STATISTICAL ANALYSIS PLAN

PROTOCOL TITLE

A Phase II randomized, placebo-controlled study of GBT440 to evaluate the safety, tolerability, pharmacokinetics and effect on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF)

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Protocol Number: GBT440-006

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Statistical Analysis Plan Approval

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List of Abbreviations

6MWT	6-Minute Walk Test
AE	Adverse Event
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AST	Aspartate Aminotransferase
ATAQ	A Tool to Assess Quality of Life
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CI	Confidence Interval
CPET	Cardiopulmonary Exercise Test
CRF	Case Report Form
CS	Clinically Significant
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DBP	Diastolic Blood Pressure
DLco	Diffusing Capacity of the Lung for Carbon Monoxide
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
ETCO2	End Tidal Carbon Dioxide
ETO2	End Tidal Oxygen
FEV1	Forced Expiratory Volume in 1 second
FVC	Forced Vital Capacity
GGT	Gamma Glutamyl-transferase
HR	Heart Rate
ICH	International Conference on Harmonisation
INR	International Normalized Ratio
IQR	Interquartile Range
IPF	Idiopathic Pulmonary Fibrosis
IxRS	Interactive Response System
LactThrsh	Lactic Acid Threshold
LFT	Liver Function Tests
MedDRA	Medical Dictionary for Regulatory Activities
NCS	Not clinically significant
PDF	Portable Document Format
PK	Pharmacokinetics
PP	Per-protocol
PPT	Partial Prothrombin Time
PR	Pulse Rate
PRO	Patient-Reported Outcomes

PT	Preferred Term
RBC	Red Blood Cells
RER	Respiratory Exchange Ratio
RR	Respiratory Rate
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDC	Statistics and Data Corporation, Incorporated
SGRQ	Saint George's Respiratory Questionnaire
SMC	Safety Monitoring Committee
SOC	System Organ Class
SpO2	Peripheral Oxygen Saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TIBC	Total Iron Binding Capacity
TVOL	Tidal Volume
UCSD	University of California San Diego
VAS	Visual Analog Scale
VentThrsh	Ventilatory Threshold
VCO2	Carbon Dioxide Production
VO2	Oxygen Production
WBC	White Blood Cells
WCT	Worldwide Clinical Trials
WHO DDE	World Health Organization Drug Dictionary Enhanced

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for protocol GBT440-006, version Amendment 3, dated December 21, 2016.

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

This SAP describes the data that will be analyzed and the subject characteristics, efficacy, and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used. The statistical analysis methods presented in this document will supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP they may be completed and will be identified in the clinical study report (CSR).

Planned pharmacokinetic (PK) analyses will be described in a separate analysis plan.

2. Study Objectives

Primary Objective:

To evaluate the safety and tolerability of multiple doses of GBT440 administered to subjects with IPF.

Secondary Objectives:

- To evaluate the effect of GBT440 on oxygen saturation at Days 15 and 28 compared to baseline during the 6-minute walk testing (6MWT).
- To evaluate the pharmacokinetic (PK) parameters of GBT440 in plasma and whole blood.

Exploratory Objectives:

- To evaluate the effect of GBT440 on distance walked during the 6MWT at Days 15 and 28 compared to baseline.
- To evaluate the effect of GBT440 on IPF-related symptoms using patient reported outcomes (PROs) at Day 28 compared to baseline.
- To evaluate the effect of GBT440 on cardiopulmonary exercise testing (CPET) parameters at Day 29 compared to baseline.
- To evaluate pulmonary function, including assessment of spirometry and Diffusing Capacity of the Lung for Carbon Monoxide (DLco) at Day 28 compared to baseline.

- To evaluate the PK-PD relationship of GBT440 at Days 15 and 28 compared to baseline.

3. Study Endpoints

3.1 Primary Endpoint

The primary endpoint is treatment-emergent adverse events (TEAE) and tolerability.

