PROTOCOL

Title:	**Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Dose-Escalation Study of STX-100 in Patients with Idiopathic Pulmonary Fibrosis (IPF)**
Protocol Number:	**203PF201 (Formerly STX-003)**
Product:	**BG00011 (Formerly STX-100)**
Phase of Development:	**2a**
Sponsor:	**Biogen MA Inc.** **250 Binney Street** **Cambridge, MA 02142** **United States**
Date of Protocol:	**16 July 2015**
Version:	**4**
	Final

Supersedes previous version 3 dated 01 June 2015.

Sponsor Signature

Protocol 203PF201 was approved by:

[redacted]

7/16/2015

[redacted], MD

Date

[redacted]

Biogen MA Inc.

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1. SPONSOR INFORMATION

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For urgent medical issues in which the study's Medical Director should be contacted, please refer to the Study reference manual for complete contact information.

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

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
αvβ6	alpha v beta 6
AE	adverse event
ALAT	Latin American Thoracic Association
ALT	alanine transaminase
AST	aspartate transaminase
ATS	American Thoracic Society
AUC	area under the concentration-time curve
BAL	bronchoalveolar lavage
BG00011	humanized anti-αvβ6 monoclonal antibody
CBC	complete blood count
C_{max}	maximum observed concentration
Col1A1	collagen type 1 alpha 1
CRF	case report form
DEFA1-3	alpha defensins
DL_{CO}	carbon monoxide diffusion capacity
DSMB	data safety monitoring board
ECG	electrocardiogram
ERS	European Respiratory Society
FDA	Food and Drug Administration
FEV_1	forced expiratory volume over 1 second
FU	follow-up
FVC	forced (expiratory) vital capacity
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBsAg	hepatitis B surface antigen
HCV	hepatitis C antibody
HIV	human immunodeficiency virus
HRCT	high resolution computed tomography
ICF	informed consent form
ICH	International Conference on Harmonisation

Abbreviation	Definition
IFN-γ	interferon-gamma
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
JRS	Japanese Respiratory Society
LAP	latency-associated protein
LLOQ	lower limit of quantification
MD	Multiple-dose
MedDRA	Medical Dictionary for Regulatory Activities
MMP	matrix metalloproteinase
mRNA	messenger RNA
NOAEL	no observable adverse effect level
NOEL	no observable effect level
OPN	osteopontin
PAI-1	plasminogen activator inhibitor-1
PFT	pulmonary function test
PHI	protected health information
PK	pharmacokinetic(s)
SAE	serious adverse event
SC	subcutaneous(ly)
SP-A	surfactant A
SP-D	surfactant D
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TE	Treatment-emergent
TGF-β	transforming growth factor-beta
TIMP-1	tissue inhibitor of metalloproteinase 1
TLC	total lung capacity
UIP	usual interstitial pneumonia
WBC	white blood cell

3. SYNOPSIS

Title of study:
Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Dose-Escalation Study of STX-100 in Patients with Idiopathic Pulmonary Fibrosis (IPF)

Protocol number: 203PF201(Formerly STX-003)

Sponsor:
Biogen MA Inc.
250 Binney Street
Cambridge, MA 02142
United States

Contract research organization:
[redacted]

Investigators and study centers:
Approximately 15 centers in North America will participate.

Phase: 2a

Primary objective:

- To evaluate the safety and tolerability of subcutaneously (SC) administered multiple, escalating doses of BG00011 (humanized monoclonal antibody directed against the αvβ6 integrin, formerly known as STX-100) in subjects with IPF

Secondary objectives:

- To estimate the pharmacokinetic (PK) parameters after the first dose and after the last dose of multiple, escalating doses of BG00011 in subjects with IPF
- To assess the immunogenicity of BG00011 in subjects with IPF
- To assess the effect of BG00011 on biomarkers isolated from bronchoalveolar lavage (BAL) and peripheral blood in subjects with IPF

Study design:
This is a multi-center, randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study designed to evaluate the safety, tolerability, PK, immunogenicity, and impact on BAL and peripheral blood biomarkers of BG00011 in subjects with IPF. Approximately 40 subjects will be enrolled into 5 sequential ascending dose cohorts. All cohorts will include 8

subjects randomized to receive either BG00011 (6 subjects) or placebo (2 subjects). The Data Safety Monitoring Board (DSMB) may require that additional subjects be included in a cohort if needed to better understand safety prior to dose escalation.

The doses to be administered are shown below:

Cohort	Dose-level	Number of Subjects	
		BG00011	Placebo
1	0.015 mg/kg	6	2
2	0.1 mg/kg	6	2
3	0.3 mg/kg	6	2
4	1.0 mg/kg	6	2
5	3.0 mg/kg	6	2
Total Number of Subjects		**30**	**10**

Subjects with clinical symptoms and features consistent with IPF prior to screening; forced vital capacity (FVC) ≥ 50% of predicted value; diffusing capacity of the lung for carbon monoxide (DLco), corrected for hemoglobin, ≥ 30% of predicted value; oxygen (O_2) saturation > 90% at rest while breathing ambient air or receiving ≤ 2 L/minute of supplemental oxygen; residual volume ≤ 120% of predicted value; a ratio of the forced expiratory volume in 1 second (FEV_1) to FVC ≥ 0.65 after the use of a bronchodilator on screening pulmonary function tests (PFTs); high resolution computed tomography (HRCT) consistent with usual interstitial pneumonia (UIP) pattern, and who meet the other inclusion/exclusion criteria are eligible to enroll in the study. Subjects with IPF who do not otherwise qualify for study eligibility may be rescreened at the discretion of the Principal Investigator.

Concomitant medications:

Subjects should not be receiving high dose corticosteroid (i.e., > 15 mg/day of prednisone or its equivalent), cytotoxic therapy (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), nintedanib (Ofev®), vasodilator therapy for pulmonary hypertension (e.g., bosentan), unapproved (e.g., interferon gamma, penicillamine, cyclosporine, mycophenolate, N-acetylcysteine), and/or investigational therapy for IPF while participating in this study, nor can they have received such within 5 half-lives of the agent prior to initial screening.

Use of pirfenidone (Esbriet®) is permitted, provided that the subject has been on a stable dose for at least 4 weeks prior to randomization.

Pirfenidone should be kept at a stable dose, if possible. Dose decreases in response to adverse events are permitted and should be done in a manner consistent with the prescribing information for pirfenidone. Dose increases of pirfenidone, including an increase back to baseline dose after a dose decrease, are prohibited.

Following enrollment into the study, every attempt should be made to avoid changes in the subject's drug regimen. Exceptions would include episodes of infections requiring treatment (e.g., antibiotics or antiviral drugs), exacerbations of their underlying disease requiring immediate intervention, or any other situation requiring modification of the subject's therapy for their safety at the discretion of the treating physician.

Study periods:

Screening:

Qualifying assessments including medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), and clinical laboratory tests including pregnancy testing (if applicable) and testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C (HCV) antibody will be performed within 5 weeks or 35 days (8 weeks or 56 days, for cohorts 4 and 5 only) prior to dosing. Pulmonary function tests (PFTs), HRCT and BAL are also included as part of the screening process and must be performed within 5 weeks (35 days) prior to dosing in all cohorts. **It is recommended that the BAL and PFTs be performed after the subject has met the other inclusion criteria, including the screening HRCT.** Following confirmation of eligibility on a screening PFT, subjects will perform 1 additional PFT, which can be performed at any time up to and including Day 1 of the MD period (Day 1-MD) provided it is at least 1 day after the screening PFT, to establish their baseline lung function. Screening assessments (e.g., clinical laboratory tests or PFTs) may be repeated if there are questionable results or if abnormalities are felt to be due to inherent variability of the test procedure. If the 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.

Upon fulfilling all of the inclusion and none of the exclusion criteria, subjects will be randomized to receive either BG00011 or placebo. The subject will be instructed to return to the clinic on Day 1-MD for baseline, pre-dose evaluations and to ensure that they still qualify for the study by meeting all criteria with the exception of PFTs. If a subject's PFT values from the Screening visit meet the inclusion criteria, they should not be excluded from the study based upon their baseline PFT values.

MD Period

On Day 1-MD, the subject's medical history, physical examination, inclusion/exclusion criteria, vital signs, oxygen saturation, and pregnancy status (if applicable) will be assessed, as well as blood samples collected for baseline laboratory, biomarker, PK, and antibody assessments. The first dose of study treatment will then be administered and the subject will remain in the clinic for at least 8 hours for monitoring, with a PK sample obtained 8 hours following dosing. The subject will be discharged with instructions to return to the clinic for follow-up visits on Days 2-MD, 3-MD, and 5-MD for safety evaluations and PK sampling.

Study treatment will be administered once weekly for 8 doses on Days 1-MD, 8-MD, 15-MD, 22-MD, 29-MD, 36-MD, 43-MD, and 50-MD. Prior to dosing on Days 8-MD, 15-MD, 29-MD, and 43-MD, a physical examination, vital signs, oxygen saturation, laboratory assessments, and PK blood draws will be performed, and then the study treatment will be administered. On Days 22-MD, 36-MD, and 50-MD, pre-dose vital signs and oxygen saturation will be performed and a trough PK level will be drawn prior to administration of study medication. An ECG will be performed at the Day 15-MD visit, and PFTs will be performed at the Day 29-MD visit. Serum for biomarkers will be obtained on Days 29-MD and 50-MD. All subjects will be observed at the study center for a minimum of 30 minutes following dosing at each study visit, after which vital signs will be checked, instructions will be provided, and the subject will be discharged. After the final (8^{th}) dose of study treatment, Day 50-MD PK samples will be collected at 8 hours following dose administration, and the subject will be discharged with instructions for procedures during the FU period.

FU Period

After completing the MD period of the study, each subject will be monitored for an additional 12

weeks (8 weeks for subjects in cohorts 4 or 5). Study days during the FU period will be dependent on when the last dose of study medication is administered, which will be Day 50 if all doses are received on schedule. The day of the last dose of study treatment is designated as Day 1 of the FU period (Day 1-FU). Visits during the FU period will occur on Days 2-FU, 3-FU, 5-FU, 8-FU, 15-FU, 22-FU, 29-FU, 57-FU (8 weeks), and, for those in cohorts 1 to 3 only, 85-FU. Vital signs, PK levels, and monitoring of health status will be assessed at each visit. An ECG will be performed on Days 8-FU and 85-FU (Day 57-FU for cohorts 4 and 5). The Day 8-FU visit assessments will include BAL, PFTs and HRCT; the BAL should be performed between Day 3-FU and Day 8-FU, and PFTs and HRCT scan should be performed within 21 days following administration of the last dose of study medication. If performed on the same day, HRCT and PFTs must be performed prior to BAL. If a BAL is performed first, at least 2 days must have elapsed before PFTs or HRCT are performed. Serum for assessment of antibody development to BG00011 will be collected on Days 29-FU (all cohorts) and 57-FU (cohorts 4 and 5 only) or 85-FU (cohorts 1 to 3). Serum for biomarkers will be obtained and additional safety assessments will be performed on Days 8-FU, 29-FU, 57-FU, and 85-FU (12 weeks after the final dose for cohorts 1 to 3 only), which is the final study visit. At Day 57-FU the Investigator will also record their assessment of the subject's respiratory status relative to baseline: better, worse or the same (for cohorts 4 and 5 only). Following this visit, the subject will be discharged from study participation.

Subjects who discontinue prior to Day 8-FU should undergo all assessments described for the Day 8-FU visit, if possible, including BAL, PFTs, and HRCT that are to be performed within a specified period after the subject receives their last dose of study medication. Also, samples should be collected for serum pregnancy testing (if applicable) and anti-BG00011 antibody testing. Subjects who discontinue subsequent to having Day 8-FU assessments performed should have Day 85-FU (Day 57-FU for cohorts 4 and 5) assessments performed at the time of termination.

Dose escalation:

This study comprises 5 sequential escalating dose cohorts. The independent DSMB will review unblinded safety and PK data from each dose cohort. The DSMB members' responsibilities and the process for data review are described in the DSMB charter.

Dose escalation will be based on the DSMB's review of PK and safety data through Day 15 for the initial 4 subjects in each cohort administered BG00011 or placebo (3:1, respectively) in each cohort. Safety assessments will include a review of adverse events (AEs), vital signs, physical examination, clinical laboratory tests, ECG, and pulse oximetry from these visits. Therefore, it is anticipated that the DSMB will convene approximately 7-8 weeks after the first 4 subjects in the previous cohort are dosed, in order to allow for compilation and evaluation of the data. A DSMB meeting will not occur for the final cohort except on an ad hoc basis, as no dose escalation decision needs to be made.

After reviewing the safety and PK data, the DSMB may recommend initiation of the next dose escalation cohort. Alternatively, the DSMB may recommend monitoring subjects within a cohort for a longer period of time or reviewing safety and PK data from additional subjects prior to recommending dose escalation. If indicated, another cohort may be enrolled at a dose level similar to or lower than prior cohorts (see the section below titled "Criteria for stopping or temporarily suspending the study").

Updated safety (including BAL, PFTs, and HRCT results) and PK information on all participants will be provided in each subsequent DSMB data package. Additionally, information on serious adverse events (SAEs) will be provided to the DSMB on an ongoing basis throughout the study.

Criteria for stopping or temporarily suspending the study:

- If 2 subjects receiving study medication in a cohort experience an SAE that is considered possibly or probably related to study treatment by the Investigator, the DSMB will determine whether the nature, severity, or the number of AEs would permit 1 of the following:
  - Continuation of enrollment and dosing of the current cohort
  - Initiation of the next dose escalation cohort
  - Enrollment of an additional 4 subjects in that cohort
  - Enrollment of an intermediate dose cohort
  - Discontinuation of dose escalation
- If 2 subjects receiving study medication in a cohort experience a clinically significant, sustained decrease from baseline respiratory status as determined by both the Investigator and the DSMB.
- If 2 subjects receiving study medication demonstrate a significant increase in matrix metalloproteinase (MMP)-12 levels between baseline and post-treatment BAL assessments as determined by the DSMB.
- Exposure as measured by area under the concentration-time curve (AUC) is greater than the comparable systemic exposure at the no observable effect level observed in nonhuman primate studies.
- The DSMB feels there is a need to temporarily suspend subject enrollment until further assessments are made.

Inclusion criteria:

1. Male or female subjects, 45 to 84 years old, inclusive.
   - Subjects 18 to 44 years of age are eligible if they have a histopathological diagnosis of UIP based upon a surgical lung biopsy in the appropriate clinical setting, and meet all other inclusion/exclusion criteria.
2. Clinical features consistent with IPF prior to screening (based on the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association consensus criteria for the diagnosis of IPF.
3. FVC $\geq$ 50% of predicted value.
4. DLco (corrected for hemoglobin) $\geq$ 30% predicted value.
5. Oxygen saturation > 90% at rest by pulse oximetry while breathing ambient air or receiving $\leq$ 2 L/minute of supplemental oxygen
6. Residual volume $\leq$ 120% predicted value.
7. Ratio of FEV_1 to FVC $\geq$ 0.65 after the use of a bronchodilator.
8. Other known causes of interstitial lung disease have been excluded (e.g., drug toxicities, environmental exposures, connective tissue diseases).
9. HRCT image fulfills the criteria for 'UIP pattern' (surgical lung biopsy not required. The radiographic diagnosis of UIP must be confirmed on the screening HRCT by an independent central radiologist experienced in the evaluation of interstitial lung diseases.
10. If the HRCT image does not fulfill the criteria for 'UIP pattern' a surgical lung biopsy is

necessary for the diagnosis of IPF (lung biopsy performed prior to screening is acceptable). In this setting the HRCT image must meet the criteria for 'possible UIP pattern' **and** the lung biopsy must fulfill the histopathological criteria for either 'UIP pattern' or 'probable UIP pattern'. If the HRCT image fulfills the criteria for UIP pattern, results from a surgical lung biopsy are not necessary. If however, a lung biopsy has been performed, it must fulfill the histopathological criteria for either 'UIP pattern' or 'probable UIP pattern' with the appropriate HRCT correlate.

11. Adequate bone marrow and liver function as demonstrated by:
    - Hemoglobin ≥ 10 g/dL
    - White blood cell (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
    - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times upper limit of normal
12. Subject has a life expectancy of at least 12 months.
13. Subject must provide written informed consent. If required by local law, candidates must also authorize the release and use of protected health information (PHI).
14. Female subjects must be surgically sterile, postmenopausal (minimum 1 year without menses), or agree to use 1 or more of the following forms of contraception from the time of signing the ICF through 12 weeks following the last injection of study medication: hormonal (i.e., oral, transdermal, implant, or injection); double barrier (i.e., condom, diaphragm with spermicide); intrauterine device; vasectomized partner (6 months minimum); 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 through 12 weeks following the last injection of study medication.

