STATISTICAL ANALYSIS PLAN

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

Statistical Analysis Plan Status: Final V2.0
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Study Drug: BG00011

Sponsor Reference: 203PF201(Formerly STX-003)
[redacted]

Clinical Phase 2a

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1. STATISTICAL ANALYSIS PLAN APPROVAL SIGNATURES

By signing this page when the Statistical Analysis Plan (SAP) is considered final, the signatories agree to the statistical analyses to be performed for this study, and to the basic format of the tables, figures, and listings (TFLs).

[redacted] approval:

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[redacted], MD (SMT Physician)	**Date**
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3. ABBREVIATIONS

Abbreviations pertain to the SAP only (not the TFLs).

αvβ6	alpha v beta 6
AE	adverse event
ALAT	Latin American Thoracic Association
ALOX5	arachidonate 5-lipoxygenase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
BAL	bronchoalveolar lavage
BUN	blood urea nitrogen
CBC	complete blood count
CSR	clinical study report
CV	coefficient of variation
DL_{co}/Hb	carbon monoxide diffusion capacity, corrected for hemoglobin
DSMB	Data Safety Monitoring Board
ECG	electrocardiogram
ERS	European Respiratory Society
ETS1	v-ets erythroblastosis virus E26 oncogene homolog 1
FEV_1	a ratio of the forced expiratory volume in one second
FN1	fibronectin
FU	follow-up
FVC	forced vital capacity
GGT	gamma-glutamyl transpeptidase
HCO_3	bicarbonate
HRCT	high resolution computed tomography
ICH	International Conference on Harmonization
I/E	inclusion/exclusion

IPF	idiopathic pulmonary fibrosis
JRS	Japanese Respiratory Society
LDH	lactate dehydrogenase
LDL	low density lipoprotein
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MD	multiple dose
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NA	not applicable
OLR1	oxidized low density lipoprotein receptor 1
O_2	oxygen
PAI-1	plasminogen activator inhibitor-1 (SERPINE1)
PFT	pulmonary function test
PK	pharmacokinetic
pSMAD2	phosphorylated SMAD2
PT	preferred term
RV	residual volume
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
SD	standard deviation
SE	standard error
SLB	surgical lung biopsy
SOC	system organ class
SOP	Standard Operating Procedure
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
TFLs	Tables, Figures, and Listings
TGF-β	transforming growth factor-beta
TGM2	transglutaminase 2

TREM1	triggering receptor expressed on myeloid cells 1
tSMAD2	total SMAD2
UIP	usual interstitial pneumonia

4. INTRODUCTION

The intent of this document is to provide guidance for analyses of data for this Phase 2a study. This statistical analysis plan (SAP) has been developed after review of the Clinical Study Protocol 203PF201 (version 4 dated 16 July 2015).

This SAP describes the planned analyses to evaluate the safety, tolerability, pharmacokinetics (PK), immunogenicity, and impact on bronchoalveolar lavage (BAL) and peripheral blood biomarkers of multiple doses of STX-100 (BG00011) in subjects with idiopathic pulmonary fibrosis (IPF). Please note that study drug names STX-100 and BG00011 are equivalent, and the study drug will be referred to as BG00011 in the SAP and associated tables, figures, and listings (TFLs). A detailed description of the planned TFLs to be presented in the clinical study report (CSR) is provided in the accompanying TFL shell document. This SAP must be finalised prior to the lock of the clinical database and unblinding for this study. When the SAP and TFL shells are agreed upon and finalized, they will serve as the template for this study's CSR.

This version 2.0 SAP supersedes the statistical considerations identified in the protocol and the statistical considerations identified in the version 1.0 SAP dated 06 March 2012; where considerations are substantially different, they will be so identified. If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified in the CSR. Any substantial deviations from this SAP will be agreed upon between Biogen MA Inc. and [redacted] and identified in the CSR.