3.2 Secondary Endpoints

- Change and percentage change from baseline in resting peripheral oxygen saturation (SpO_2) at Days 15 and 28 measured prior to beginning the 6MWT.
- Change and percentage change from baseline in end-of-6MWT SpO_2 at Days 15 and 28.
- Change and percentage change from baseline in lowest SpO_2 value measured during the 6MWT at Days 15 and 28.
- Pharmacokinetic (PK) parameters of GBT440 in plasma and whole blood, including but not limited to maximum concentration (Cmax), minimum concentration (Cmin) at steady state in GBT440 treated subjects.

3.3 Exploratory Endpoints

- Change and percentage change from baseline in distance walked during the 6MWT at Days 15 and 28.
- Time to first $SpO_2 < 88\%$ that is sustained for at least 10 seconds during the 6MWT at Days 15 and 28.
- Area under the SpO_2 curve (AUC) during the 6MWT measured at baseline, Day 15 and Day 28.
- Change from baseline in PRO scores using Saint George's Repiratory Questionnaire (SGRQ), University of California, San Diego (UCSD) Shortness of Breath Questionnaire, A Tool to Assess Quality of Life (ATAQ) in IPF (only subjects enrolled in Part B), and the Borg Scale of Perceived Exertion questionnaires and cough visual analog scale (VAS) at Days 15 and 28.
- Change and percentage change from baseline in cardiopulmonary exercise testing parameters at Day 29.
- Change and percentage change from baseline in lung function, including forced vital capacity (FVC) and DLco at Day 28.
- PK/PD relationship in subjects receiving GBT440 from Baseline to Days 15 and 28

3.4 Statistical Hypotheses

This phase 2 study is designed to evaluate the safety and tolerability of multiple doses of GBT440 administered to subjects with IPF. No formal hypotheses are specified for this study.

4. General Study Design

This study is a randomized, placebo-controlled trial that will be conducted in two parts. Together, Parts A and B will provide safety and efficacy data across a range of GBT440 doses that are expected to improve oxygen saturation in the enrolled subjects.

- In Part A (Figure 1), eligible IPF subjects will be randomized 1:1:1 to receive GBT440 900 mg (n = 6) or 600 mg (n = 6), or placebo (n = 6) administered orally as 300 mg capsules once daily for 28 days. The study site, subjects, CRO statistician and Sponsor will be blinded to study treatment.
- In Part B (Figure 2), eligible IPF subjects will be randomized 3:1:1 to receive GBT440 1500 mg (n = 9) or 600 mg (n = 3), or placebo (n = 3) administered orally as 300 mg capsules once daily for 28 days in which the study site and subjects are blinded to study treatment. The Sponsor and CRO statistician will be unblinded to study treatment.

Subjects on a stable dose of pirfenidone or nintedanib and/or N-acetyl cysteine are eligible for entry into the study.

After the Screening visit, the study includes the following study periods:

- Treatment period (28 days)**:** subjects will be randomized (1:1:1) to one of three treatment groups in Part A and randomized (3:1:1) to one of three treatment groups in Part B; subjects will receive:

  Part A:
  - Group 1: GBT440 900 mg; three 300 mg GBT440 capsules, daily orally.
  - Group 2: GBT440 600 mg; two 300 mg GBT440 capsules and one placebo capsule, daily orally.
  - Group 3: Placebo: three placebo capsules, daily orally.

  Part B:
  - Group 1: GBT440 1500 mg; five, 300 mg GBT440 capsules, daily orally.
  - Group 2: GBT440 600 mg; two 300 mg GBT440 capsules and three placebo capsule, daily orally.
  - Group 3: Placebo: five placebo capsules, daily orally.
- Safety follow-up (30 days): safety will be assessed for at least 5 half-lives after the last dose of GBT440.