Exclusion criteria:

1. Unable to perform PFTs.
2. Findings that are diagnostic of a condition other than UIP on surgical lung biopsy (performed either before or after screening), HRCT imaging, transbronchial lung biopsy, or BAL.
3. Currently receiving high dose corticosteroid, cytotoxic therapy (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), nintedanib (Ofev®), vasodilator therapy for pulmonary hypertension (e.g., bosentan), unapproved (e.g., INF-γ, penicillamine, cyclosporine, mycophenolate, N-acetylcysteine), 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 ≤ 15 mg/day of prednisone or its equivalent is acceptable if it is anticipated that the dose will remain stable during enrollment.
   Pirfenidone (Esbriet®) is permitted, provided that the subject has been on a stable dose for at least 4 weeks prior to randomization and it is anticipated that the dose will remain stable during enrollment.
4. History of malignancy, including carcinoma during the preceding 5 years. However, subjects with a history of excised or treated basal cell, squamous cell, or cervical carcinomas are eligible to participate in this study.

5. 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; or uncontrolled atrial or ventricular cardiac arrhythmias).
6. Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) within 3 months prior to screening.
7. Significant reaction to previous injection of a monoclonal antibody.
8. Female who is pregnant or breastfeeding.
9. 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.
10. Fever (body temperature > 38°C) or symptomatic viral or bacterial infection within 1 week prior to screening.
11. Positive test for HBsAg, HCV antibody (if confirmed by HCV RNA), or HIV antibody at screening.
12. Drug or alcohol abuse (as defined by the Investigator).
13. Treatment with another investigational drug, investigational device, or approved therapy for investigational use within 5 half-lives of the agent prior to screening in this study
14. End-stage fibrotic disease requiring organ transplantation within 6 months.
15. Any other condition that, in the opinion of the Investigator, may compromise the safety or compliance of the subject or would preclude the subject from successful completion of the study.

Test product, dose, and mode of administration:

BG00011 is a humanized monoclonal antibody (human immunoglobulin G1 subgroup III, kappa) and consists of 2 heavy and 2 light chains connected by inter-chain disulfide bonds. The molecular weight of the intact BG00011 molecule is 148,000 daltons, including its carbohydrate moiety.

BG00011 is provided as a lyophilized drug product in vials, must be kept refrigerated (2°C to 8°C), be protected from light and may not be frozen.

BG00011 will be administered as an SC injection (e.g., in the upper arm) after reconstitution. Each BG00011 lyophilized drug product vial is reconstituted using 1.3 mL of preservative-free sterile water for injection/USP to yield a final concentration of 75.0 mg/mL.

Additional dilution is required for lower doses and instructions for dilution will be provided to the pharmacy. The reconstituted drug product does not contain a preservative and should be used within 4 hours.

Dose cohorts are 0.015, 0.1, 0.3 1.0 mg/kg, and 3.0 mg/kg. Placebo subjects will be injected with normal saline (0.9% Sodium Chloride for Injection) at a volume equivalent to that administered if they were assigned to BG00011. An injection volume greater than 1.5 mL should be split between 2 injection sites.

Study medication for each subject will be double-blinded. An unblinded pharmacist not associated with the operational conduct of the study will prepare appropriate medication for injection according to the provided randomization code and instructions for preparation. This individual will keep the randomization code locked in a secure place and will not disclose the code to anyone else (except for a quality assurance person in the pharmacy) or discuss subject information with study staff. In the event of a medical emergency, when knowledge of the subject's treatment

assignment may influence the subject's clinical care, the Investigator or designee may open the code-break envelope for the subject experiencing the emergency.

Duration of study

In cohorts 1 to 3, each subject's participation in the study will be for approximately 24 weeks (~5.5 months), i.e., up to 5 weeks to perform screening/entry evaluations, followed by 7 weeks of double-blind study dosing (8 doses) and a Follow-up period of 12 weeks. For subjects in cohorts 4 or 5, the subject's participation in the study will be approximately 23 weeks (~5.5 months), i.e., up to 8 weeks to perform screening/entry evaluations, followed by 7 weeks of double-blind study dosing (8 doses) and Follow-up period of 8 weeks.

Reference therapy, dose, and mode of administration

Sterile normal saline (0.9% Sodium Chloride for Injection) administered as an SC injection.

Criteria for evaluation:

Safety

- AEs, including injection site assessment
- SAEs
- Physical examinations
- Vital signs
- 12-lead ECGs
- Hematology: complete blood count (CBC) with differential and platelet counts. CBC includes red blood cells, WBCs, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration
- Serum chemistry: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen, calcium, chloride, carbon dioxide, creatinine, direct bilirubin, gamma-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, total cholesterol, total protein, uric acid
- Urinalysis: including determination of the presence of protein, glucose, ketones, occult blood, and WBCs by dipstick, with microscopic examination if indicated
- Pulse oximetry
- PFTs: 2 PFTs will be performed during the screening period (within 5 weeks prior to dosing). The first of these tests (Screening) will be performed both before and after bronchodilator administration to determine if the subject qualifies for the study, whereas the second, will be performed without bronchodilator administration and will establish the subject's baseline values; these 2 PFT sets must be performed on separate days during the screening period up to and including Day 1-MD. PFTs will also be performed at the Day 29 visit during the MD period and within 21 days after receiving the last dose of study medication.
- PFT parameters include:

  FVC

  FEV_1

  TLC (total lung capacity)

DL_{CO}

Residual volume

PFTs may be performed prior to but not within 2 days after BAL.

- BAL: BAL will be performed during the screening period (within 5 weeks prior to dosing) and between Day 3-FU and Day 8-FU after receiving the last dose of study medication. Analysis of the BAL macrophage MMP-12 mRNA levels (which are increased when macrophages are activated) will be performed at a central laboratory.
- HRCT scans will be performed during screening to establish the pre-dosing pattern and extent of disease. HRCT will be repeated within 21 days after receiving the last dose of study medication during the MD period. An independent central radiologist experienced in the evaluation of diffuse lung diseases and blinded to treatment assignment will read all scans during the MD and FU periods.

Formation of antibodies to BG00011:

Blood samples for immunogenicity testing will be collected during screening, on Day 1-MD prior to dosing, and at Day 29-FU and Day 85-FU (Day 57-FU for subjects in cohorts 4 or 5) after the last dose of study medication

Pharmacokinetics:

Blood samples for standard PK measures will be collected prior to the initial dose of study treatment (screening and pre-dose on Day 1) and 8 hours after dosing. Samples for PK measures will be collected at the same times, relative to dosing, at the final administration of study treatment on Day 50-MD (i.e., prior to dosing and 8 hours after dosing). Additional PK samples will be collected on Days 2-MD and 2-FU (24 hours following dosing), Days 3-MD and 3-FU (72 hours after dosing), Days 5-MD and 5-FU, and Days 8-MD and 8-FU at approximately the same time of day. Trough serum levels (samples obtained prior to dosing) will be obtained weekly during the dosing period. PK samples will also be obtained during all subsequent follow-up visits for subjects, i.e., Days 15-FU, 22-FU, 29-FU, 57-FU and 85 FU (cohorts 1 to 3, only).

PK parameters include:

- C_{max} (maximum observed concentration)
- Time to reach C_{max}
- Area under the concentration-time curve from time zero (just prior to dose) to the last measurable concentration
- Area under the concentration-time curve from time zero to infinity
- Area under the concentration-time curve from time zero (time of dosing) to tau (within a dosing interval)
- Terminal elimination rate constant
- $t_{½}$ (elimination half-life)
- Clearance (unadjusted for bioavailability)
- Volume of distribution (unadjusted for bioavailability)

Efficacy

There are no efficacy objectives in this study.

Pharmacodynamics

Blood samples for blood biomarkers will be collected at screening and on Days 1-MD, 29-MD, 50-MD, 8-FU, 29-FU, 57-FU, and for subjects in cohorts 1 to 3 only, 85-FU.

Peripheral blood biomarkers may include, but are not limited to the following:

- MMP-7
- Osteopontin
- Tissue inhibitor of metalloproteinase 1
- Collagen type 1 alpha1
- Surfactant A
- Alpha defensins (DEFA1-3)

BAL will be performed during screening and between Day 3-FU and Day 8-FU, and analyses of BAL fluid and cell pellet will be performed at a central laboratory. Biomarkers, which may include mRNA levels for plasminogen activator inhibitor-1 and osteopontin, as well as protein levels for phosphorylated SMAD, will be measured in macrophages isolated from BAL. Additional biomarkers may be added prior to the initiation of analysis and will be included in the statistical analysis plan.

Statistical methods:

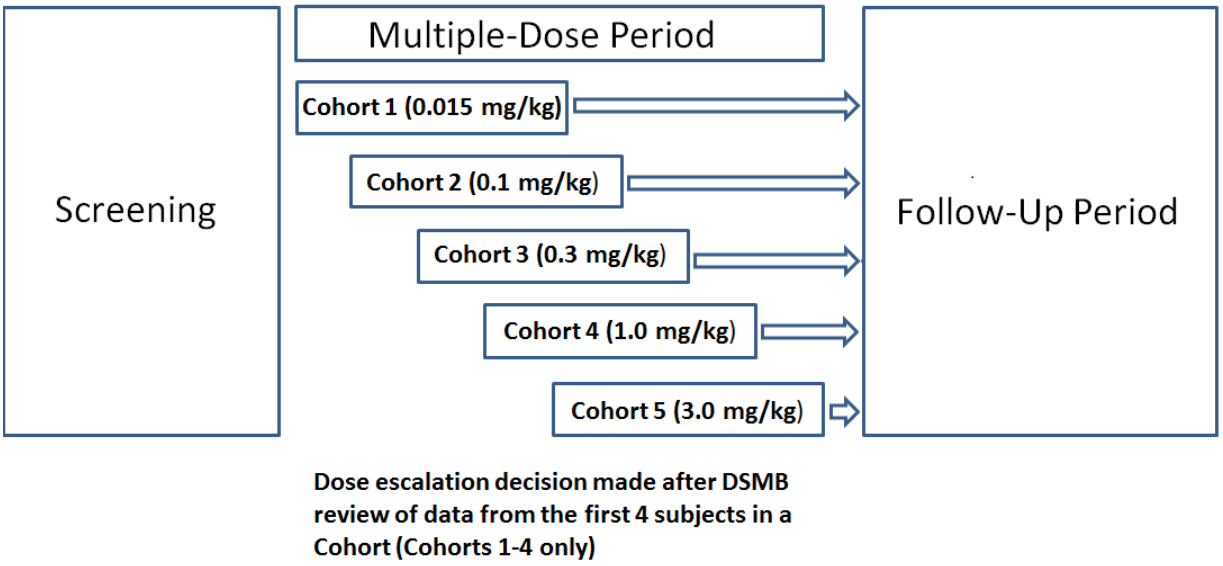
Data for BG00011 treated subjects will be grouped by dose cohort. Data for all placebo subjects, regardless of dosing cohort, will be treated as 1 group. Exposure to study treatment and reasons for discontinuation of study treatment will be tabulated, and demographics will be presented using descriptive statistics (i.e., mean, standard deviation, median, and range). Safety variables will be tabulated and presented for all subjects who receive BG00011 or placebo. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1 or higher. The incidence of treatment-emergent AEs (TEAEs) will be presented by system organ class and preferred term. TEAEs will also be presented by severity and relationship to study treatment. For each treatment group, descriptive statistics will be used to summarize and present subject demographics, vital signs, and clinical laboratory parameters within each protocol-specified visit.

Shift tables will be presented for selected laboratory parameters. Physical examination results, oxygen saturation, PFT results and ECG parameters will be presented in listings. The incidence of antibodies to BG00011 will be tabulated by treatment group and dose cohort for each subject. Listing of individual subject serum BG00011 concentrations, actual blood sampling times, and PK parameters as well as graphs of concentration versus time will be prepared by dose cohort. Serum concentrations and PK parameters will be summarized through descriptive statistics and compared among dosing cohorts (and to placebo) using mixed effects models. Dose proportionality will be assessed following log-transformation and dose normalized AUC and C_{max} will be analyzed using mixed modeling. Exploratory exposure-response relationship will be evaluated post-hoc and as applicable for both safety and pharmacodynamics to assist with determining the appropriate dosing regimen for BG00011 in this clinical setting.

BAL and peripheral blood biomarkers will be tabulated and presented for all BG00011 subjects within a dose cohort (or placebo). Changes from baseline in BAL and blood biomarkers will be compared among treatment groups and to the placebo group.

Interim Analysis: An administrative interim analysis may be performed on all subject data up to and including the Day 8-FU visit for the last subject in cohort 4. The interim analysis will provide safety, PK, and PD information to aid in internal (Biogen MA Inc) decision-making only and will not affect the study design of the current protocol.

Figure 1 Subject Disposition During Study 203PF201



4. INTRODUCTION

4.1. Background

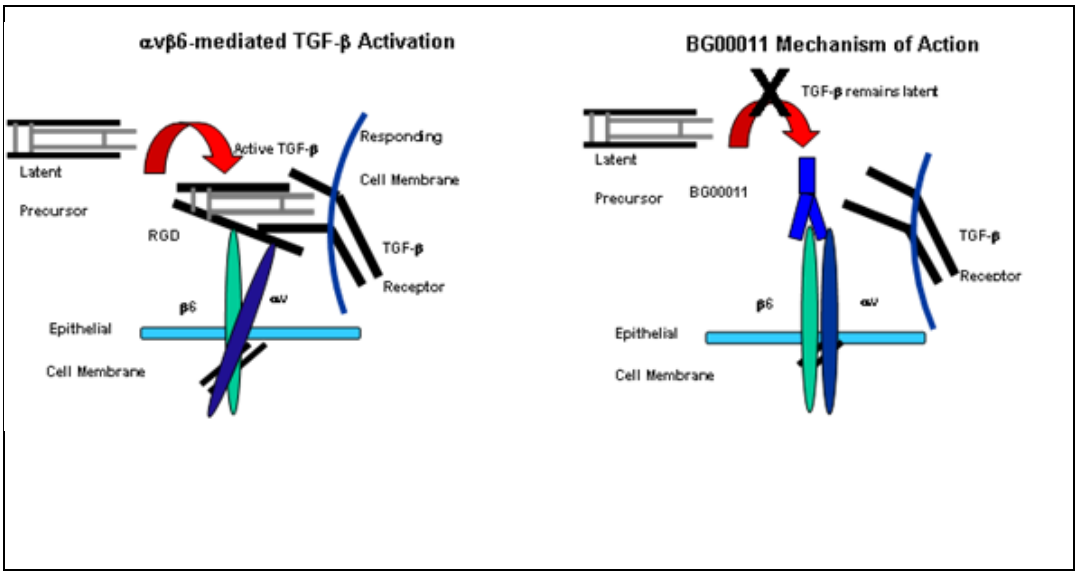
BG00011 (formerly known as STX-100) [anti-alpha v beta 6 [αvβ6] monoclonal antibody] previously in development by Stromedix, Inc, is currently being developed by Biogen MA Inc, as a novel therapeutic for patients with idiopathic pulmonary fibrosis (IPF). In fibrotic disease, active transforming growth factor-beta (TGF-β) is thought to be critical to the initiation and maintenance of fibrosis. BG00011 blocks the binding of αvβ6 to the latent form of TGF-β, thereby inhibiting its activation in response to tissue injury or inflammation. The clinical development plan for BG00011 is designed to demonstrate that inhibition of TGF-β activation by BG00011 in patients with idiopathic pulmonary fibrosis (IPF) can prevent or reduce alveolar epithelial injury and the progression of fibrosis, resulting in preservation of pulmonary function. The objective of this Phase 2a study is to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and impact on bronchoalveolar lavage (BAL) and peripheral blood biomarkers of multiple doses of BG00011 in subjects with IPF.

4.2. Rationale for Clinical Use of BG00011

There is a strong rationale for targeting the TGF-β pathway as a means of inhibiting fibrosis. The TGF-β cytokine is central to the initiation and maintenance of fibrosis, a pathological process characterized by the replacement of diseased tissue with excess extracellular matrix, leading to organ scarring and failure [Bartram and Speer 2004; Border and Noble 1994; Shihab 1995; Yamamoto 1993; Yamamoto 1996]. TGF-β is synthesized as a latent precursor protein that is cleaved and secreted with the N-terminal latency-associated protein (LAP) non-covalently associated with the mature active C-terminal TGF-β cytokine (Figure 2). This complex cannot bind to the TGF-β receptor and is not biologically active.

A critical regulator of TGF-β activation is the αvβ6 integrin, which binds to LAP, leading to localized activation of this cytokine [Munger 1999]. 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 [Breuss 1995; Breuss 1993; Häkkinen 2000; Trevillian 2004; Zambruno 1995]. By blocking the binding of αvβ6 to latent TGF-β, anti-αvβ6 antibodies (including BG00011) prevent TGF-β activation and inhibit the development of tissue fibrosis. By inhibiting local activation of TGF-β only in αvβ6-expressing tissues, BG00011 offers a potentially safer alternative to systemic inhibition of TGF-β in diseases where the αvβ6 integrin is upregulated.