This SAP is written with consideration of the recommendations outlined in the International Conference on Harmonization (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials[1] and the ICH E3 Guideline entitled Guidance for Industry: Structure and Content of Clinical Study Reports[2].

5. STUDY OBJECTIVES

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) in subjects with IPF

Secondary Objectives:

- To estimate the 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 BAL and peripheral blood in subjects with IPF

6. 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 activity in subjects with IPF conducted at approximately 15 centers in North America.

Approximately 40 subjects will be enrolled into 5 sequential ascending dose cohorts (Table 1). Cohorts will include 8 subjects randomized to receive either BG00011 (6 subjects) or placebo (2 subjects). Additional subjects may be enrolled if deemed appropriate by the Data Safety Monitoring Board (DSMB). Doses to be administered are as follows:

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

Each subject within a dose cohort will be randomized to receive either BG00011 or placebo and will participate in 2 consecutive study periods: 1) each subject will receive 8 consecutive weekly doses of BG00011 (or placebo) (Period 1; Multiple Dose [MD] phase); and, 2) each subject will be monitored for 12 weeks (8 weeks for Cohorts 4 and 5) following administration of the last dose of study drug (Period 2; Follow-Up [FU] Phase).

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).

7. TREATMENT

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 study. At the end of a screening period, eligible subjects will return for dosing on Day 1-MD. Study drug 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 of the multiple-doseperiod.

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.

8. SAMPLE SIZE JUSTIFICATION

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%.

9. DEFINITION OF ANALYSIS POPULATIONS

The "Safety" population will consist of all subjects who received at least one dose of BG00011 or placebo.

The "Pharmacodynamic" population will consist of all subjects who received at least 1 multiple dose injection of BG00011 and have a corresponding sample collected for BAL and/or blood biomarkers (e.g., Visit 16 Day 8-FU).

All protocol deviations that occur during the study will be considered for their severity/impact prior to treatment assignment unblinding and will be taken into consideration when subjects are assigned to analysis populations. Details of subject assignment to the analysis populations will be listed.

10. STATISTICAL METHODOLOGY

10.1 General

Data listings will be provided by treatment group, subject and visit, if applicable. Summary statistics and statistical analyses will only be presented for data where detailed in this SAP. For continuous data, summary statistics will include the arithmetic mean, arithmetic standard deviation (SD), median, minimum (Min), maximum (Max) and n; for log-normal data the geometric mean and geometric coefficient of variation (CV) will also be presented. For categorical data, frequency count and percentages will be presented. Data listings will be provided for all subjects up to the point of withdrawal, with any subjects excluded from the relevant population highlighted. Summary statistics and statistical analyses will generally only be performed for subjects included in the relevant analysis population. For the calculation of summary statistics and statistical analysis, unrounded data will be used.

Due to the small number of subjects expected to enroll at each participating center, all summaries and analyses will be performed using data pooled across centers. Data for BG00011 treated subjects will be grouped by treatment group. Data for all placebo subjects, regardless of treatment group, will be treated as one group. Data will be summarized and presented by treatment group, defined as each of the BG00011 dose groups and the combined placebo group. Data will be listed by treatment group. Exposure to study medication will be tabulated by treatment group.

Mean change from baseline is the mean of all individual subject's change from their baseline value. Each individual change from baseline will be calculated by subtracting the individual subject's baseline value from the value at their subsequent visit(s). The individual subject's change from baseline values will be used to calculate the mean change from baseline using a SAS® procedure such as Proc Univariate.

Data analyses will be performed using SAS® Version 9.1.3 or greater.

As previously stated (Section 4), this document describes the planned analyses for this Phase 2a study evaluating the safety, tolerability, PK, immunogenicity, and impact on BAL and peripheral blood biomarker of multiple doses of BG00011 in subjects with IPF. Some of the analyses described in this SAP will be performed by outside vendors. These data will be imported to the Biometrics database for study 203PF201 or, alternatively, provided as separate reports.