Figure 1 Study Design – Part A

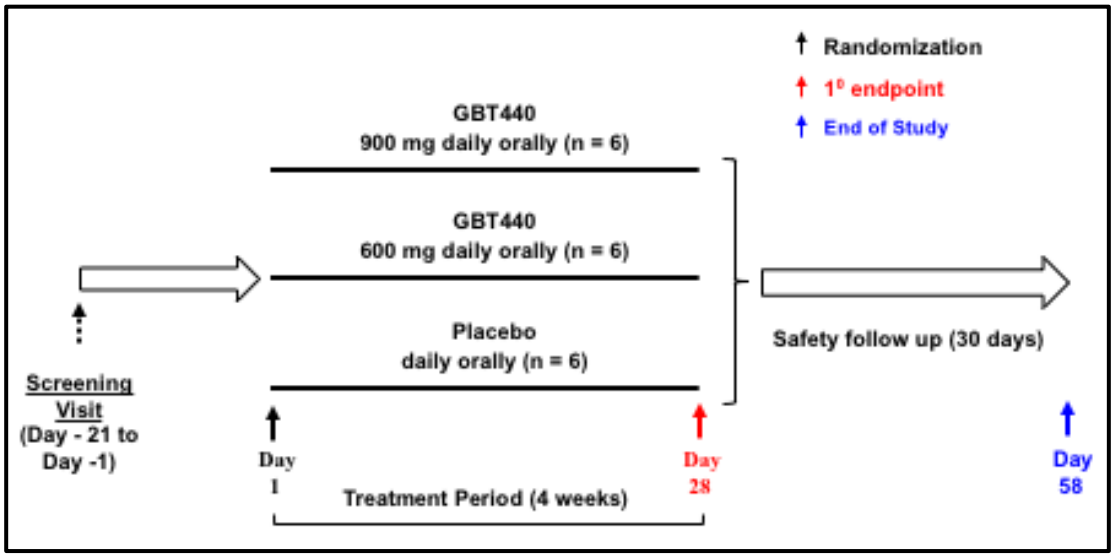
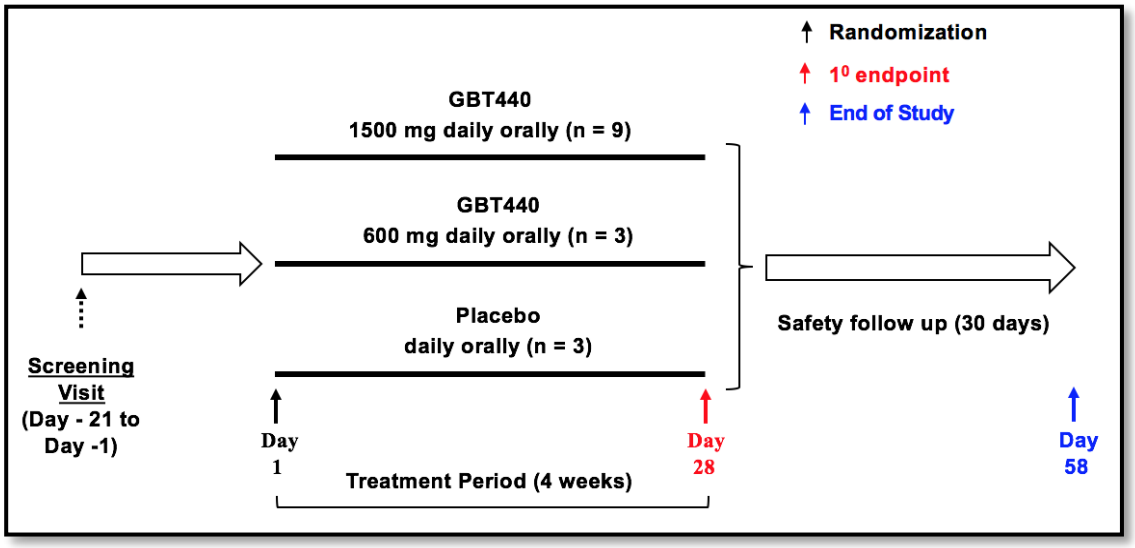


Figure 2 Study Design – Part B



Subjects who do not complete at least 10 days of dosing for reasons unrelated to toxicity may be replaced.

In Part A, two unblinded interim analyses of the primary and secondary endpoints are planned: i) when approximately 9 subjects have completed their Day 28 study visit and ii) when approximately 18 subjects have completed their Day 15 study visit.