Figure 2 αvβ6–Mediated TGF-β Activation and BG00011 Mechanism of Action



4.3. Population To Be Studied

Idiopathic pulmonary fibrosis is a chronic, progressive, and fibrosing disease of the lungs that typically strikes the middle aged and elderly (median age at diagnosis: 66 years) with male predominance (1.5 to 1.7:1) [Adamali and Maher 2012; King 2011]. The annual incidence of IPF is between 4.6 and 16.3 per 100,000 and has been rising over the past 30 years [Adamali and Maher 2012]. The most common symptoms that patients with IPF experience include shortness of breath, cough, and fatigue.

Idiopathic pulmonary fibrosis is diagnosed based on the appearance of usual interstitial pneumonia, either histologically after lung biopsy or via high resolution computerized tomography) [American Thoracic Society/European Respiratory Society 2002]. Usual interstitial pneumonia is characterized by spatially and temporally heterogeneous fibrosis with honeycombing within the lung. The disease pattern is often diffuse with loci of fibrosis, often at varying stages, interspersed with healthy tissue. The median survival for patients is between 2.5 and 3.5 years after diagnosis of IPF, with a 5-year survival rate of 20% [Adamali and Maher 2012].

Progression of disease is the rule in untreated patients, and there are currently 2 approved therapies, pirfenidone and nintedanib, that slow progression of, but do not arrest, the disease. Other agents including nonspecific anti-inflammatory or immunosuppressive therapy have been tried. Corticosteroids alone, as well as azathioprine or cyclophosphamide as single agents or in combination with corticosteroids have shown limited efficacy. Methotrexate, colchicine, penicillamine, and cyclosporine have been combined with prednisone with poor results. In 2 large Phase 3 studies, interferon gamma-1b (IFN-γ1b) treatment did not improve lung function or survival [Raghu 2004].

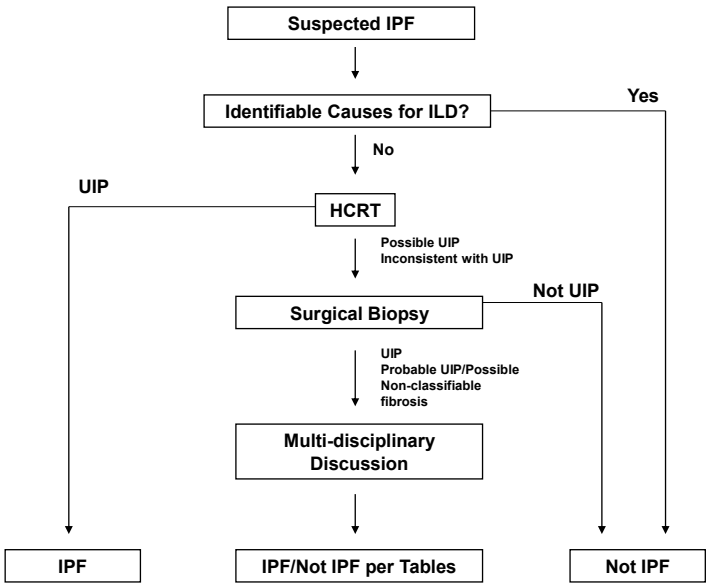
4.3.1. Diagnostic Criteria for IPF

The diagnostic criteria for IPF used in this protocol are based on the 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].

IPF is a chronic, progressive fibrosing interstitial pneumonia of unknown cause occurring in adults and limited to the lungs. Evidence of restrictive physiology and impaired gas exchange on pulmonary function studies is characteristic, although pulmonary function may be normal or only slightly impaired in the early stages of IPF. The diagnosis requires histopathological and/or radiologic evidence of usual interstitial pneumonia (UIP) and exclusion of other causes of idiopathic interstitial pneumonia and interstitial lung diseases (e.g., occupational or environmental exposures, drug toxicities, and collagen vascular diseases).

The ATS/ERS/JRS/ALAT joint task force concludes that in the appropriate clinical setting the diagnosis of IPF is ascertained if the high resolution computed tomography (HRCT) image fulfills the criteria for 'UIP pattern' (surgical lung biopsy is not required). However, if the HRCT image differs from the 'UIP pattern', a surgical lung biopsy is necessary and specific combinations of the HRCT **and** histopathological criteria are required for the diagnosis of IPF (lung biopsy performed prior to screening is acceptable) (Figure 3). The task force also recommends that multidisciplinary discussions between pulmonologists, radiologists, and pathologists experienced in the diagnosis of interstitial lung diseases be conducted to increase the accuracy of the diagnosis of IPF.

Figure 3 Diagnostic Algorithm for IPF (Adapted from the ATS/ERS/JRA/ALAT Guidelines)



It is imperative that all subjects enrolled in Study 203PF201 have a confident diagnosis of IPF. Therefore, only subjects who meet the following HRCT imaging and/or lung histology criteria for UIP (in addition to the other inclusion/exclusion criteria) are eligible for this study:

- The HRCT image fulfills the criteria for 'UIP pattern' (i.e., surgical lung biopsy is not required [see Figure 3 and Table 1]).
- If the HRCT image does not fulfill the criteria for 'UIP pattern' a surgical lung biopsy is necessary for the diagnosis of IPF (lung biopsy performed prior to screening is acceptable). In this setting the HRCT image must meet the criteria for 'possible UIP pattern' **and** the lung biopsy must fulfill the histopathological criteria for either 'UIP pattern' or 'probable UIP pattern' (see Table 1 and histopathological criteria summarized below).

Therefore only patients who meet the radiographic and/or histopathological criteria resulting in 'Yes' for the 'Diagnosis of IPF (see Table 1) are eligible to participate in this study; i.e., individuals with a 'probable' or 'possible' diagnosis of IPF do not qualify for this study. However, if the HRCT and/or surgical lung biopsy are repeated due to concern regarding the adequacy of the HRCT technique or sampling error on the lung biopsy, the patient may be rescreened for eligibility at the Principal Investigator's discretion.

Table 1 HRCT and Histopathological UIP Patterns and the Level of Confidence for the Diagnosis of IPF (Adapted from the ATS/ERS/JRA/ALAT Guidelines)

HRCT Pattern	Histopathology Pattern	Diagnosis of IPF?[1]
UIP	UIP Probable UIP Possible UIP Non-classifiable fibrosis[2]	**Yes**
	Not UIP	No
Possible UIP	UIP Probable UIP	**Yes**
	Possible UIP Non-classifiable fibrosis[2]	Probable[3]
	Not UIP	No
Inconsistent with UIP	UIP	Possible[3]
	Probable UIP Possible UIP Non-classifiable fibrosis[2] Not UIP	No

[1] The accuracy of the diagnosis increases with the use of a multidisciplinary team decision, particularly where radiologic and histopathological patterns are discordant.

[2] Non-classifiable fibrosis: a pattern of fibrosis that does not meet the criteria for UIP pattern or other idiopathic interstitial pneumonias.

[3] Multidisciplinary discussion among interstitial lung disease experts should include the potential for sampling error on lung biopsy and re-evaluation of the adequacy of the HRCT technique.

4.3.1.1. HRCT Imaging Criteria for UIP pattern

As described in the recently updated ATS/ERS/JRA/ALAT guidelines for the diagnosis and management of IPF, HRCT lung imaging can be categorized in descending order of confidence as: 1) UIP pattern, 2) possible UIP pattern, or 3) inconsistent with UIP pattern.

If the following four features are present, the HRCT image fulfills the criteria for 'UIP pattern':

- Subpleural, basal predominance
- Reticular abnormalities
- Honeycombing with or without traction bronchiectasis
- Absence of features listed as inconsistent with UIP pattern

If each of these features is present except for honeycombing, then the HRCT image fulfills the criteria for 'possible UIP pattern'.

Conversely, if any of the following 7 features are present, the HRCT would be classified as 'inconsistent with UIP pattern':

- Upper or mid lung predominance
- Peri-bronchovascular predominance
- Extensive ground glass abnormality (extent greater than reticular abnormality)
- Profuse micro nodules (bilateral, predominantly upper lobes)
- Discrete cysts (multiple, bilateral, away from areas of honeycombing)
- Diffuse mosaic attenuation/air trapping (bilateral, in 3 or more lobes)
- Consolidation in bronchopulmonary segments(s)/lobe(s)

4.3.1.2. Surgical Lung Biopsy Criteria for UIP pattern

If the HRCT image does not fulfill the criteria for the 'UIP pattern', then a surgical lung biopsy is necessary and assessment of both the HRCT image and lung histopathology is required for the diagnosis of IPF (lung biopsy performed prior to screening is acceptable). Histopathology on surgical lung biopsy can be categorized in descending order of confidence as: 1) UIP pattern, 2) probable UIP pattern, 3) possible UIP pattern, or 4) not UIP pattern.

The histopathological criteria for 'UIP pattern' include the following four features:

- Evidence of marked fibrosis/architectural distortion, +/- honeycombing in a predominantly subpleural/paraseptal distribution
- Presence of patchy involvement of lung parenchyma by fibrosis
- Presence of fibroblast foci
- Absence of features against a diagnosis of UIP, suggesting an alternate diagnosis

The histopathological criteria for 'probable UIP pattern' are summarized below:

- Evidence of marked fibrosis/architectural distortion, +/- honeycombing

- Absence of either patchy involvement or fibroblastic foci, but not both
- Absence of features against a diagnosis of UIP, suggesting an alternate diagnosis

OR

- Honeycomb changes only
  - This scenario usually represents end-stage fibrotic lung disease where honeycombed segments have been sampled but where a UIP histopathological pattern might be present in other areas. Such areas are usually represented by overt honeycombing on HRCT and can be avoided by pre-operative targeting of biopsy sites away from these areas using HRCT.

The histopathological criteria for 'not UIP pattern' include any of the six following features:

- Hyaline membranes
  - Can be associated with acute exacerbation of IPF.
- Organizing pneumonia
  - Can be associated with acute exacerbation of IPF.
  - An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.
- Granulomas
  - An isolated or occasional granuloma and/or a mild component of organizing pneumonia pattern may rarely be coexisting in lung biopsies with an otherwise UIP pattern.
- Marked interstitial inflammatory cell infiltrate away from honeycombing
- Predominant airway centered changes
- Other features suggestive of an alternate diagnosis

4.3.1.3. Treatment in IPF subjects on Approved Therapy

Cohorts 4 and 5 will allow for the inclusion of subjects who are on a stable dose of pirfenidone (Esbriet®). Pirfenidone is one of two approved therapies for patients with IPF and understanding the safety, PK and PD of BG00011 in subjects on background pirfenidone treatment is important.

4.3.2. TGF-β Activation and αvβ6 Expression in IPF

In human disease, the αvβ6 integrin is highly upregulated in alveolar epithelium from patients with IPF and other inflammatory and/or fibrotic lung diseases, such as scleroderma, radiation-induced fibrosis, and bronchiolitis obliterans with organizing pneumonia [Breuss 1995; Sheppard 2003]. TGF-β is also abundant on the alveolar epithelium in focal areas of fibrosis [Broekelmann 1991; Khalil 1996], and the pattern of αvβ6 expression mirrors that of TGF-β in lung tissue from patients with IPF. Moreover, progression of pulmonary fibrosis has been observed in patients with higher levels of TGF-β [Bartram and Speer 2004]. TGF-β plays a central role in the initiation and maintenance of fibrosis and both β6 null mice [Hahm 2007; Ma

2003; Munger 1999; Pittet 2001; Puthawala 2008], and mice treated with αvβ6-blocking antibodies[Hahm 2007; Horan 2008; Puthawala 2008] are protected from fibrosis in lung and kidney models of disease. Therefore, selective inhibition of the αvβ6/TGF-β pathway by BG00011, a novel anti-fibrotic agent directed against the αvβ6 integrin, may be an effective treatment for IPF and other fibrotic diseases.

4.3.3. Evaluating the Impact of BG00011 on Biomarkers in IPF

Identification of biomarkers associated with IPF has been challenging, in part due to limited access to lung tissue, heterogeneity of disease involvement, and safety concerns related to performing repeated lung biopsies in this patient population.

Increased blood levels of surfactant proteins-A and -D (SP-A and SP-D), KL-6, soluble Fas ligand (sFasL), and α-defensins (DEFA1-3), have been reported in patients with IPF and other interstitial lung diseases [Greene 2002; Kuwano 2002; Mukae 2002; Yokoyama 1998]. Elevated serum levels of SP-A and SP-D were predictive of mortality risk, and KL-6 (MUC1 mucin, a sensitive indicator of damage to alveolar type II cells) has been reported to be correlated with disease activity and prognosis in patients with IPF. Plasma α-defensin levels were inversely correlated with arterial oxygen tension and lung function (i.e., percent predicted forced vital capacity (FVC), forced expiratory volume over 1 second [FEV_1], and carbon monoxide diffusion capacity [DL_{CO}]) suggesting they may be useful as biomarkers of disease severity and activity in patients with IPF [Mukae 2002]. Two matrix metalloproteinases (MMPs), MMP-1 and MMP-7, implicated in the pathogenesis of IPF, were significantly increased in lung tissue, BAL fluid, and blood from patients with IPF, suggesting that increased levels in peripheral blood reflect the pathologic changes in the IPF alveolar micro-environment [Rosas 2008]. Moreover, serum MMP-7 concentrations in patients with subclinical IPF were significantly elevated when compared with control patients; while significantly lower than observed in patients with symptomatic IPF. Finally, serum MMP-7 was negatively correlated with lung function as measured by percent predicted FVC and DL_{CO}.

MMP-12 is a matrix-degrading metalloproteinase that is expressed only by tissue macrophages and placental trophoblasts. Since MMP-12 is highly upregulated in alveolar macrophages of β6-null mice and is mechanistically linked to the mild empysema-like histologic changes observed in later life [Morris 2003], the doses where m3G9 (the murine form of BG00011) treatment induced expression of this marker of macrophage activation were determined. Analysis of lung mRNA collected from mice treated with m3G9 (0.3 to 30 mg/kg/week for 4 weeks) revealed a significant increase in MMP-12 mRNA expression at doses of 10 and 30 mg/kg, but not at doses of 3 mg/kg or lower [Horan 2008]. All of the molecular changes induced by high-dose m3G9 treatment (including MMP-12) reverted to baseline after discontinuing m3G9 treatment.

In contrast to mice, no significant change in the expression of inflammatory genes (including MMP-12) or proteins in lung tissue and BAL fluid were observed in cynomolgus monkeys receiving vehicle, 0.1 or 10 mg/kg BG00011 weekly for 4 weeks (see BG00011 Investigator's Brochure). Conversely, the expression of TGF-β-inducible proteins tissue inhibitor of metalloproteinase 1, plasminogen activator inhibitor-1, and endothelin-1 were significantly downregulated in BAL fluid in both the 0.1 and 10 mg/kg BG00011 treatment groups, suggesting that the antibody was attenuating profibrotic activity at these doses. This observation

suggests that in monkeys, as in mice, the potential inhibition of profibrotic activity by BG00011 is seen at lower doses than the potential proinflammatory activity.

In summary, BAL and peripheral blood biomarkers may provide a means to assess treatment-associated changes in IPF patients in a minimally invasive manner.

4.4. BG00011 Nonclinical Experience

4.4.1. Functional Analysis of αvβ6 Integrin in β6 Null Mice

Evaluation of β6 null mice has provided direct insight into the function of the αvβ6 integrin and its role in disease (see BG00011 Investigator's Brochure). The β6 null mice are protected from fibrosis in models of lung, liver, and kidney disease. The β6 null mice develop mild pulmonary inflammation, defined as minimally increased numbers of lymphocytes, neutrophils, eosinophils, and enlarged vacuolated (foamy) macrophages in the lungs and in bronchoalveolar lavage (BAL) fluid. In later life, the β6 null mice develop mild emphysema-like histologic changes that are functionally correlated with increased matrix-metalloproteinase (MMP)-12 expression and directly linked to inactivation of TGF-β [Morris 2003].

4.4.2. 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 (SMA) positive fibroblasts [Hahm 2007; Horan 2008; Puthawala 2008](BG00011 Investigator's Brochure).

4.4.3. 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. BG00011 had no treatment-related safety pharmacology changes (CNS, cardiovascular and respiratory). In the SC repeat-dose mouse studies with m3G9, treatment-related findings were observed in the lung and the injection site. Pulmonary findings of greater lung weights and histologic changes of alveolar histiocytosis (greater number and increased size of macrophages), minimal inflammation, and necrosis were observed at 10 mg/kg. Alveolar histiocytosis and inflammation were partially reversed after the recovery period. At the injection sites (1 and 10 mg/kg), a higher incidence of minimal to mild fibroplasia was observed compared with the control group. After repeat-dose of m3G9, the NOAEL was 1 mg/kg in mice.