10.2 Definitions

The following definitions apply:

Baseline - last observation collected prior to the date/time of study drug administration, unless otherwise noted.

Treatment group - each of the five BG00011 dose groups and the combined placebo group.

10.3 Demographics and Baseline Characteristics

Subject disposition will be summarized for the safety and efficacy populations. Reasons for discontinuation will be summarized by treatment group. The demographic variables age, sex, race, ethnicity, body weight, height, and body mass index will be summarized. By-subject listings of these variables will be provided.

Listings will also be created for subject eligibility, smoking history, and general/IPF-specific medical history.

10.4 Prior and Concomitant Medications

Prior and concomitant medications will be listed in the by-subject data listings. WHODRUG Version March 2011 or higher will be used to encode these medications.

10.5 Protocol Deviations

Protocol deviations will be listed.

10.6 Study Medication Administration

Study medication administration will be listed and the frequency of subjects who were administered treatment at each of the 8 visits will be summarized.

10.7 Pharmacokinetic Assessment

The date and time of pharmacokinetic (PK) blood sample collections by treatment group and by subject will be listed. The analysis of PK data will be described in a separate PK analysis plan and provided in a separate report.

10.8 Safety and Tolerability Assessments

Data will be summarized and presented by treatment group, defined as each of the BG00011 dose groups, the combined BG00011 group, and the combined placebo group. Data will be listed by treatment group. The safety population will be used for the following safety analyses. No inferential statistical analyses are planned.

10.8.1 Adverse Events

Adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 14.0 or later). Summary tables will be based on treatment emergent AEs (TEAE). A TEAE is defined as an AE that occurs during or after first dose or which is present prior to study drug administration and becomes more severe during or after first dose. Any event occurring prior to the first dose of study medication will be recorded as medical history. Related events are those classified as Possible, Probable, or Definite by the investigator. All AE analyses will be performed on TEAEs. All TEAEs will be listed by subject.

The following will be summarized and presented for each treatment group:

- The total number of TEAEs for each treatment group overall, by highest severity, by strongest causal relationship to study medication, the frequency of adverse events, the number of subjects with treatment emergent serious adverse events (TESAEs), and the number of subjects with TEAEs leading to study discontinuation;
- The number and percentage of subjects experiencing a TEAE for each system organ class (SOC) and each preferred term (PT) within each SOC;
- The number and percentage of subjects experiencing a TEAE for each preferred term (PT) in descending frequency;
- The number and percentage of subjects experiencing a TEAE by greatest severity for each system organ class (SOC) and each preferred term (PT) within each SOC;
- The number and percentage of subjects experiencing a related TEAE for each system organ class (SOC) and each preferred term (PT) within each SOC;
- A listing of subjects experiencing a TESAE;
- A listing of subjects experiencing a TEAE leading to withdrawal; and
- A listing of subject deaths occurring on study and relatedness to TEAE.

The incidence of TEAEs will be calculated by dividing the number of subjects who have experienced the event by the number of subjects in the treatment group. Thus, the incidence of TEAEs counts only the first occurrence of an event for each subject in that treatment group that experiences the event, and does not represent the total number of episodes of the particular event in the treatment group. If a subject has repeated episodes of a particular TEAE, only the most severe episode or the episode with the strongest causal relationship to study medication, as appropriate, will be counted.

A subject with more than one TEAE for a particular PT will be counted only once in the total of subjects experiencing TEAEs in that particular PT. Likewise, a subject with more than one type of TEAE in a particular SOC will be counted only once in the total of subjects experiencing

TEAEs in that particular SOC. Similarly, a subject who has experienced a TEAE in more than one SOC will be counted only once in the total number of subjects experiencing TEAEs in all SOCs.

All occurrences of all TEAEs will be listed for each subject. In the listing of individual subjects who have TEAEs, the following information on each episode will be provided: verbatim term, PT, SOC, severity of the event, relationship to study medication, onset date, resolution date, treatment given to treat the adverse event, the outcome, and whether the event was a TESAE.

