be 110 mL/year. A 60% reduction in the FVC decline rate in the subjects receiving placebo would be a treatment effect of 132 mL/year. A 30% reduction in the FVC decline rate in subjects receiving background therapy would be a treatment effect of 33 mL/year. With the assumption that 50% of each type of subject are randomized in the study, the combined treatment effect is approximately 82.5 mL/year. The 15% dropout rate for this study was estimated based on prior experience for the placebo arms in the Phase 3 studies for nintedanib and pirfenidone [King 2014; Richeldi 2014].

17. ETHICAL REQUIREMENTS

Biogen, any designee, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The investigator is responsible for endorsing all data on completed CRFs electronically, prior to any Interim lock or Database lock.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the investigational site must submit a close-out letter to the ethics committee and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected during the study (unless the collection is not permitted by applicable law or not approved by the governing ethics committee) and the data will be used during analysis of study results. (See Section 17.4.)

A copy of the signed and dated ICFs must be given to the subject or the subject's legally authorized representative. The original signed and dated ICFs will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, subjects' race will be collected (unless the collection is not permitted by applicable law or not approved by the governing ethics committee). These data will be used in the analysis of the safety and/or pharmacokinetic profile of the study treatment. Subjects' race is required for the calculation of the percent predicted equations used in pulmonary function testing.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate.

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes.

During these visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to Biogen or designee in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the investigational site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, monitoring, and management of SAE reports, and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic or Remote Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool configured by the CRO and hosted by the electronic data capture vendor.

Electronic Clinical Outcome Assessment (eCOA) data will be entered by the subject, the subject's caregiver, and/or study site staff on a device developed and supported by the eCOA vendor. Site staff will monitor data via a secure Web portal developed and supported by the eCOA vendor.

19.1.4. Central Laboratories for Laboratory Assessments

A central laboratory has been selected by Biogen to store samples collected from subjects in this study for [redacted], [redacted] drug concentrations, and anti-BG00011 antibodies in whole blood, plasma, and serum. These samples may be analyzed by a central laboratory or a third-party laboratory, as applicable. A central laboratory will also perform the safety laboratory tests noted in the Schedule of Events (Table 2): blood chemistry, hematology, urinalysis, serum pregnancy, HBsAg, HBcAb, HCVAb, HIV panels.

A local laboratory may be used by the study site to analyze repeat tests if needed.

19.1.5. Central Facility for Other Assessments

A central vendor has been selected by Biogen to read and interpret all HRCT scans for this study.

A central vendor has been selected by Biogen to read and interpret lung function assessment data.

A central vendor has been selected by Biogen to read and interpret ECG data.

19.2. Study Committees

19.2.1. Advisory Committee

Advisory committees will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committees will be blinded to subject treatment assignments.

19.2.2. Data Safety Monitoring Board

An independent DSMB will be established to assess the overall safety profile throughout the conduct of the study. A DSMB charter will be developed to guide the overall governance plan for the DSMB in alignment with the Safety Monitoring Plan. The DSMB will review the unblinded safety (including but not limited to AEs, clinical laboratory data, ECGs, pulmonary function testing, and imaging data) and available PK data on an ongoing basis until the last subject completes dosing. The meeting intervals and the procedures used to provide and assess the data will be described in detail in the DSMB charter. Upon review of the data, the DSMB may recommend that the Sponsor discontinue the study, modify the study conduct, or continue the study with no changes.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study, and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the site.

19.6. Study Report Signatory

Biogen will designate one of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by Biogen.

Biogen will follow all applicable local regulations pertaining to study report signatories.

20. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of BG00011 in Patients With Idiopathic Pulmonary Fibrosis," and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

_____

Investigator's Signature Date

_____

Investigator's Name (Print)

_____

Study Site (Print)

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