In the SC repeat-dose studies in monkeys, clinical signs of watery feces and dry skin were observed. The only other treatment-related finding was minimal to mild alveolar macrophage infiltration in the 1 and 10 mg/kg dose groups. The histologic change in the lung was observed at a lower incidence and was reversible. The NOAEL in monkeys was 10 mg/kg.

In repeat-dose mouse studies with m3G9, low incidences of tumors (bronchoalveolar adenoma, lymphoma) 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.

In the mouse reproductive development studies, m3G9 did not have any effect on the male or female fertility, and there was no treatment-related malformation in fetuses.

4.4.4. BG00011 Pharmacokinetics

In mice, systemic exposure of m3G9 after SC administration was highly not dose-proportional. BG00011 exhibited a high bioavailability following SC administration in the monkey. In a 26-week monkey toxicity study, BG00011 showed a slightly greater than dose-proportional increase in systemic exposure.

4.5. Previous Experience in Humans

A Phase 1 randomized, double-blind, placebo-controlled, single-dose, dose escalation study has conducted to evaluate the safety, tolerability, and PK of SC administered BG00011 in healthy volunteers. Forty subjects were enrolled into 5 ascending dose cohorts (6 active: 2 placebo subjects per cohort) to receive a single SC dose of BG00011 (range: 0.003 mg/kg to 0.3 mg/kg) or placebo (saline injection) and were monitored for 3 months after dosing. Dose escalation was based on the data safety monitoring board's (DSMB's) review of safety and PK data through Day 8 post-dose. One subject in the placebo group was prematurely withdrawn from the study at 14 days post-dosing due to non-compliance with the protocol.

The mean age across all dose cohorts was 32 years of age (range: 19 to 48 years), the majority of enrolled subjects were white (90%; 36 of 40 subjects), and slightly more than half of the subjects were female (58%; 23 of 40 subjects). The placebo group and 5 BG00011 dose cohorts were generally balanced for baseline demographic characteristics including age, gender, height, weight, and body mass index.

4.5.1. Safety and Tolerability

Single SC doses of BG00011 from 0.003 to 0.3 mg/kg were well tolerated in this healthy volunteer study. In general, subjects in the Phase 1 trial reported mild to moderate adverse events (AEs). There were no SAEs, including deaths, or premature discontinuations related to an AE. No dose-related trends were noted for any safety measures, including AEs, and no dose-related changes were noted in physical examinations, vital signs, or clinical laboratory parameters. Pulmonary function parameters remained stable after dosing across all dose levels.

Seventy-nine AEs were reported by 29 subjects during the study. Twenty-one of 30 subjects (70%) who received BG00011 and 8 of 10 subjects (80%) who received placebo reported an AE.

Four subjects experienced 7 AEs assessed as possibly related to study treatment. Three of these AEs were reported in 2 BG00011-treated subjects (abdominal discomfort and hyperhidrosis in 1 subject and pain in the extremity in 1 subject). Four AEs were reported as possibly related to study treatment in 2 subjects who received placebo (diarrhea, gastroenteritis, and rash in 1 subject and pedal flushing in another subject).

The majority of AEs were mild to moderate in severity. Severe events included headache (1 subject in the placebo group); elevated blood potassium (1 subject in the placebo group); neck muscle spasms, neck pain, and headache (1 subject in the 0.01 mg/kg dose group); and elevated serum cholesterol (1 subject in the 0.03 mg/kg dose cohort). None of the events were considered related to study treatment, all resolved, and the incidence of these AEs did not appear related to dose.

PFTs were monitored frequently during the Phase 1 study; i.e., 3 assessments prior to dosing and then at 1, 4, and 12 weeks following administration of study treatment. PFT parameters remained stable following dosing across all dose levels. AEs related to the respiratory system were mild to moderate in severity, and assessed as unrelated to study treatment. Similarly, changes in respiratory rate and pulse oximetry were unremarkable following dosing in all cohorts.

In summary, single SC doses of BG00011 over the range of 0.003 to 0.3 mg/kg were well tolerated in the healthy volunteer population with the incidence and severity of AEs, or changes in physical examination, vital signs, or clinical laboratory parameters comparable to the placebo treated subjects.

4.5.2. BG00011 Pharmacokinetics

The PK parameters of a single SC dose of BG00011 administered to healthy volunteers was evaluated with assessment of serum levels for 12 weeks following administration of study treatment. The lower limit of quantitation for the validated enzyme-linked immunosorbent assay in humans is 25 ng/mL.

Serum levels were not quantifiable in the initial 2 dose cohorts (0.003 and 0.01 mg/kg). For cohorts 3 to 5 (0.03, 0.1, or 0.3 mg/kg doses, respectively), the data fit a one compartment first order, no lag time, first order elimination model well. For cohorts 3 to 5, in which serum levels were above the limit of quantitation, the AUC from time 0 to time of the last measurable concentration and C_{max} exhibited dose proportionality ($R^2 = 0.99$ and 0.98, respectively). Based on the PK parameters from cohorts 4 and 5 (i.e., 0.1 and 0.3 mg/kg), the serum $t_{½}$ of BG00011 was approximately 6 days, and serum concentrations peaked at approximately 5 days. The maximum observed exposure was 319,693 ng*hr/mL.

4.5.3. Immunogenicity

In the Phase 1 study, serum was collected predose and at 1, 2, and 3 months following administration of study treatment and tested for the presence of anti-BG00011 antibodies using a validated electrochemiluminescence method. Three of 30 subjects receiving BG00011 tested positive for anti-BG00011 antibodies. Two subjects (0.01 and 0.03 mg/kg dose cohorts) tested positive at the 2- and 3-month time points, and these antibodies were neutralizing. The remaining subject (0.1 mg/kg dose cohort) tested positive at all time points (including predose); however, the samples from this subject were negative in the neutralization assay. Neither the incidence nor severity of AEs appeared to be correlated with the presence of antibodies to BG00011, and no hypersensitivity reactions were observed in the Phase 1 study.

4.6. Dose and Dose Interval Rationale

The selection of once weekly SC dosing of BG00011 at doses of 0.015, 0.1, 0.3, 1.0, and 3.0 mg/kg in this study is based on the nonclinical toxicology, PK, and research studies as well as the Phase 1 study in healthy volunteers.

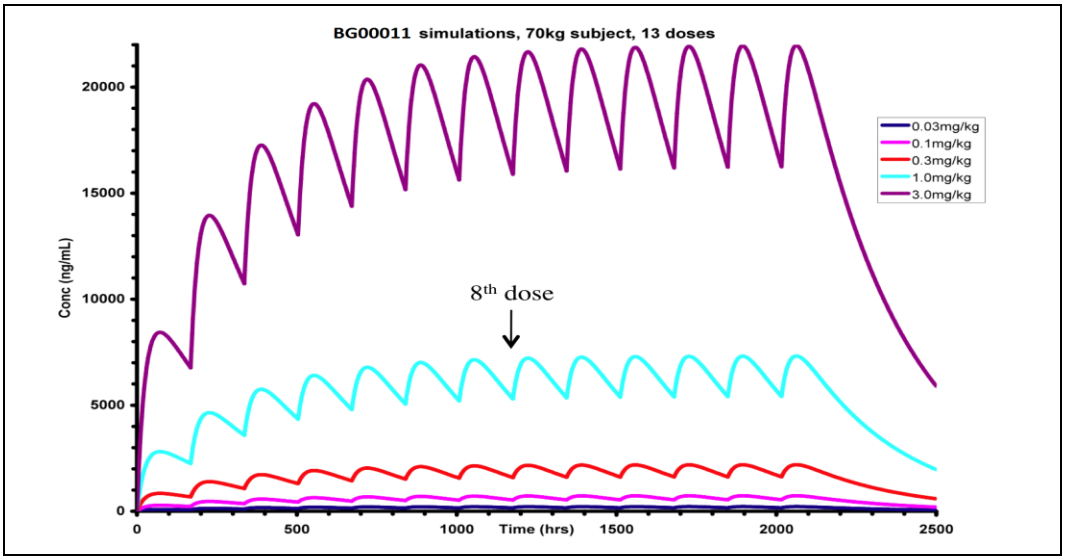
In the nonclinical models of lung, liver and kidney fibrosis, the efficacious dose range for m3G9 was 0.2 mg/kg to 10 mg/kg with an effective dose 50% range of 0.2 to < 1 mg/kg (Table 3 in the Investigator Brochure). In the 3-month GLP toxicology studies, the NOEL in non-human primates receiving BG00011 was 10 mg/kg (see Section 4.4.3).

BG00011 was well tolerated in healthy volunteers following single SC doses ranging from 0.003 mg/kg to 0.3 mg/kg. The lowest dose of BG00011 that provided reliable estimates of PK parameters was 0.1 mg/kg (assay LLOQ = 25 ng/mL). Based on PK parameters from the 0.1 and 0.3 mg/kg dose cohorts, the serum half-life of BG00011 was approximately 6 days, supporting once weekly administration (see Section 4.5.2). In addition, the serum BG00011 AUC exhibited dose proportionality in the 3-month monkey toxicology study (up to 10 mg/kg) and in humans (up to the highest dose tested, 0.3 mg/kg).

Using the PK parameters from the 0.3 mg/kg dose group in the healthy volunteer study, modeling was performed to predict the steady-state PK parameters following once weekly administration for 5 different doses (range: 0.03 mg/kg to 3.0 mg/kg). The modeling and simulations with once weekly SC dosing indicate that steady-state BG00011 concentrations were achieved by the 8th dose (i.e., 2 months) and accumulation was estimated to be approximately 2.5 fold (Figure 4). At the highest anticipated dose of 3.0 mg/kg in the current study, the estimated AUC exposure ratios (monkey/human) indicate that the human exposure is approximately 7 times lower than the estimated exposure at the NOAEL in the 6-month monkey toxicology study. Therefore, repeat dosing to subjects in this protocol is anticipated to achieve tolerable, steady-state levels for all dose cohorts that encompass the anticipated therapeutic range.

The initial dose of 0.015 mg/kg was selected to provide BG00011 exposure in humans comparable to the AUC observed at the NOAEL in the 3-month murine toxicology study. After the first dose increase, dose escalation will proceed by half-log increments between dose cohorts. In summary, the dose escalation regimen selected for this study is 8 once weekly SC administrations of BG00011 at doses of 0.015, 0.1, 0.3, 1.0 and 3.0 mg/kg.

Figure 4 Simulation Plot of BG00011 After 13 Doses, Once Weekly Dosing



4.7. Potential Risks of Human Use

BG00011 was well tolerated following administration of a single dose in the Phase 1 healthy volunteer study. No dose-related trends were noted for AEs, vital signs, physical examination, or laboratory safety parameters including PFTs (see Section 4.5.1).

As with any protein therapeutic, BG00011 may be immunogenic. Two of 30 subjects (7%) receiving BG00011 in the Phase 1 healthy volunteer study tested positive following negative pre-dose testing for anti-BG00011 antibodies. There was no observed correlation between the incidence and severity of AEs with the presence of anti-BG00011 antibodies, nor were any hypersensitivity reactions observed. Ultimately, the presence of neutralizing antibodies may affect the safety, PK, or efficacy profile of BG00011.

Based on data from animal studies, there is a risk that repeated doses of BG00011 may induce pulmonary inflammation. Therefore, exposure to BG00011 in this study will be limited to drug exposure below which no observable effects have been reported in the 6-month monkey toxicology study (Section 4.4.3). Subjects' respiratory status will be monitored throughout the study (e.g., clinical symptoms and signs, pulse oximetry and PFTs), while status of lung disease will be monitored by HRCT. In addition, β6 knockout mice developed emphysema with an associated increase in MMP-12 levels. As such, MMP-12 mRNA levels (which are increased when macrophages are activated) will be assessed in pulmonary macrophages isolated from BAL in an attempt to validate this test as a safety biomarker for use with this agent.

In the repeat-dose mouse studies with m3G9, low incidences of tumors (bronchoalveolar adenoma, lymphoma) were observed sporadically and in a non-dose-related manner. Spontaneous bronchoalveolar lesions have been reported in mouse historical control data (Section 4.4.3). An increased incidence of benign and malignant tumors has also been reported in β6 null mice [Ludlow 2005]. No tumors were noted in monkeys treated for 3 or 6 months with BG00011 or after 4 months of recovery. The relevance of the reported tumor findings in mice to humans is not clear.

The reproductive toxicity of BG00011 in humans is unknown. Women of childbearing potential must use contraception from the time of signing the informed consent form (ICF) through the end of the 12-week follow-up (FU) period and must be informed that there are potential hazards to the fetus should pregnancy occur during treatment. Male subjects must also agree to use contraception for either themselves or their partners throughout the duration of the study.

BG00011 is an investigational therapy and human exposure has been limited to date. Thus, there may be unforeseen or unknown risks for this patient population either from administration of BG00011 alone or in combination with other medications the patient may be receiving.

The potential risks of lung inflammation, emphysema, transplant rejection and malignancy based on the nonclinical findings described above will be conveyed to subjects in the ICF. The ICF also identifies procedures that may pose a risk to the subject beyond the potential systemic effects of administering BG00011. Risks due to phlebotomy may include bruising, localized bleeding or swelling, infection, syncope, and pain associated with the procedure. Risks associated with SC injection of study treatment may include pain, erythema, swelling, tenderness, inflammation, and/or bruising at the site of injection. Injection site reactions were not observed in the Phase 1 healthy volunteer study. An HRCT exposes the patient to a small dose of radiation. The risks of BAL include sore throat, cough, hoarseness, fever, chills, nausea, vomiting, myalgia, hypoxia, bronchospasm, infection, arrhythmias, hypotension, and/or myocardial infarction (rare). Aspiration may occur if the patient has not fasted adequately prior to the procedure.

4.8. GCP Compliance Statement

This trial will be conducted in compliance with all instructions, regulations, and agreements in this protocol and in the applicable International Conference on Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines, and must also be conducted in accordance with local regulations.

5. STUDY OBJECTIVES

5.1. Primary Objective:

- To evaluate the safety and tolerability of subcutaneously (SC) administered multiple, escalating doses of BG00011 in subjects with IPF

5.2. Secondary Objectives:

- To estimate the pharmacokinetic (PK) parameters after the first dose and after the last dose of multiple, escalating doses of BG00011 in subjects with IPF
- To assess the immunogenicity of BG00011 in subjects with IPF
- To assess the effect of BG00011 on biomarkers isolated from bronchoalveolar lavage (BAL) and peripheral blood in subjects with IPF

6. INVESTIGATIONAL PLAN

This is a multi-center, randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study designed to evaluate the safety, tolerability, PK, immunogenicity, and impact on BAL and peripheral blood biomarkers of BG00011 in subjects with IPF. Approximately 40 subjects will be enrolled into 5 sequential ascending dose cohorts. All cohorts will include 8 subjects randomized to receive either BG00011 (6 subjects) or placebo (2 subjects). The DSMB may require that additional subjects be included in a cohort if needed to better understand safety prior to dose escalation.

Doses to be administered are shown in Table 2:

Table 2 Dosing Cohorts

Cohort	Dose	Number of Subjects	
		BG00011	Placebo
1	0.015 mg/kg	6	2
2	0.1 mg/kg	6	2
3	0.3 mg/kg	6	2
4	1.0 mg/kg	6	2
5	3.0 mg/kg	6	2
Total Number of Subjects		30	10

Subjects with clinical symptoms and features consistent with IPF prior to screening, FVC ≥ 50% of predicted value; DLco, corrected for hemoglobin, ≥ 30% of predicted value; oxygen (O_2) saturation > 90% at rest while breathing ambient air or receiving ≤ 2 L/minute of supplemental oxygen; residual volume ≤ 120% of predicted value; a ratio of the forced expiratory volume in 1 second (FEV_1) to FVC ≥ 0.65 after the use of a bronchodilator on screening pulmonary function tests (PFTs); HRCT consistent with UIP pattern, and who meet the other inclusion/exclusion criteria are eligible to enroll in the study. Subjects with IPF who do not otherwise qualify for study eligibility may be rescreened at the discretion of the Principal Investigator.

6.1. Nomenclature for Study Periods and Study Days

Days for the MD period are designated with an "MD" and days for the FU period are designated with an "FU".

- Day 1-MD is the day the subject receives the first dose during the MD period of the study.
- Day 1-FU is first day of the follow-up period, which should coincide with the day of last dose during the MD period (Day 50-MD).

See the Schedule of Events in Table 3 which illustrates the sequence of study visits and treatment periods.