A listing of any subject deaths occurring on study will be provided. Deaths on study are those which occur after randomization but prior to early discontinuation or completion of study.

10.8.2 Clinical Laboratory Parameters

Serum chemistry and hematology data will be summarized by treatment group and visit. Descriptive statistics will be presented at each visit by treatment group for the parameters listed below. Shift tables of the baseline value compared to each post baseline value will be presented for the following selected laboratory parameters: a) alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, direct bilirubin, glucose, and cholesterol for chemistry; and b) hemoglobin, hematocrit, white blood cell (WBC) count, neutrophil count, lymphocyte count, and platelet count for hematology. Urinalysis data and pregnancy data will be listed only. In addition, all serum chemistry, hematology and urinalysis data outside the central laboratory standard reference ranges will be listed by parameter and treatment group.

Individual subject listings of clinical laboratory parameters at each visit will be provided. Values for any serum chemistry, hematology, and urinalysis values outside the central laboratory reference ranges will be flagged on the individual subject data listings.

The following laboratory safety assessments will be included in the subject listings:

- Hematology: complete blood count (CBC) with differential and platelet counts. CBC includes red blood cells (RBCs), WBCs, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC)

- Serum chemistry: albumin, alkaline phosphatase, ALT, AST, BUN, calcium, chloride, bicarbonate (HCO_3), creatinine, direct bilirubin, gamma-glutamyl transpeptidase (GGT), glucose, lactate dehydrogenase (LDH), magnesium, phosphorus, potassium, sodium, 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

10.8.3 Vital Signs

Descriptive statistics will be used to summarize and present vital sign measurements at each nominal timepoint for each treatment group. Individual subject listings of vital signs at each timepoint will also be provided by treatment group.

10.8.4 Electrocardiogram (ECG)

The ECG data will be obtained directly from the 12-lead ECG traces. These data include the PR interval, QTcB interval, QRS duration, and heart rate. The ECG data will be listed by subject. Descriptive statistics will be used to summarize ECG measurements at each visit for each treatment group. In addition, a shift table of ECG interpretation results will be presented at each visit by treatment group. Individual subject listings of ECG parameters at each timepoint will also be provided by treatment group.

10.8.5 Physical Examination

Individual subject listings of physical examination results will be provided by treatment group.

10.8.6 Pulmonary Function Tests (PFT)

Under Protocol Version 1, for screening and baseline PFTs, 3 PFTs will be performed on separate days during the screening period (within 5 weeks prior to dosing). The first of these tests will be performed before and after bronchodilator administration to determine if the subject qualifies for the study, whereas the other 2 will be averaged to serve as the subject's baseline value.

Under Protocol Version 2 and later, for screening and baseline PFTs, 2 PFTs will be performed on separate days during the screening period (within 5 weeks prior to dosing). The first of these tests will be performed before and after bronchodilator administration to determine if the subject qualifies for the study, whereas the other PFT (performed without bronchodilator administration) will serve as the subject's baseline value. If the baseline PFT does not meet quality criteria, the pre-bronchodilator screening PFT (or repeat pre-bronchodilator screening PFT, if appropriate) will be substituted as the baseline value.

PFT parameters include:

FVC: forced (expiratory) vital capacity

FEV_1: forced expiratory volume over one second

TLC: total lung capacity

DLco/Hb: carbon monoxide diffusion capacity, corrected for hemoglobin

RV: residual volume

The assessment of changes in lung function during this study will be performed by comparing the subject's follow-up PFT parameters (i.e., Visit 9 Day 29-MD and Visit 16 Day 8-FU visits) to

their baseline value. Each subject's percent change from baseline will be calculated by subtracting the individual subject's baseline value from the value at the desired time point and then dividing this calculated value by the individual subject's baseline value and multiplying by 100. The individual subject's percent change from the baseline value will be used to calculate the mean percent change from baseline for the treatment group using a SAS procedure such as Proc Univariate.