6.2. Overall Study Duration and Follow-up

6.2.1. Duration of Study

In cohorts 1 to 3, each subject's participation in the study will be for approximately 24 weeks (~5.5 months), i.e., up to 5 weeks to perform screening/entry evaluations, followed by 7 weeks of double-blind study dosing (8 doses) and a Follow-up period of 12 weeks. For cohorts 4 and 5, the subject's participation in the study will be for approximately 23 weeks (~5.5 months), i.e., up to 8 weeks to perform screening/entry evaluations, followed by 7 weeks of double-blind study dosing (8 doses) and Follow-up period of 8 weeks.

6.2.2. Screening

Subjects will undergo screening assessments within 5 weeks or 35 days (8 weeks or 56 days, for cohorts 4 and 5 only) prior to dosing. Pulmonary function tests (PFTs), HRCT and BAL are also included as part of the screening process and must be performed within 5 weeks (35 days) prior to dosing in all cohorts. Qualifying assessments including medical history, physical examination, vital signs, 12-lead electrocardiogram (ECG), oxygen saturation, PFTs (before and after bronchodilator administration), HRCT, and clinical laboratory tests including pregnancy testing (if applicable) and testing for human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C (HCV) antibody will be performed. ***It is recommended that the BAL and PFTs be performed after the subject has met the other inclusion criteria, including the screening HRCT***. Following confirmation of eligibility on a screening PFT, subjects will perform 1 additional set of PFTs without bronchodilator administration to establish their baseline lung function which can be performed at any time up to and including Day 1-MD of the study provided it is at least 1 day after the screening PFT. Screening assessments (e.g., clinical laboratory assessments or PFTs) may be repeated 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.

Upon fulfilling all of the inclusion and none of the exclusion criteria, subjects will be randomized to receive either BG00011 or placebo. Subjects will be instructed to return to the clinic on Day 1-MD for baseline, pre-dose evaluations and to ensure that they still qualify for the study by meeting all criteria with the exception of PFTs. If a subject's Screening PFT values meet the inclusion criteria, they should not be excluded from the study based upon their baseline PFT values.

6.2.3. Multiple-Dose Period

On Day 1-MD the subject's medical history, physical examination, inclusion/exclusion criteria, vital signs, oxygen saturation, and pregnancy status (if applicable) will be assessed, as well as blood samples collected for baseline laboratory, biomarker, PK, and antibody assessments. The first dose will be administered and the subject will be observed at the study center for at least 8 hours for monitoring and laboratory tests. A PK sample will be collected at 8 hours after dosing. The subject will then be discharged with instructions to return to the study center for follow-up

visits on Days 2-MD, 3-MD, 5-MD, and at each of the weekly dosing visits for safety evaluations and PK sampling.

Study treatment will be administered weekly on Days 1-MD, 8-MD, 15-MD, 22-MD, 29-MD, 36-MD, 43-MD, and 50-MD, for a total of 8 doses. Prior to dosing on Days 1-MD, 8-MD, 15-MD, 29-MD, and 43-MD, a physical examination, oxygen saturation, vital signs, laboratory assessments, and a PK blood draw will be performed, and then the study medication will be administered. On Days 22-MD, 36-MD and 50-MD, pre-dose vital signs and oxygen saturation will be obtained, and a trough PK level will be drawn prior to administration of study medication. Serum for biomarkers will be obtained on Days 29-MD and 50-MD, and other assessments (e.g., ECG) will be performed as indicated in the Schedule of Events (Table 3)

Following dosing at each study visit, subjects will be observed at the study center for a minimum of 30 minutes, vital signs will be checked, instructions will be given, and the subject will be discharged.

After administration of the final (8^{th}) dose of study treatment in the MD period (Day 50-MD), PK samples will be collected at 8 hours, and the subject will be discharged with instructions for procedures during the FU period.

Except for the first and eighth (last) doses, there are no scheduled interim visits between dosing days, but subjects should be assessed if there are clinical concerns.

6.2.4. Follow-up Period

After completing the MD period of the study, each subject will be followed up for an additional 12 weeks (8 weeks for subjects in cohorts 4 or 5). Study days during the follow-up period will be dependent on when the last dose of study medication is administered. The day of the last dose of study treatment is designated as Day 1 of the FU period (Day 1-FU). Visits during the FU period will occur on Days 2-FU, 3-FU, 5-FU, 8-FU, 15-FU, 22-FU, 29-FU, 57-FU (8 weeks), and, for those in cohorts 1 to 3 only, 85-FU.

Vital signs, PK levels, and monitoring of health status will be assessed at each visit. The BAL should be performed between Day 3-FU and Day 8-FU, and PFTs and HRCT scan should be performed within 21 days following administration of the last dose of study medication. If performed on the same day, HRCT and PFTs must be performed prior to BAL. If a BAL is performed first, at least 2 days must have elapsed before PFTs and HRCT are performed. Serum for assessment of antibody development to BG00011 will be collected on Days 29-FU (all cohorts) and 57-FU (cohorts 4 and 5 only) or 85-FU (cohorts 1 to 3). Serum for biomarkers will be obtained and additional safety assessments will be performed on Days 8-FU, 29-FU, 57-FU, and 85-FU (12 weeks after the final dose for cohorts 1 to 3 only), which is the final study visit. At Day 57-FU the Investigator will also record their assessment of the subject's respiratory status relative to baseline: better, worse or the same (for cohorts 4 and 5 only). Following this visit, the subject will be discharged from study participation.

6.3. Discontinuation or Temporary Suspension of the Study

Biogen MA Inc. may terminate this study at any time for safety or administrative reasons. Biogen MA Inc. will terminate the study if the occurrence of AEs or other findings suggests an unacceptable risk to the health of the subjects.

Criteria for stopping or temporarily discontinuing the study include:

1. If 2 subjects receiving study medication in a cohort experience an SAE that is considered possibly or probably related to the study treatment by the Investigator, the DSMB will determine whether the nature, severity, or the number of AEs would permit 1 of the following:
   - Continuing enrollment and dosing of the current cohort
   - Initiation of the next dose escalation cohort
   - Enrollment of an additional 4 subjects in that cohort
   - Enrollment of an intermediate dose cohort
   - Discontinuation of dose escalation
2. If 2 subjects receiving study medication in a cohort experience a clinically significant, sustained decrease from baseline respiratory status as determined by both the Investigator and the DSMB.
3. If 2 subjects receiving study medication demonstrate a significant increase in MMP-12 levels between baseline and post-treatment BAL assessments as determined by the DSMB.
4. Exposure as measured by AUC is greater than the comparable systemic exposure at the NOEL observed in nonhuman primate studies.
5. The DSMB feels there is a need to temporarily suspend subject enrollment until further assessments are made.

6.4. Blinding Procedure

This study is double-blinded. The study execution contract research organization, site investigators, site staff, and subjects will remain blinded throughout the entirety of the study with the exception of designated pharmacy staff and other key individuals as listed in the unblinding plan. An unblinded pharmacist at each site, not associated with the operational conduct of the study, will prepare appropriate medication for injection according to the provided unblinded randomization code and instructions for preparation. This individual will keep the unblinded code locked in a secure place and will neither disclose the code to anyone else (except for an unblinded quality assurance person to monitor the pharmacy) nor discuss the subjects with site staff. Members of the DSMB will be unblinded to review safety and available PK data, to assess safety and tolerability, and to make informed decisions regarding dose escalation.

An administrative interim analysis may be performed on all subject data up to and including the Day 8-FU visit for the last subject in cohort 4. The analysis will include a review of unblinded data that will be limited to a core unblinded team as specified in the unblinding plan.

See Section 15.3 for a description of unblinding procedures in case of a medical emergency. If a subject's treatment assignment is unblinded accidentally, this should be noted in the study file and reported to the Sponsor. The subject should remain in the study and continue the protocol-specified dosing and follow-up evaluations.

7. SELECTION AND WITHDRAWAL OF SUBJECTS

7.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening:

1. Consenting male or female subjects, 45 to 84 years old, inclusive.
   - Subjects 18 to 44 years of age are eligible if they have a histopathological diagnosis of UIP based upon a surgical lung biopsy in the appropriate clinical setting, and meet all other inclusion/exclusion criteria.
2. Clinical features consistent with IPF prior to screening (based on the ATS/ERS/JRS/ALAT consensus criteria for the diagnosis of IPF [see Section 4.3.1]).
3. FVC ≥ 50% of predicted value.
4. DLco (corrected for hemoglobin) ≥ 30% predicted value.
5. Oxygen saturation > 90% by pulse oximetry while breathing ambient air at rest or receiving ≤2 L/minute of supplemental oxygen.
6. Residual volume ≤ 120% predicted value.
7. Ratio of FEV1 to FVC ≥ 0.65 after the use of a bronchodilator.
8. Other known causes of interstitial lung disease have been excluded (e.g., drug toxicities, environmental exposures, connective tissue diseases).
9. HRCT image fulfills the criteria for 'UIP pattern' (surgical lung biopsy not required [see Section 4.3.1]). The radiographic diagnosis of UIP must be confirmed on the screening HRCT by an independent central radiologist experienced in the evaluation of interstitial lung diseases.
10. If the HRCT image does not fulfill the criteria for 'UIP pattern' a surgical lung biopsy is necessary for the diagnosis of IPF (lung biopsy performed prior to screening is acceptable). In this setting the HRCT image must meet the criteria for 'possible UIP pattern' **and** the lung biopsy must fulfill the histopathological criteria for either 'UIP pattern' or 'probable UIP pattern' (see Section 4.3.1). If the HRCT image fulfills the criteria for UIP pattern, results from a surgical lung biopsy are not necessary. If however, a lung biopsy has been performed, it must fulfill the histopathological criteria for either 'UIP pattern' or 'probable UIP pattern' with the appropriate HRCT correlate.
11. Adequate bone marrow and liver function as demonstrated by:
    - Hemoglobin ≥ 10 g/dL
    - White blood cell (WBC) count ≥ 3,000/mm^3
    - Neutrophils ≥ 1,500/mm^3
    - Platelets ≥ 80,000/mm^3

- Total bilirubin ≤ 1.5 mg/dL
- Aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times upper limit of normal

12. Subject has a life expectancy of at least 12 months.
13. Subject must provide written informed consent. If required by local law, candidates must also authorize the release and use of protected health information (PHI).
14. Female subjects must be surgically sterile, postmenopausal (minimum 1 year without menses), or agree to use 1 or more of the following forms of contraception from the time of signing the ICF through 12 weeks following the last injection of study medication: hormonal (i.e., oral, transdermal, implant, or injection); double barrier (i.e., condom, diaphragm with spermicide); intrauterine device; vasectomized partner (six months minimum); 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 through 12 weeks following the last injection of study medication.

7.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening:

1. Unable to perform PFTs.
2. Findings that are diagnostic of a condition other than UIP on surgical lung biopsy (performed either before or after screening) HRCT imaging, transbronchial lung biopsy, or BAL
3. Currently receiving high dose corticosteroid, cytotoxic therapy (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), nintedanib (Ofev®), vasodilator therapy for pulmonary hypertension (e.g., bosentan), unapproved (e.g., IFN-γ, penicillamine, cyclosporine, mycophenolate, N-acetylcysteine), 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 ≤ 15 mg/day of prednisone or its equivalent is acceptable if it is anticipated that the dose will remain stable during the study. Pirfenidone (Esbriet®) is permitted, provided that the subject has been on a stable dose for at least 4 weeks prior to randomization and it is anticipated that the dose will remain stable during enrollment.
4. History of malignancy, including carcinoma during the preceding 5 years. However, subjects with a history of excised or treated basal cell, squamous cell, or cervical carcinomas are eligible to participate in this study.
5. 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; or uncontrolled atrial or ventricular cardiac arrhythmias).

6. Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) within 3 months prior to screening.
7. Significant reaction to previous injection of a monoclonal antibody.
8. Female who is pregnant or breastfeeding.
9. 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.
10. Fever (body temperature > 38°C) or symptomatic viral or bacterial infection within 1 week prior to screening.
11. Positive test for HBsAg, HCV antibody (if confirmed by HCV RNA), or HIV antibody at screening.
12. Drug or alcohol abuse (as defined by the Investigator).
13. 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.
14. End-stage fibrotic disease requiring organ transplantation within 6 months.
15. Any other condition that, in the opinion of the Investigator, may compromise the safety or compliance of the subject or would preclude the subject from successful completion of the study.

7.3. Withdrawal Criteria

Subjects will be informed that they have the right to withdraw from the study at any time for any reason without prejudice to their medical care.

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

- Subject request
- Subject is unwilling or unable to comply with the protocol
- Medical reason, at the discretion of the Investigator and/or the Medical Monitor

The reasons for subject withdrawal must be recorded in the subject's case report form (CRF) and in the source records. The Investigator must notify Biogen MA Inc. and the Medical Monitor immediately when a subject has been discontinued/withdrawn due to an AE.

Subjects who discontinue prior to Day 8-FU should undergo all assessments described for the Day 8-FU visit, if possible, including BAL, PFTs, and HRCT that are to be performed within a specified period after the subject receives their last dose of study medication. Also, samples should be collected for serum pregnancy testing (if applicable) and anti-BG00011 antibody testing. Subjects who discontinue the FU period subsequent to having Day 8-FU assessments performed should have Day 85-FU (Day 57-FU for cohorts 4 and 5) assessments performed at the time of termination.

Subjects who discontinue participation during the MD period of the study for reasons unrelated to the study or study treatment (e.g., withdraw consent, lost to follow-up) may be replaced as

required for the study to meet its objectives. Replacement subjects will be assigned unique identification numbers.

8. INVESTIGATIONAL PRODUCT

8.1. Identity of Investigational Product

BG00011 is a humanized monoclonal antibody (human immunoglobulin G1 subgroup III, kappa) and consists of 2 heavy and 2 light chains connected by inter-chain disulfide bonds. The molecular weight of the intact BG00011 molecule is 148,000 daltons, including its carbohydrate moiety.

BG00011 is provided as a lyophilized drug product in vials, must be kept refrigerated (2°C to 8°C), be protected from light, and may not be frozen. BG00011 will be administered as an SC injection (e.g., in the upper arm) after reconstitution.

Each BG00011 lyophilized drug product vial is reconstituted using 1.3 mL of preservative-free sterile water for injection/USP to yield a final concentration of 75.0 mg/mL BG00011 in 15 mM sodium citrate, 7.5% (w/v) sucrose, 0.0075 % polysorbate 80, at pH 6.1.

Additional dilution is required for lower doses and instructions for dilution will be provided to the pharmacy. The reconstituted drug product does not contain a preservative and should be used within 4 hours.

8.2. Reference Product

The placebo (control agent) to be used in this study will be sterile normal saline (0.9% Sodium Chloride for Injection) administered as an SC injection. The investigational site's pharmacist will supply sterile, normal saline. The manufacturer's directions for material storage and handling are to be followed, as are standard clinical practices for ensuring sterility of the material. The volume will be calculated as if the subject was to receive BG00011, and the equivalent amount of saline will be administered.

8.3. Drug Accountability

Accountability for study medication is the responsibility of the Principal Investigator.

Investigational clinical supplies must be received by a pharmacist or other designated person at the study site and kept in a secured location. The investigational site or pharmacy associated with the site must maintain accurate records indicating dates and quantity of study medication received, to whom it was dispensed (subject-by-subject accounting), and accounts of any study medication accidentally or deliberately destroyed. Unless otherwise notified, all study medication, both used and unused, must be saved for drug accountability. The Investigator must return all unused vials of study medication to the Sponsor at the end of the study, unless local destruction is agreed to in writing.

8.4. Drug Handling Guidelines

Please refer to the pharmacy instructions, provided in a separate document, for detailed drug handling, preparation, administration, and storage instructions.

9. TREATMENT

9.1. Dosing Schedule

BG00011 will be administered as an SC injection. Doses will be 0.015 mg/kg, 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, and 3.0 mg/kg. Weight obtained at initial screening will be used to calculate dose throughout the MD period.

At the end of Screening, eligible subjects will return for dosing on Day 1-MD. Study treatment will be administered once weekly for 8 doses (7 weeks), i.e., on Days 1-MD, 8-MD, 15-MD, 22-MD, 29-MD, 36-MD, 43-MD, and 50-MD.

9.2. Study Medication Administration

Investigational product (reconstituted monoclonal antibody BG00011) and the placebo control (saline solution) will be administered via SC injections (e.g., in the upper arm). Study medication must be administered within 4 hours after preparation. An injection volume greater than 1.5 mL should be split between 2 injection sites.

9.3. Safety Monitoring and Dose Escalation

The Sponsor is committed to assuring subject safety during this study and the Phase 2a IPF protocol was designed with input from leading physicians experienced with conducting clinical trials in this setting. Eligibility criteria stipulate that subjects are clinically stable, meet accepted criteria for the diagnosis of IPF, and have PFTs consistent with moderate disease severity (e.g., FVC ≥ 50% and DLCO ≥ 30% of predicted values, respectively).

9.3.1. Safety Monitoring

Subjects will be closely monitored during the study periods as described below.

9.3.1.1. Multiple-Dose Period

After receiving the first dose of study treatment, subjects are observed for 8 hours and then discharged with additional visits on Days 2-MD, 3-MD, 5-MD, and then weekly throughout the 7-week dosing period.

9.3.1.2. Follow-up Period

After administration of the final (eighth) dose of study treatment, subjects in cohorts 1 to 3 and subjects in cohorts 4 or 5, will have 7 visits over the subsequent 4 weeks followed by a clinic visit at Month 3 (Month 2 for cohorts 4 and 5).

9.3.2. Dose Escalation

An independent DSMB experienced in the oversight and monitoring of the conduct of clinical trials will determine whether dose escalation should proceed. Dose escalation will be based on the DSMB's review of unblinded PK and safety data through at least Day 15 from the initial 4 subjects administered BG00011 or placebo (3:1, respectively) in each cohort. Safety

assessments will include a review of AEs, vital signs, physical examination, clinical laboratory tests, and pulse oximetry from these visits. Updated safety (including BAL, PFTs, and HRCT results) and PK information on all participants will be provided in each subsequent DSMB data package. For example, at the DSMB meetings for cohorts 2 and 3, updated safety and PK data will be available through at least week 8 of the FU period (i.e., complete PK data through the dosing period and follow-up BAL, PFT, and HRCT) for all participants in cohorts 1 and 2, respectively.

Reports of SAEs will be provided to the DSMB on an ongoing basis throughout the study. In addition, Biogen MA Inc. will review AEs in a blinded manner on an ongoing basis and alert the DSMB of any safety concerns.

In order to allow for compilation and evaluation of the data, it is anticipated that the DSMB will convene approximately 7 to 8 weeks after the first 4 subjects in the previous cohort are dosed. After reviewing the safety and PK data, the DSMB may recommend initiation of the next dose escalation cohort. Alternatively, the DSMB may recommend monitoring subjects within a cohort for a longer period of time or reviewing safety and PK data from additional subjects prior to recommending dose escalation. If indicated, another cohort may be enrolled at a dose level similar to or lower than prior cohorts (see Section 6.3 'Discontinuation or Temporary Suspension of the Study').

A DSMB meeting will not occur during the final cohort except on an ad hoc basis, as no dose escalation decision needs to be made.

9.4. Prior and Concomitant Medications

It is recognized that this subject population will be taking various medications. All concomitant medications (including herbals, vitamins, and over-the-counter medications) taken during the entire study, starting with what is currently being taken by subjects at the initial screening visit (even if the medication is discontinued at that time), will be recorded on a CRF. Subjects must not have received 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, nor are they allowed to participate in another investigational study during this study.

Subjects should not be receiving high dose corticosteroid (i.e., > 15 mg/day of prednisone or its equivalent), cytotoxic therapy (e.g., chlorambucil, azathioprine, cyclophosphamide, methotrexate), nintedanib (Ofev®), vasodilator therapy for pulmonary hypertension (e.g., bosentan), unapproved (e.g., interferon gamma, penicillamine, cyclosporine, mycophenolate, N-acetylcysteine), and/or investigational therapy for IPF while participating in this study, nor can they have received such within 5 half-lives of the agent prior to initial screening. All treatments previously used for treatment of IPF will be captured on a CRF.

Use of Pirfenidone (Esbriet®) is permitted, provided that the subject has been on a stable dose for at least 4 weeks prior to randomization.

Pirfenidone should be kept at a stable dose, if possible. Dose decreases in response to adverse events are permitted and should be done in a manner consistent with the prescribing information

for pirfenidone. Dose increases of pirfenidone, including an increase back to baseline dose after a dose decrease, are prohibited.

Following enrollment into the study, every attempt should be made to avoid changes in the subject's drug regimen. Exceptions would include episodes of infections requiring treatment (e.g., antibiotics or antiviral drugs), exacerbations of their underlying disease requiring immediate intervention, or any other situation requiring modification of the subject's therapy for their safety at the discretion of the treating physician.

9.5. Subject Compliance

Study medication is administered SC by site personnel while the subjects are at the study center. Therefore, monitoring for subject compliance with the treatment regimen is unnecessary.

10. SAFETY, PHARMACODYNAMICS, AND PHARMACOKINETICS ASSESSMENTS

10.1. Safety Assessments

10.1.1. Adverse Events

AE information will be collected throughout the study. See Section 14 for a full description of AE definitions, AE and SAE reporting procedures, and emergency procedures.

10.1.2. Clinical Laboratory Tests

The following laboratory safety assessments will be performed:

- Hematology: complete blood count (CBC) with differential and platelet counts. CBC includes red blood cells, WBCs, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration.
- Serum chemistry: albumin, alkaline phosphatase, ALT, AST, blood urea nitrogen (BUN), calcium, chloride, carbon dioxide, creatinine, direct bilirubin, gamma-glutamyl transferase, glucose, lactate dehydrogenase, magnesium, phosphorus, potassium, sodium, total bilirubin, total cholesterol, total protein, and uric acid.
- Urinalysis: including determination of the presence of protein, glucose, ketones, occult blood, and WBCs by dipstick, with microscopic examination, if indicated.

A blood sample for hematology/serum chemistry testing will be collected at the following time points: screening, prior to dosing on Day 1-MD, and on Days 8-MD, 15-MD, 29-MD and 43-MD, and then on Days 8-FU, 29-FU, 57-FU, and those in cohorts 1 to 3 only, 85-FU after the final dose.

At screening, blood samples for HCV antibody, HBsAg, and HIV antibody will be collected to establish eligibility. Appropriate referrals must be made for any positive HCV, HBsAg, or HIV test that is obtained according to applicable state laws.

Collection, handling, and shipping procedures for the BAL specimens and serum samples for PK, antibodies to BG00011, and biomarkers are provided in the study manual. Validated bioanalytical methods will be used to measure BG00011 serum levels and antibodies to BG00011.

10.1.3. Pulmonary Function Tests

Screening and Baseline PFTs

Two PFTs will be performed during Screening (within 5 weeks prior to dosing). The first of these tests (screening PFT) will be performed before and after bronchodilator administration and will be used to determine if the subject qualifies for the study, whereas the other 1 (performed without bronchodilator administration) will serve as the subject's baseline value. These 2 PFTs must be performed on separate days during Screening up to and including Day 1-MD. The baseline PFT must not be performed until the results from the Screening PFT have been

received. Additional PFTs will be performed on Day 29-MD ± 5 days and within 21 days after receiving the last dose of study medication. PFT parameters include:

- FVC
- FEV_1
- TLC (total lung capacity)
- DL_{CO}
- Residual Volume

A subject who qualifies for inclusion in 1 cohort but is unable to participate (e.g., cohort fully enrolled) may be assessed for inclusion in a subsequent cohort without repeating the screening PFTs, unless it will fall outside the 5 week window prior to dosing.

Assessment of PFT Changes from Baseline

The assessment of changes in lung function during this study will be performed by comparing the subject's FU PFT parameters to their baseline value. Quality control assessment of all PFTs will be performed by a blinded independent expert.

PFTs showing clinically significant change(s) from baseline should be repeated to confirm the change prior to reporting the observation as an AE. Since the variability in lung function measurements is related to both biological and technical factors and is greater than observed in most other clinical laboratory tests [Jensen 2007a; Jensen 2007b; Pellegrino 2005]), when evaluating changes in PFTs it is important to consider the inherent variability in the PFT parameter being measured. For example, a ≥ 12% change from baseline in FEV_1 is considered significant and may be clinically important [Pellegrino 2005]. Therefore, a subject whose FEV_1 decreases by 14% from their baseline value (i.e., 86% of baseline) will be confirmed with repeat PFT testing, and if the decrease persists, the subject will be considered to have had an AE. For TLC, FVC, and DL_{CO}, a ≥ 8%, ≥ 12%, and ≥ 15% decline from baseline, respectively, is considered to be clinically meaningful [Pellegrino 2005]; personal communication with R Crapo).

10.1.4. Bronchoalveolar Lavage

BAL will be performed during Screening and between Day 3-FU and Day 8-FU after receiving the last dose of study medication. Analysis of the BAL macrophage MMP-12 mRNA levels (which are increased when macrophages are activated) will be performed at a central laboratory.

10.1.5. High Resolution Computed Tomography

HRCT scans will be performed during screening to establish the pre-dosing pattern and extent of disease. HRCT will be repeated within 21 days after receiving the last dose of study treatment during the MD period. An independent central radiologist experienced in the evaluation of diffuse lung diseases and blinded to treatment assignment will read all scans during the MD and FU periods.

10.1.6. Other Safety Assessments

The following assessments will be performed:

- Medical history
- 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
- Oxygen saturation (pulse oximetry) after at least 5 minutes rest
- Serum pregnancy test
- Urine pregnancy test
- Formation of antibodies to BG00011: blood samples for immunogenicity testing will be collected during screening, and on Day 1-MD (prior to dosing), Day 29-FU, and Day 85-FU (Day 57-FU for subjects in cohorts 4 or 5).

10.2. Efficacy Assessments

There are no efficacy objectives in this study.

10.3. Pharmacodynamic Assessments

10.3.1. Peripheral Blood Biomarkers

Peripheral blood will be collected to determine whether administration of BG00011 has a beneficial effect on blood biomarkers of TGF-β activation, tissue remodeling and lung injury, and epithelial function in subjects with IPF. These biomarkers may include the TGF-β inducible proteins TIMP-1 and Col1A1; matrix proteins such as osteopontin (OPN) and MMP-7; and indicators of epithelial function including SP-A and alpha defensins (DEFA1-3). Additional biomarkers may be added prior to the initiation of the analyses and will be included in the statistical analysis plan. Blood samples for blood biomarkers will be collected at screening and on Days 1-MD, 29-MD, 50-MD, 8-FU, 29-FU, 57-FU, and for subjects in cohorts 1 to 3 only, 85-FU.

10.3.2. Bronchoalveolar Lavage

Biomarkers which may include mRNA levels for PAI-1 and OPN, as well as protein levels for phosphorylated SMAD, will be measured in macrophages isolated from BAL. BAL will be performed during screening and between Day 3-FU and Day 8-FU following administration of the last dose of study treatment. Analyses of BAL fluid and cell pellet will be performed at a central laboratory.

10.4. Pharmacokinetic Assessments

The following parameters will be assessed during the study to evaluate the PK profile of BG00011.

PK parameters include:

- C_{max}
- Time to reach C_{max}
- Area under the concentration-time curve from time zero (time of dosing) to the last measurable concentration
- Area under the concentration-time curve from time zero (time of dosing) extrapolated to infinity
- Area under the concentration-time curve from time zero (time of dosing) to tau (within a dosing interval)
- Terminal elimination rate constant
- $t_{½}$: elimination half-life
- Clearance (unadjusted for bioavailability)
- Volume of distribution (unadjusted for bioavailability)

Blood samples for PK evaluation will be collected at screening, prior to dosing on Day 1-MD and at 8 hours after dosing; and prior to dosing on Days 2-MD (24 hours), 3-MD, 5-MD, 8-MD, 15-MD, 22-MD, 29-MD, 36-MD, 43-MD, and 50-MD. After the final dose of the MD period, PK samples will be obtained at 8 hours, and on Days 2-FU, 3-FU, 5-FU, 8-FU, 15-FU, 22-FU, 29-FU, 57-FU, and, for cohorts 1 to 3 only, 85-FU during the FU period. BG00011 PK samples should be drawn as close as possible to the sampling times shown in the Schedule of Events (Table 3).

Exposure-response relationships will be explored for both safety and pharmacodynamics to assist with determining the appropriate dosing regimen for BG00011 in this clinical setting.

11. STUDY PROCEDURES AND SCHEDULE

11.1. Subject Management

Female subjects of childbearing potential must practice effective contraception for the entire study period, i.e., from the time of signing the ICF through 12 weeks following the last injection of study treatment. Female subjects are exempt from contraception requirements if they are postmenopausal for a least 1 year before dosing or are surgically sterile (i.e., no uterus or no ovaries). Females who have their fallopian tubes tied or cut are not considered surgically sterile. Male subjects must have had a vasectomy performed at least 6 months prior to screening or must agree to use contraception for either themselves or their partner(s) from the time of signing the ICF through 12 weeks following the last injection of study treatment.

Subjects will undergo screening assessments within 5 weeks (8 weeks for selected assessments in cohorts 4 and 5) prior to dosing. Upon fulfilling all of the inclusion and none of the exclusion criteria, subjects will be randomized to receive either BG00011 or placebo.

Subjects will receive 8 doses of their assigned medication at weekly intervals, with visits and assessments as detailed below and in the Schedule of Events. Subjects will be followed for 12 weeks (8 weeks for cohorts 4 and 5) after their final dose of study treatment.

11.2. Timing of Visits and Missed Visits

As described in Section 6.1, to help prevent confusion between the periods of the study, days specific to the MD dosing period will be designated as “Day X-MD”. The follow-up period begins at the visit where the last dose of study treatment is administered, and study days after the final dose of study treatment is administered are designated as “Day X-FU.”

Table 3 shows specific days for each visit. If a dosing visit is delayed during the multiple-dose period the dose should be administered as soon as possible thereafter. If a missed dose is delayed no more than 2 days beyond the protocol-specified visit date, i.e., within the allowed ± 2 day window, all subsequent doses should still be administered on the originally scheduled day (e.g., Day 22, Day 29). If a dose is delayed by 3 or more days beyond the specified visit date then either 1) the missed dose should be omitted and dosing should then resume as per the Schedule of Events, or 2) the subsequent dosing visit dates should be adjusted appropriately, if this can still be done within the allowed visit windows, to ensure there is always an interval of at least 5 days between doses.

Subjects who discontinue prior to Day 8-FU should undergo all assessments described for the Day 8-FU visit, if possible, including BAL, PFTs, and HRCT that are to be performed within a specified period after the subject receives their last dose of study treatment. Also, samples should be collected for serum pregnancy testing (if applicable) and anti-BG00011 antibody testing. Subjects who discontinue the study subsequent to having Day 8-FU assessments performed should have Day 85-FU (57-FU for subjects in cohorts 4 or 5) assessments performed at the time of termination.

11.3. Randomization

A central randomization will be used that is blinded to the Sponsor, site staff, subject, and personnel responsible for data verification, entry, and analysis. An unblinded statistician for the contract research organization who is independent of study conduct will develop the randomization scheme. The subject randomization number indicates the cohort and randomization sequence that is unique to each subject (e.g., Number 101 indicates cohort 1, Subject 1). If the subject qualifies for randomization based on results obtained during Screening, central randomization may be contacted and the randomization number assigned. A subject will be considered randomized once a randomization number has been assigned and the subject receives the first dose of study treatment.

The unblinded pharmacist will be notified of the randomization number and treatment assignment and will prepare appropriate medication for injection according to the provided randomization code and instructions for preparation. The unblinded pharmacist will keep the randomization code locked in a secure place and will not disclose the code to anyone else (except for a quality assurance person in the pharmacy) or discuss subject information with study staff. A sealed blind break envelope will be completed by the unblinded statistician for the contract research organization and provided to the study staff in the event emergency unblinding is necessary. If there has been a significant change in the subject's condition on Day 1-MD, the Medical Monitor should be consulted before dosing occurs.

11.4. Screening

Visit 1 – Within 5 Weeks (8 weeks for Cohorts 4 and 5) Prior to Dosing

Subjects will be required to sign an ICF prior to any study related procedures, including screening evaluations that are not part of their routine medical follow-up. After written informed consent is obtained, the subject will be given a screening number. Subjects who are screened and fail the inclusion/exclusion criteria will not be allowed in the study. "Screening" is designated as Visit 1, but it is recognized that these procedures may encompass more than 1 visit.

Screening assessments (e.g., clinical laboratory tests or PFTs) may be repeated 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. ***It is recommended that the BAL and PFTs be performed after the subject has met the other inclusion criteria, including the screening HRCT***.

A detailed list of screening procedures is provided in Table 3.

Further details regarding the PFT procedures may be found in Section 10.1.3.

11.5. Multiple-dose Treatment

If the laboratory and other tests performed during screening indicate continued eligibility, subjects will return to the study center during the morning of Day 1-MD and remain there for 8 hours after dose administration.

A detailed list of pre-dose assessments, with recommendations for timing, is provided in Table 3. Actual times will be recorded in the subject's CRF.

The dosing schedule and regimen are described in Section 9.1.

11.6. Follow-up Period

A detailed list of follow-up assessments, with recommendations for timing, is provided in Table 3.

Actual times will be recorded in the subject's CRF.