The following decreases in PFT parameters have been prospectively defined as significant and may be clinically important: TLC ≥ 8%, FEV_1 ≥ 12%, FVC ≥ 12%, and/or DLco/Hb ≥ 15% change from the baseline value. PFTs demonstrating a potentially clinically significant decline from baseline must be confirmed by repeating the abnormal parameter. A confirmed decline in a PFT parameter will be reported as an adverse event and will be used for analysis purposes.

Listings of individual subject data by study visit and treatment assignment will be provided for each of the PFT parameters as well as the percent change from baseline. Summary statistics of the PFT parameters will be provided by treatment group for the actual PFT value and the percent predicted for each of the PFT parameters specified above (reference populations are NHANES III for Spirometry and Crapo 1982 for DL_{co}/Hb [3,4]).

10.8.7 Bronchoalveolar Lavage (BAL) MMP-12

A BAL will be performed during the screening period and after receiving the last dose of study medication (i.e., from Visit 14 Day 3-FU to Visit 16 Day 8-FU). Analysis of the BAL macrophage MMP-12 mRNA levels (which are increased when macrophages are activated) will be measured.

Subject listings of the screening and Visit 16 Day 8-FU MMP-12 levels, as well as the % change from screening, will be provided. Summary statistics of the relative expression of MMP-12 levels at screening and following the last dose of study medication, as well as the percent change from Screening, will also be provided for each treatment group.

10.8.8 High Resolution Computed Tomography (HRCT)

The diagnostic criteria for IPF in study 203PF201 are based on the recently updated evidence-based guidelines developed by the ATS/ERS/JRS/ALAT joint task force for the diagnosis and management of IPF[5]. An HRCT scan will be performed during screening to establish subject eligibility as well as the pre-dosing pattern and extent of disease. Each subject will have a repeat HRCT performed within 21 days after receiving the last dose of study medication to assess for changes in the extent of IPF. The details of the independent HRCT and surgical lung biopsy (SLB) assessments are described in the Perceptive Informatics 'Independent Review Manual'.

For the eligibility review, a minimum of 2 and a maximum of 3 independent radiologists will evaluate the screening HRCT images to determine whether they fulfill the radiographic criteria for UIP pattern. If a SLB is available at screening (lung biopsy performed prior to screening is acceptable), a minimum of 2 and a maximum of 3 independent pathologists will assess the SLB for UIP pattern. For all subjects that have a SLB available at the time of screening, the combined results of radiology and pathology assessments will be used to determine subject eligibility. If a

subject does not have a SLB available at the time of screening, eligibility will be determined by radiology assessment alone. A consensus panel will be convened if subject eligibility is not clear based upon the initial independent review of the HRCT and SLB.

For the safety review, the independent radiologists will also compare each subject's screening and follow-up HRCT images to determine whether a change in IPF by HRCT has occurred. A *qualitative* and *semi-quantitative* assessment will be performed. The *qualitative* assessment will summarize the change in the combination of honeycombing and reticulation (i.e., same, better, much better, worse, much worse, unknown). For the *semi-quantitative* assessment, the extent of fibrosis including the extent of reticular abnormalities and honeycombing together will be scored for each lung separately as well as for both lungs combined using the following categories: absent, 1-25%, 26-50%, 51-75%, 76-100%, or unknown. At the time of review the radiologists will also assess the HRCT images for technical adequacy and quality (i.e., noting anatomy that is not complete, motion artifacts present, crucial anatomy is out of the field of view, other, etc.).

Shift tables of the semi-quantitative HRCT assessments will be presented by treatment group. Individual subject listings of all HRCT and SLB eligibility assessments, as well as the qualitative and semi-quantitative HRCT safety assessments, will also be provided (including reviewer comments and consensus panel assessments).

10.8.9 Pulse Oximetry

Descriptive statistics will be used to summarize and present O_2 saturation at each visit, and change from baseline, for each treatment group. Individual subject listings of O_2 saturation at each visit will be provided.