11.7. Early Termination

If a subject terminates at Day 8-FU or before, all Day 8-FU assessments need to be performed, as well as the following:

- Serum pregnancy test (if applicable)
- Sample collection for anti-BG00011 antibody analysis
- BAL (between Day 3 and Day 8 [i.e., 48 hours to 168 hours] after the last dose of study treatment)
- PFTs (within 21 days after the last dose of study treatment); PFTs should not be performed within 2 days after BAL
- HRCT (within 21 days after the last dose of study treatment), HRCT should not be performed within 2 days after BAL
- Completion of the Study Termination form

If a subject terminates during the follow-up period after Day 8-FU (and all Day 8-FU assessments were performed), all Day 85-FU (Day 57-FU for cohorts 4 and 5) assessments should be performed at the time of termination, if possible.

12. SCHEDULE OF EVENTS

Table 3 Schedule of Events

Tests and Evaluations	SCREENING[1]	MD Period							
	Visit 1	*Visit 2*					*Visit 3*	*Visit 4*	*Visit 5*
		Day 1-MD (Day of first Dose)					Day 2-MD	Day 3-MD	Day 5-MD
	Qualification assessments	Pre-dose	Dosing with BG00011	Post-dose					
				2 h (±10 min)	4 h (±10 min)	8 h (±10 min)	24 h (±4 h)	48 h(±4 h)	96 h(±4 h)
Informed Consent	X								
Medical History	X	X[2]							
Inclusion/Exclusion Criteria	X	X[3]							
Physical Examination	X	X					X		
Vital Signs[4]	X	X[5]		X	X	X	X	X	X
Body Weight and Height	X[6] [7]								
12-lead ECG	X								
BAL	X[8]								
Pulmonary Function Tests	X[9]								
Oxygen Saturation[10]	X	X					X		
HRCT	X[11]								
Serum Pregnancy	X[12]								
Urine Pregnancy		X[13]							
Blood Chemistry	X	X							
Hematology	X	X							
Urinalysis	X	X							
HIV, HCV, HBsAg Testing	X								
Serum for Biomarkers	X	X							
Serum for BG00011 PK	X	X				X[14]	X	X	X
Serum for anti-BG00011 Ab	X	X							
Study treatment Administration			X						
Investigator assessment of subject's respiratory status									
Monitoring of AEs		Monitor and record throughout the study[15]							
Monitoring of Concomitant Therapy	Monitor and record throughout the study[16]								

Tests and Evaluations	MD Period							
	Visit 6 *Dose 2*		*Visit 7* *Dose 3*		*Visit 8* *Dose 4*		*Visit 9* *Dose 5*	
	Day 8-MD (±1 day)		Day 15-MD (±2 days)		Day 22-MD (±2 days)		Day 29-MD (±2 days)	
	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose
Informed Consent								
Medical History								
Inclusion/Exclusion Criteria								
Physical Examination	X		X				X	
Vital Signs[4]	X[5]	X[17]	X[5]	X[17]	X[5]	X[17]	X[5]	X[17]
Body Weight and Height								
12-lead ECG			X					
BAL								
Pulmonary Function Tests							X[18]	
Oxygen Saturation[10]	X[5]		X[5]		X[5]		X[5]	
HRCT								
Serum Pregnancy								
Urine Pregnancy								
Blood Chemistry	X		X				X	
Hematology	X		X				X	
Urinalysis	X		X				X	
HIV, HCV, HBsAg Testing								
Serum for Biomarkers							X	
Serum for BG00011 PK	X		X		X		X	
Serum for anti-BG00011 Ab								
Study treatment Administration	X		X		X		X	
Investigator assessment of subject's respiratory status								
Monitoring of AEs	Monitor and record throughout the study[15]							
Monitoring of Concomitant Therapy	Monitor and record throughout the study[16]							

Tests and Evaluations	MD Period						FU Period	
	Visit 10 Dose 6		*Visit 11 Dose 7*		*Visit 12 Dose 8*		*Visit 13*	*Visit 14*
	Day 36-MD (±2 days)		Day 43-MD (±2 days)		Day 50-MD (1-FU) (±2 days)		Day 2-FU	Day 3-FU
	Pre-dose	Post-dose	Pre-dose	Post-dose	Pre-dose	Post-dose	24 h (±4 h)	48 h (±4 h)
Informed Consent								
Medical History								
Inclusion/Exclusion Criteria								
Physical Examination			X					
Vital Signs[4]	X[5]	X[17]	X[5]	X[17]	X[5]	X[19]	X	X
Body Weight and Height								
12-lead ECG								
BAL								X[20]
Pulmonary Function Tests								
Oxygen Saturation[10]	X[5]		X[5]		X[5]			X
HRCT								
Serum Pregnancy								
Urine Pregnancy								
Blood Chemistry			X					
Hematology			X					
Urinalysis			X					
HIV, HCV, HBsAg Testing								
Serum for Biomarkers					X			
Serum for BG00011 PK	X		X		X	X[14]	X	X
Serum for anti-BG00011 Ab								
Study treatment Administration	X		X		X			
Investigator assessment of subject's respiratory status								
Monitoring of AEs	Monitor and record throughout the study[15]							
Monitoring of Concomitant Therapy	Monitor and record throughout the study[16]							

Tests and Evaluations	FU Period						
	Visit 15	*Visit 16*	*Visit 17*	*Visit 18*	*Visit 19*	*Visit 20*	*Visit 21*
	Day 5-FU	Day 8-FU (or early termination)	Day 15-FU	Day 22-FU	Day 29-FU	Day 57-FU[21]	Day 85-FU (for Cohorts 1 to 3 only)
	96 h (±4 h)	(±1 day)	(±2 days)	(±2 days)	(±3 days)	(±7 days)	(±7 days)
Informed Consent							
Medical History							
Inclusion/Exclusion Criteria							
Physical Examination		X	X		X	X	X
Vital Signs[4]	X	X	X	X	X	X	X
Body Weight and Height		X				X[22]	X
12-lead ECG		X				X[22]	X
BAL		X[20]					
Pulmonary Function Tests		X[23]					
Oxygen Saturation[10]		X			X	X	X
HRCT		X[23]					
Serum Pregnancy		X				X[22]	X
Urine Pregnancy							
Blood Chemistry		X			X	X	X
Hematology		X			X	X	X
Urinalysis		X			X	X	X
HIV, HCV, HBsAg Testing							
Serum for Biomarkers		X			X	X	X
Serum for BG00011 PK	X	X	X	X	X	X	X
Serum for anti-BG00011 Ab					X	X[22]	X
Study treatment Administration							
Investigator assessment of subject's respiratory status						X[22]	
Monitoring of AEs	Monitor and record throughout the study[15]						
Monitoring of Concomitant Therapy	Monitor and record throughout the study[16]						

Ab = antibody; AE = adverse event; BAL = bronchoalveolar lavage; ECG = electrocardiogram; FU = follow-up; HBsAg = Hepatitis B surface antigen; HCV = hepatitis C antibody; HIV = human immunodeficiency virus; HRCT = high resolution computed tomography; MD = Multiple-dose; PK = pharmacokinetics

[1] Within 5 weeks for cohorts 1 to 3 and 8 weeks for cohorts 4 and 5

[2] Update medical history with any changes prior to dosing, including existing conditions.

[3] Entry criteria re-checked prior to dosing on Day 1-MD to confirm eligibility.
[4] Vital signs include blood pressure, pulse, temperature, and respiration rate. Blood pressure to be performed sitting, after at least 5 minutes rest.
[5] To be performed within 30 minutes prior to study treatment administration.
[6] Weight obtained at initial screening will be used to calculate dose throughout the study.
[7] Height will be measured at initial screening only.
[8] BAL must be performed within 5 weeks prior to the first dose.
[9] A screening PFT (before and after bronchodilator) will be performed to determine eligibility. If the subject qualifies for the study, 1 subsequent PFT, without bronchodilator administration, (may be performed on the same day prior to a BAL or at least 2 days after a BAL) will be performed during screening (up to Day 1-MD) and used for baseline values, all within 5 weeks of dosing.
[10] Using pulse oximeter, oxygen saturation will be measured after at least 5 minutes at rest. The amount of supplemental oxygen the subject is receiving, if any, should be noted.
[11] Historical HRCT scan is acceptable for determining subject eligibility; however, an HRCT is required to also be performed within 5 weeks prior to the initial dose
[12] Serum pregnancy test for females of childbearing potential. Results must be negative for inclusion into the study.
[13] Urine pregnancy test for females of childbearing potential must be performed and determined negative prior to dosing.
[14] Obtain samples at 8 h (± 10 min) after dose administration.
[15] AEs are captured after first dose of study treatment. Events prior to dosing should be entered on the Medical History CRF.
[16] All concomitant medications being taken at the time of initial screening (including medications discontinued at that time) through the termination visit are to be recorded on the CRF.
[17] To be performed at 30 ± 10 minutes post injection.
[18] To be performed on Day 29 (± 5 days) of the dosing period.
[19] To be performed at 30 ± 10 minutes post injection and 8 hours ± 10 minutes post injection.
[20] To be performed between Day 3-FU and Day 8-FU
[21] End of Study for subjects in cohorts 4 or 5.
[22] For subjects in cohorts 4 or 5 only.
[23] Must be performed within 21 days of last administration of study drug.

13. STATISTICS

The objectives of this Phase 2a study are to evaluate the safety, tolerability, PK, immunogenicity, and impact on BAL and peripheral blood biomarkers of multiple-doses of BG00011 in subjects with IPF.

13.1. Analysis Populations

All subjects who have received at least 1 dose of BG00011 or placebo will be included in the safety analyses. All subjects who received at least 1 dose of BG00011 and have a corresponding sample collected for BAL and/or blood biomarkers (e.g., Day 8-FU) will be considered for the pharmacodynamic analyses. All subjects who received study treatment will be included in the PK analyses, provided that a pre-dose and at least 1 post-dose blood sample with detectable drug concentrations were collected during the specified sampling period.

13.2. Statistical Analysis

13.2.1. Subject Accountability and Demographics

Data will be summarized and presented by dose cohort, defined as each of the BG00011 dose groups and the combined placebo group. Data will be listed by cohort.

Exposure to study treatment and reasons for discontinuation of study treatment will be tabulated by dosing cohort and study period. Demographics will be presented using descriptive statistics (i.e., mean, standard deviation, median, and range).

13.2.2. Safety Analysis

Data for BG00011 treated subjects will be grouped by dose cohort and study period. Data for all placebo subjects, regardless of dosing cohort, will be treated as 1 group.

An AE or SAE will be considered treatment-emergent (TE) if it was newly acquired or worsened during or after the administration of investigational drug. Descriptive analysis of treatment-emergent AEs (TEAEs) and treatment-emergent SAEs (TESAEs) will include the following:

- Incidence of all TEAEs, and of TESAEs.
- TEAEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1 or higher.
- TEAEs will be grouped by system organ class and preferred term.
- TEAEs will be presented by severity and relationship to study treatment (see Section 14.2).
- Individual listing of all TEAEs (including accompanying symptoms).
- Descriptive statistics will be tabulated for all TEAEs.

For each treatment group, descriptive statistics will be used to summarize and present vital signs and clinical laboratory parameters within each protocol-specified visit. Shift tables will be presented for selected laboratory parameters. Physical examination results, oxygen saturation, BAL, PFT, HRCT, and ECG parameters will be presented in listings.

13.2.3. Pharmacodynamic Analyses

Variables related to potential pharmacodynamics (i.e., biomarkers in BAL and peripheral blood) will be tabulated and presented for all BG00011 subjects within a dose cohort (or placebo). Changes from baseline in the pharmacodynamic variables will be compared among treatment groups and with the placebo group.

Peripheral blood biomarkers may include, but will not be limited to tissue remodeling markers, such as MMP-7 and OPN; TGF-β-inducible markers, such as TIMP-1 and Col1A1; and epithelial injury markers, including SP-A, and DEFA1-3. mRNA for tissue remodeling markers which may include PAI-1 and osteopontin, and protein levels for the TGF-β-inducible marker phosphorylated SMAD, will be measured in macrophages isolated from BAL. Additional biomarkers may be added prior to the initiation of analysis. The complete list of peripheral blood and BAL biomarkers will be provided in the statistical analysis plan.

13.2.4. Pharmacokinetic Analyses

Listings of individual subject serum BG00011 concentrations, actual blood sampling times, and PK parameters as well as graphs of concentration vs. time will be prepared by dosing cohort. Serum concentrations and PK parameters will be summarized through descriptive statistics and compared among dosing cohorts (and to placebo) using mixed effects models. Dose proportionality will be assessed following log-transformation, and dose normalized AUC and C_{max} will be analyzed using mixed modeling. Exposure-response relationships will be evaluated post-hoc and as applicable, for both safety and pharmacodynamics, to assist with determining the appropriate dosing regimen for BG00011 in this clinical setting.

13.2.5. Immunogenicity Analyses

The incidence of antibodies to BG00011 will be tabulated for each subject by treatment group and dose cohort using descriptive statistics. A test for trend will be conducted to assess the relationship between dose level and incidence. The antibody titer and natural-log transformed results will be summarized and presented using descriptive statistics. Samples that test positive for antibodies to BG00011 will be further assessed to determine if these antibodies are neutralizing. The effect of anti-BG00011 antibodies on PK parameters will also be explored.

13.3. Determination of Sample Size

No formal statistical justification for the sample size was performed for this Phase 2a study. Cohort size was determined based on requirements for PK analyses and safety assessments. With 6 subjects per cohort administered BG00011 the probability of observing an event is 82% if the actual probability of such an event is 25%.

13.4. Interim Analysis

An administrative interim analysis may be performed on all subject data up to and including the Day 8-FU visit for the last subject in cohort 4. The interim analysis will provide safety, PK, and PD information to aid in internal (Biogen MA Inc.) decision-making only and will not affect the study design of the current protocol.

14. ADVERSE EVENTS

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 must be given the names and telephone numbers of study site staff for reporting of AEs and medical emergencies.

14.1. Adverse Event Definitions

14.1.1. Serious Pretreatment Event

A serious pretreatment event is any event that meets the criteria for SAE reporting (as defined in Section 14.1.3) and occurs after the subject signs the ICF, but before administration of study treatment.

14.1.2. 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 meets the definition of an AE will be made by the Investigator. The following laboratory abnormalities should be captured as AEs:

- Any laboratory test result that meets the criteria for an SAE (Section 14.1.3).
- Any laboratory test result that requires the subject to receive specific corrective therapy.
- Any laboratory abnormality that the Investigator considers to be clinically significant.

14.1.3. 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, or
- results in a congenital anomaly/birth defect.

An SAE may also be any other medically important event 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.)

14.2. Adverse Event Classification

Relationship to Investigational Drug

The following classifications should be used when evaluating the relationship of AEs and SAEs to the investigational drug.

None:	No relationship between the experience and the administration of study treatment; related to other etiologies such as concomitant medications or subject's clinical state.
Unlikely:	The current state of knowledge indicates that a relationship is unlikely.
Possible:	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment. The reaction might have been produced by the subject's clinical state or other modes of therapy administered to the subject, but this is not known for sure.
Probable:	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment. The reaction cannot be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject.
Definite:	A reaction that follows a plausible temporal sequence from administration of the study treatment and follows a known response pattern to the suspected study treatment and can be confirmed with a positive re-challenge test or supporting laboratory data.

Severity

Mild:	Awareness of sign or symptom, but easily tolerated
Moderate:	Discomfort enough to cause interference with normal daily activities
Severe:	Inability to perform normal daily activities
Life-threatening:	Immediate risk of death from the reaction as it occurred

14.3. Documentation and Reporting of Adverse Events by Investigator

Subjects will be evaluated and questioned generally to identify AEs during the course of the study. All AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures will be recorded on the appropriate CRF for that visit. In all instances, the

Investigator should follow subjects until the outcome of the AE is known, until it is considered to be chronic or stable, or until it is no longer considered clinically significant. AEs will be reported and followed only through the subject's final study visit.

Events occurring after administration of the first dose of study treatment will be reported on the AE CRF. Any events occurring prior to dosing will be reported on the Medical History CRF. Any post-dosing clinically relevant deterioration in laboratory assessments or other clinical findings is considered an AE and must be recorded on the AE Form. AE information recorded on AE forms will be entered into the database on an ongoing basis.

For SAEs, a SAE form must also be completed with as much information as possible and submitted in the time frame described in Section 14.4. SAEs must be reported from the signing of the ICF through the Final Safety Visit. When new significant information is obtained as well as when the outcome of an event is known, the Investigator should record the information on a new SAE form. If the subject was hospitalized, a copy of the discharge summary, as well as any other relevant hospital records, must be included as part of the subject medical file.

14.4. Notification of Serious Adverse Events

Investigator Reporting to Sponsor

All SAEs (including deaths) that occur from signing of the ICF through the Final Safety Visit must be reported by the Investigator to [redacted] by faxing the SAE form within 24 hours from the point in time when the Investigator becomes aware of the SAE. Investigators must report to [redacted] any SAE, whether or not considered drug related, including those listed in the protocol or Investigator Brochure. The report must include an assessment of whether there is a reasonable possibility that the drug caused the event.

SAE Reporting Contact Information

[redacted]
DSS Hotline No.: [redacted]
DSS Fax No.: [redacted]

14.4.1. Expectedness of Events

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

14.4.2. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen MA Inc. to be related to the study treatment administered. Biogen MA Inc. or designee will report SUSARs and other applicable SAEs to the appropriate regulatory authorities, central institutional review boards (IRBs)/ECs and Investigators as required, according to local law.

15. PROCEDURES FOR HANDLING SPECIAL CIRCUMSTANCES

15.1. 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 (or designee) should contact the [redacted] 24-hour emergency medical support number ([redacted])

15.2. Emergency Contact

In the event of a medical emergency (i.e., an event that requires immediate attention regarding the treatment of a subject, operation of the clinical study, and/or the use of investigational drug), investigational site personnel must immediately contact the Medical Monitor by phone, followed by details in a fax or e-mail. Full contact information for the Medical Monitor may be found in the Study Reference Manual.

15.3. Emergency Identification of Study treatment

In the event of a medical emergency, when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator or designee may open the code-break envelope of the subject experiencing the emergency. However, prior to unblinding, the Investigator should attempt to contact the Medical Monitor.

If unblinding is necessary, the Investigator must document the reasons for unblinding in the subject's source documents, but should not divulge the subject's treatment assignment to any individuals except the Medical Monitor and those individuals involved in the direct medical care of the subject. The date and the reasons for breaking the blind must be submitted to Biogen MA Inc. within 24 hours. Any opened envelopes will be returned to the secure location.

If a subject's treatment assignment is unblinded, the subject should remain in the study and continue the protocol-specified dosing schedule and follow-up evaluations, unless the reason for unblinding indicates otherwise.

Biogen MA Inc. reserves the right to review the unblinded data if required for the safe and proper treatment of a subject, or if the severity of an AE if drug-related, would lead to early termination of the study.

15.4. Pregnancy

Female subjects should not become pregnant during the study. The Investigator must report any pregnancy, occurring in a female subject from the first dose of study treatment to 12 weeks post last dose, to [redacted] (DSS Fax No.: [redacted]) within 24 hours of the study site staff becoming aware of the pregnancy. All subsequent injections of the study treatment will be stopped and the subject will enter the standard FU period. The Investigator or study site staff must follow the pregnancy until outcome and report the outcome to [redacted]. Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.5. Procedure for Death

Deaths must be reported to [redacted] by fax using the SAE form within 24 hours of the investigational site's awareness of the event. The appropriate CRF must be completed. Investigators are requested to send death certificates and autopsy reports to [redacted] per the SAE reporting procedures described in Section 14.4.

If a subject's treatment assignment is unblinded for a medical emergency that ultimately leads to death, the Investigator must also document the reason for unblinding in the subject's CRF.

16. ETHICS

16.1. Institutional Review Board or Independent Ethics Committee

This protocol will be reviewed and approved by the IRB where the study is conducted. The IRB will meet all Food and Drug Administration (FDA) requirements governing IRBs (Code of Federal Regulations, Title 21, Part 56).

16.2. Ethical Conduct of the Study

Biogen MA Inc., the Medical Monitor, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and in the applicable ICH and GCP guidelines, and must also conduct the study in accordance with local regulations.

16.3. Subject Information

16.3.1. Informed Consent

Informed written consent is required from each subject prior to any testing under this protocol, including screening tests and evaluations. The ICF, as specified by the clinical site's IRB, must follow the Protection of Human Subjects regulations listed in the Code of Federal Regulations, Title 21, Part 50.

The background of the proposed study and the benefits and risks of the procedures and study must be explained to the subjects. It is the responsibility of the Investigator to obtain consent and to provide the subject with a copy of the signed and dated ICF. Confirmation of a subject's informed consent must also be documented in the subject's medical record prior to any testing under this protocol, including screening tests and evaluations.

All ICFs used in this study must be approved by the appropriate IRB and by Biogen MA Inc. or its designee. The ICF must not be altered without the prior agreement of the relevant IRB and Biogen MA Inc. or its designee.

16.3.2. Subject Data Protection

Prior to any testing under this protocol, including screening tests and evaluations, subjects must authorize the release and use of PHI, as required by local law.

The subject will not be identified by name in the CRF or in any study reports. These reports will be used for research purposes only. Biogen MA Inc., its designee, and various government health agencies may inspect the records of this study. Every reasonable effort will be made to keep the subject's personal medical data confidential.

17. STUDY ADMINISTRATION

17.1. Investigator Responsibilities

The Investigator's responsibilities include the following:

- Monitor and record all AEs, which include SAEs occurring any time during the study after signing of the ICF, 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 and follow-up on the outcome of the pregnancy and status of the infant.
- Complete an SAE form for each SAE and fax it to [redacted] within 24 hours of the Investigator becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to [redacted] within 24 hours of the Investigator becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Notify the IRB of any unexpected SAEs involving risks to human subjects. Copies of appropriate IRB documentation should be retained for the site and Sponsor study files.

17.2. Biogen Responsibilities

The Sponsor's (or its designee's) responsibilities include the following:

- Before study site activation and subject enrollment, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AEs and SAEs, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.
- Biogen MA Inc. (or designee) is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.
- Biogen MA Inc. (or designee) is responsible for forwarding copies of documents that are submitted to regulatory authorities to the Investigators for submission to the local IRB, if applicable, and for inclusion in the study site files.

17.3. Data Quality Control and Quality Assurance

The Clinical Monitor will arrange to visit the Investigators at regular intervals during the study. The monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, quality of data, drug accountability, compliance with regulatory

requirements, and continued adequacy of the investigational site and its facilities. During these visits, CRFs and other data related to the study will be reviewed and any discrepancies or omissions will be resolved. The Clinical Monitor will be given access to study-relevant source documents (including medical records) for purposes of source data verification.

During and/or after completion of the study, quality assurance officers named by Biogen MA Inc. or the regulatory authorities may wish to perform on-site audits. The Investigator is expected to cooperate with any audit and provide assistance and documentation (including source data) as requested.

17.4. Case Report Form Completion

It is the Investigator's responsibility to ensure the accuracy, completeness, legibility, and timeliness of the data reported in the subject's CRF. Source documentation supporting the CRF data should indicate the subject's participation in the study and should document the dates and details of study procedures, AEs, and subject status.

The Investigator will maintain copies (paper or electronic) of the CRFs at the study site. Subjects who discontinue or terminate from the study, the CRFs will be completed as much as possible, and the reason for the discontinuance or termination clearly and concisely specified on the appropriate CRF.

17.5. Retention of Study Records

The Investigator will maintain all study records according to ICH-GCP and applicable regulatory requirements. Records will be retained for at least 2 years after the last marketing application approval or 2 years after formal discontinuation of the clinical development of the investigational product or according to applicable regulatory requirements. If the Investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility. Biogen MA Inc. must be notified in writing if a custodial change occurs.

17.6. Confidentiality

To maintain subject privacy, all CRFs, study treatment accountability records, study reports and communications will identify the subject by the assigned subject number. The Investigator will grant monitor(s) and auditor(s) from the Sponsor or its designee and regulatory authority(ies) access to the subject's original medical records for verification of data gathered on the CRFs and to audit the data collection process. The subject's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

All information regarding the investigational product supplied by the Sponsor to the Investigator is privileged and confidential information and shall remain the sole property of Biogen MA Inc. The Investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from the Sponsor. The Investigator agrees not to disclose Biogen's confidential information to anyone except to people involved in the study that need such information to assist in conducting the study, and then only on like terms of confidentiality and nonuse. It is understood that there is an obligation to provide the Sponsor with complete test

results and all data developed in the study. The information obtained from the clinical study will be used towards the development of the investigational product and may be disclosed to regulatory authority(ies), other Investigators, corporate partners, or consultants as required.

17.7. Publication Policy

The Sponsor, Biogen MA Inc., has no objection to publication or public disclosure for non-commercial purposes by Institution or Investigator of the study data in accordance with this section. The parties recognize that because this is a multi-center study, there is a need for a coordinated approach to any publication or publicizing of the study data or results of this study. In this regard, there will be no publication or publicizing of study data or results prior to the multi-center publication. Authorship of the multi-center publication will be based on contribution to the design, conduct, or analysis of the study. Therefore, Institution and Investigator agree not to publish or present the study data or results on an individual basis, until after the first to occur of: (a) publication of the multi-center publication, (b) notification from Sponsor or Sponsor's designee that a multi-center publication is no longer planned, or (c) 18 months after completion of the study at all sites. After completion of the study, and subject to the provisions of this section, the Institution and Investigator shall be free to publish or present the study data or results. The Institution or Investigator will submit any proposed manuscript or publication to the Sponsor for comment at least 30 days prior to its release of that manuscript or publication or at least 14 days prior to submission for abstracts or presentations ("Review Period"). The Institution or Investigator will make every reasonable attempt to incorporate comments received from the Sponsor, and will upon request remove any previously undisclosed Confidential Information, prior to publication or disclosure. If during the Review Period, Sponsor notifies the Institution or Investigator that it desires patent applications to be filed on any Invention disclosed or contained in the disclosures, the Institution and Investigator will defer publication or other disclosure for a period, not to exceed an additional 90 days, sufficient to permit Sponsor or its designee to file or have filed any desired patent applications.

17.8. Direct Access to Source Data

The Investigator and clinical sites will permit trial-related monitoring, audits, IRB review, and regulatory inspections as requested by FDA or other regulatory authorities, Biogen, or Biogen's designee, including direct access to source data/documents (i.e., original medical records, laboratory reports, hospital documents, progress reports, signed ICF, etc.) in addition to CRFs.

17.9. Protocol Amendments

All protocol amendments must be approved by the IRB and submitted to the appropriate regulatory authorities before implementation of such modifications to the study.

In the event that the protocol needs to be modified immediately to eliminate an apparent hazard to a subject, Biogen MA Inc. will amend and implement the protocol change and subsequently notify the regulatory authorities and/or the IRB, as appropriate. Most such instances that require immediate action for an individual subject will be handled by a protocol deviation or waiver.

18. REFERENCES

Adamali HI, Maher TM. Current and novel drug therapies for idiopathic pulmonary fibrosis. Drug Des Devel Ther. 2012;6:261-72.

American Thoracic Society/European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med. 2002;165(2):277-304.

Bartram U, Speer CP. The role of transforming growth factor beta in lung development and disease. Chest. 2004;125(2):754-65.

Border WA, Noble NA. Transforming growth factor beta in tissue fibrosis. N Engl J Med. 1994;331(19):1286-92.

Breuss JM, Gallo J, DeLisser HM, et al. Expression of the beta 6 integrin subunit in development, neoplasia and tissue repair suggests a role in epithelial remodeling. J Cell Sci. 1995;108 (Pt 6):2241-51.

Breuss JM, Gillett N, Lu L, et al. Restricted distribution of integrin beta 6 mRNA in primate epithelial tissues. J Histochem Cytochem. 1993;41(10):1521-7.

Broekelmann TJ, Limper AH, Colby TV, et al. Transforming growth factor beta 1 is present at sites of extracellular matrix gene expression in human pulmonary fibrosis. Proc Natl Acad Sci U S A. 1991;88(15):6642-6.

Greene KE, King TE, Kuroki Y, et al. Serum surfactant proteins-A and -D as biomarkers in idiopathic pulmonary fibrosis. Eur Respir J. 2002;19(3):439-46.

Hahm K, Lukashev ME, Luo Y, et al. Alphav beta6 integrin regulates renal fibrosis and inflammation in Alport mouse. Am J Pathol. 2007;170(1):110-25.

Häkkinen L, Hildebrand HC, Berndt A, et al. Immunolocalization of tenascin-C, alpha9 integrin subunit, and alphavbeta6 integrin during wound healing in human oral mucosa. J Histochem Cytochem. 2000;48(7):985-98.

Horan GS, Wood S, Ona V, et al. Partial inhibition of integrin alpha(v)beta6 prevents pulmonary fibrosis without exacerbating inflammation. Am J Respir Crit Care Med. 2008;177(1):56-65.

Jensen RL, Teeter JG, England RD, et al. Sources of long-term variability in measurements of lung function: implications for interpretation and clinical trial design. Chest. 2007a;132(2):396-402.

Jensen RL, Teeter JG, England RD, et al. Instrument accuracy and reproducibility in measurements of pulmonary function. Chest. 2007b;132(2):388-95.

Khalil N, O'Connor RN, Flanders KC, et al. TGF-beta 1, but not TGF-beta 2 or TGF-beta 3, is differentially present in epithelial cells of advanced pulmonary fibrosis: an immunohistochemical study. Am J Respir Cell Mol Biol. 1996;14(2):131-8.

King TE, Pardo A, Selman M. Idiopathic pulmonary fibrosis. Lancet. 2011;378(9807):1949-61.

Kuwano K, Maeyama T, Inoshima I, et al. Increased circulating levels of soluble Fas ligand are correlated with disease activity in patients with fibrosing lung diseases. Respirology. 2002;7(1):15-21.

Ludlow A, Yee KO, Lipman R, et al. Characterization of integrin beta6 and thrombospondin-1 double-null mice. J Cell Mol Med. 2005;9(2):421-37.

Ma LJ, Yang H, Gaspert A, et al. Transforming growth factor-beta-dependent and -independent pathways of induction of tubulointerstitial fibrosis in beta6(-/-) mice. Am J Pathol. 2003;163(4):1261-73.

Morris DG, Huang X, Kaminski N, et al. Loss of integrin alpha(v)beta6-mediated TGF-beta activation causes Mmp12-dependent emphysema. Nature. 2003;422(6928):169-73.

Mukae H, Iiboshi H, Nakazato M, et al. Raised plasma concentrations of alpha-defensins in patients with idiopathic pulmonary fibrosis. Thorax. 2002;57(7):623-8.

Munger JS, Huang X, Kawakatsu H, et al. The integrin alpha v beta 6 binds and activates latent TGF beta 1: a mechanism for regulating pulmonary inflammation and fibrosis. Cell. 1999;96(3):319-28.

Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-68.

Pittet JF, Griffiths MJ, Geiser T, et al. TGF-beta is a critical mediator of acute lung injury. J Clin Invest. 2001;107(12):1537-44.

Puthawala K, Hadjiangelis N, Jacoby SC, et al. Inhibition of integrin alpha(v)beta6, an activator of latent transforming growth factor-beta, prevents radiation-induced lung fibrosis. Am J Respir Crit Care Med. 2008;177(1):82-90.

Raghu G, Brown KK, Bradford WZ, et al. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2004;350(2):125-33.

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

Rosas IO, Richards TJ, Konishi K, et al. MMP1 and MMP7 as potential peripheral blood biomarkers in idiopathic pulmonary fibrosis. PLoS Med. 2008;5(4):e93.

Sheppard D. Functions of pulmonary epithelial integrins: from development to disease. Physiol Rev. 2003;83(3):673-86.

Shihab FS, Yamamoto T, Nast CC, et al. Transforming growth factor-beta and matrix protein expression in acute and chronic rejection of human renal allografts. J Am Soc Nephrol. 1995;6(2):286-94.

Trevillian P, Paul H, Millar E, et al. alpha(v)beta(6) Integrin expression in diseased and transplanted kidneys. Kidney Int. 2004;66(4):1423-33.

Yamamoto T, Nakamura T, Noble NA, et al. Expression of transforming growth factor beta is elevated in human and experimental diabetic nephropathy. Proc Natl Acad Sci U S A. 1993;90(5):1814-8.

Yamamoto T, Noble NA, Cohen AH, et al. Expression of transforming growth factor-beta isoforms in human glomerular diseases. Kidney Int. 1996;49(2):461-9.

Yokoyama A, Kohno N, Hamada H, et al. Circulating KL-6 predicts the outcome of rapidly progressive idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1680-4.

Zambruno G, Marchisio PC, Marconi A, et al. Transforming growth factor-beta 1 modulates beta 1 and beta 5 integrin receptors and induces the de novo expression of the alpha v beta 6 heterodimer in normal human keratinocytes: implications for wound healing. J Cell Biol. 1995;129(3):853-65.

19. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Randomized, Double-Blind, Placebo-Controlled, Multiple Dose, Dose-Escalation Study of BG00011 in Patients with Idiopathic Pulmonary Fibrosis (IPF)" and agree to conduct the study according to the protocol and the International Conference on Harmonisation (ICH) guidelines and Good Clinical Practice (GCP) regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

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Investigator's Signature Date

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Investigator's Name (Print)

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Study Site (Print)