10.8.10 Immunogenicity (Anti-BG00011 Antibodies)

Blood samples for potential antibodies to BG00011 will be collected during screening and prior to dosing on Visit 2 Day 1-MD. Post-dose samples will be obtained on Visit 19 Day 29-FU and Visit 85 Day 85-FU.

Each blood sample will initially be tested for the presence of anti-BG00011 antibodies using a validated electrochemiluminescence (ECL) method. Confirmed positive samples using the screening assay will be titered and subsequently tested using a validated neutralization assay.

Antibody results will be presented by treatment group and subject in listings. The incidence of antibodies to BG00011 (both binding as well as neutralizing) will be tabulated over time by treatment group using descriptive statistics. The antibody titer and natural log transformed results will be summarized and presented using descriptive statistics. If antibodies are present, their effect on PK parameters will be explored.

10.8.11 Investigator Assessment of Respiratory Status

For subjects in Cohorts 4 & 5, a listing will be created of the investigator's assessment of the subject's respiratory status relative to baseline (better, worse, or the same) at Day 57-FU.

10.8.12 Other Assessments

All other safety assessments not detailed in this section will be listed but not summarized or statistically analyzed.

10.9 Data Safety Monitoring Board

An independent DSMB experienced in the oversight and monitoring of the conduct of clinical trials will determine whether dose escalation should proceed. The DSMB will be comprised of a biostatistician and two pulmonologists with expertise in interstitial lung diseases. The DSMB members' responsibilities and the process for data reviews and dose-escalation are described in the DSMB Charter.

Dose escalation will be based on the DSMB's review of unblinded PK and safety data through Day 15 from the initial 4 (of 8) 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. In order to allow for compilation and evaluation of the data, it is anticipated that the DSMB will convene approximately 9-10 weeks after the first 4 subjects in the previous cohort are initially dosed.

Serious adverse events will be provided to the DSMB on an ongoing basis throughout 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. 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 follow-up period (i.e., complete PK data through the dosing phase and follow-up BAL, PFT, and HRCT) for all participants in Cohorts 1 and 2, respectively.

10.10 Pharmacodynamic Analyses

Secondary objectives of this study are to assess the effect of BG00011 on biomarkers isolated from BAL and peripheral blood in subjects with IPF. Listings and summary tables of expression level of 7 prespecified genes (Table 2) will be provided by treatment group and visit. A listing and summary table of ratio of pSMAD2 to tSMAD2 levels will be provided by treatment group and visit. Additional analyses of gene expression data from serum or BAL may be provided in a separate report.

Table 2: Pre-Specified Genes

Gene	***Gene Description***
ALOX5 (Arachidonate 5-lipoxygenase)	A member of the lipoxygenase family of enzymes that transforms arachidonic acid into pro-inflammatory leukotrienes. Associated with fibrotic lesions in IPF lung tissue.
ETS1 (v-ets erythroblastosis virus E26 oncogene homolog 1)	A transcription factor that negatively regulates TGF-β induced collagen expression and inhibits IL-1b induced lung inflammation and MUC5AC

	production.
FN1 (fibronectin)	An extracellular matrix protein that plays a major role in cell adhesion, growth, migration, and differentiation. Altered fibronectin expression is associated with fibrosis.
OLR1 (oxidized low density lipoprotein [LDL] receptor 1)	A LDL receptor belonging to the C-type lectin superfamily. Internalizes and degrades oxidized LDL. Upregulates angiotensin II activity and knockout protected against renal injury and fibrosis. Knockout also decreases TGF-β induced collagen production from cardiac fibroblasts.
PAI-1 (plasminogen activator inhibitor-1; also known as SERPINE1)	A serine protease inhibitor and the principal inhibitor of tissue plasminogen activator and urokinase, the activators of plasminogen and hence fibrinolysis. PAI-1 inhibits the activity of matrix metalloproteinases and plays a significant role in the progression to fibrosis.
TGM2 (transglutaminase 2)	Catalyzes the crosslinking of extracellular matrix proteins including fibronectin and collagen. Acts as a co-receptor with beta integrins for binding to fibronectin enhancing cell adhesion and migration. Can enhance expression and maturation of fibrillar fibronectin.
TREM1 (triggering receptor expressed on myeloid cells 1)	Amplifies monocyte/macrophage- and neutrophil-mediated toll-like receptor inflammatory responses by stimulating release of pro-inflammatory chemokines and cytokines. Elevated soluble serum TREM1 levels are negatively correlated with pulmonary function in scleroderma subjects.

11. INTERIM ANALYSES

No formal interim statistical analyses are planned. An administrative interim analysis of data collected on Cohorts 1-4 may be used for internal (Biogen) decision making.

12. CHANGES FROM THE PROTOCOL SPECIFIED STATISTICAL ANALYSES

There were no changes from the protocol specified statistical analyses.

13. CHANGES FROM THE PREVIOUS STATISTICAL ANALYSIS PLAN

Several changes were made to SAP version 2.0 that differed from the SAP version 1.0. All changes to the SAP were finalized prior to database lock and unblinding. In addition to editorial updates, the following changes were made:

- A test for trend analysis will not be performed to assess the relationship between dose level and incidence of antibodies due to small sample sizes.

- Many of the efficacy analyses described in Section 10.8 of SAP version 1.0 will not be performed under this SAP. Additional analyses of gene expression data from serum or BAL will be provided in a separate report. ETS1 and tSMAD2 were added as biomarkers to analyze.

- The "Efficacy" analysis population was renamed to the "Pharmacodynamic" population to more accurately reflect its purpose. Also, only 1 injection of BG00011 will be necessary for part of the requirement to be included in this population, rather than the 5 injections noted in SAP version 1.0.

- The PK methods and analysis will be described in a separate PK analysis plan.

14. REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.

2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), 30 November 1995.

3. Spirometic Reference Values from a Sample of the General U.S. Population. Hankinson JL, Odencrantz JR, Fedan KB. Am J Respir Crit Care Med 159:179-187, 1999.

4. Lung Volumes in Healthy Nonsmoking Adults. Crapo RO, Morris AH, Clayton PD, Nixon CR. Bull Europ Physiopath Respir 18:419-425, 1982.

5. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management. Am J Respir Crit Care Med 183:788-824, 2011.

15. DATA PRESENTATION

Values will be presented as indicated below.

For safety data analysis:

- Report mean values to the same decimal place as the individual data to which they refer.
- Report SD and standard error (SE) of the mean to one more decimal place than the mean.
- Report Med, Min, and Max values to the same number of decimal places as the individual data to which they refer.
- Report CV, defined as the ratio of the standard deviation over the mean, as a percentage to one decimal point.
- Report n to whole numbers.

For example:

Individual Values	n	Mean	SD	SE	Min	Med	Max	CV
136, 123, 135	12	131	7.2	4.2	123	135	136	5.5%
2.3, 3.1, 2.7, 3.0	12	2.8	0.36	0.18	2.3	2.9	3.1	13.0%

15.1 Missing Data

Missing data will not be displayed in listings; the data inputs for the relevant timepoint will be left blank if the data are missing.

15.2 Presentation for Dates

Dates will be presented in format (ddmonyyyy). Dates that are missing because they are not applicable will be presented as "NA," unless otherwise specified.

15.3 Unscheduled Assessments

Unscheduled assessments in the listings will be labeled as "Unscheduled." Values obtained during unscheduled visits will not be presented in summary tables, unless requested by the Sponsor.

15.4 Insufficient Data for Presentation

Some of the TFLs may not have any data for presentation. If this occurs, the blank TFL shell will be presented with a message printed in the center of the table, such as, "No serious adverse events occurred during this study."