A Safety Monitoring Committee (SMC) is planned to review all safety data on an ongoing basis throughout the study (refer to Protocol Section 10.1). If the SMC does not identify any clinically

significant safety concerns in Part A, following review of data from approximately 18 subjects who have completed Day 15, the Sponsor will initiate Part B of the study, and randomize up to an additional 15 subjects to the three study treatment arms to better characterize the safety, tolerability, and potential treatment response of GBT440 in subjects with IPF.

In the eventuality that one treatment arm is discontinued, subjects may be randomized 1:1 to the remaining study drug treatment group or placebo. Therefore, the trial size is approximately 33 subjects.

The end of the study is defined as the date when the last subject completes the last visit, which is expected to occur approximately 58 days after the last subject is randomized.

5. Schedule of Visits and Assessments

The schedule of visits and assessments and PK sampling timepoints are provided below.

5.1 Schedule of Assessments

Study Day (Window)	Screening[a] Day -21 to Day -1	Day 1	Treatment Period Day 2	Day 8 (+/- 2)	Day 15 (+/- 2)	Day 28 (+/- 2)	Day 29 (+3)	Follow-up Visits Day 45[b] (+/- 3)	Day 58 (+/- 3)
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**
Informed Consent[c]	X								
Eligibility Assessment	X	X							
Demographic data	X	X[d]							
Medical History and baseline conditions		X[d]							
Concomitant Medications	X	X	X	X	X	X	X	X	X
Complete Physical Examination[e]	X								X
Limited Physical Examination[f]		X		X	X	X	X	X	
Height	X								
Weight	X					X			
Vital Signs[g]	X	X	X	X	X	X	X	X	X
SpO_2[h]	X	X	X	X	X	X	X	X	X
ECG (12-lead)[i]	X			X	X	X		X	X
Adverse Events[j]	X[j]	X	X	X	X	X	X	X	X
Serum Pregnancy Test (females only)[k]	X								
Urine Pregnancy Test (females only)[l]				X	X	X		X	X
Hematology	X			X	X	X		X	X
Serum Chemistry	X			X	X	X		X	X
Urinalysis	X				X	X		X	X
Coagulation Panel (PT, PTT, INR)	X					X			
Serum Erythropoietin	X					X		X	X
Serology (Hepatitis A, B, C, and HIV)	X								
PK Blood Samples[m]		X	X	X	X	X		X	X
Spirometry and DL_{CO}	X					X			X
6-Minute Walk Test[n]	X[n]				X	X			X
Cardiopulmonary Exercise Testing[n]			X				X		
Randomization (IxRS)		X							
Study Drug Dispensing to Subject[o])			X	X	X				
Study Drug Administration at site[p]		X	X	X	X	X			
St. George's Respiratory Questionnaire[q]		X		X	X	X		X	X

UCSD Shortness of Breath Questionnaire[q]		X		X	X	X		X	X
ATAQ-IPF Symptoms[q]		X		X	X	X		X	X
ATAQ-Impacts[q]		X		X	X	X		X	X
End of Study Questionnaire[r]									X
Cough Visual Analog Scale[q]		X		X	X	X		X	X

Abbreviations: ATAQ = A Tool to Assess Quality of Life; DLco = lung diffusing capacity measured using carbon monoxide; ECG = electrocardiogram; HIV = human immunodeficiency virus; INR = international normalized ratio; PK = pharmacokinetic; PRO = patient reported outcome; PT = prothrombin time; PTT = partial thromboplastin time; SGRQ = St. George's Respiratory Questionnaire, SpO_2 = oxygen saturation measured by pulse oximetry; UCSD = University of California San Diego.

Note: All assessments should be performed within the number of days (Window) as indicated for each scheduled visit day. All assessments should be performed prior to receiving study drug during the treatment period unless otherwise indicated. SGRQ, UCSD, Cough VAS should be performed before all other non-PRO assessments, followed by 12-lead ECG and then vital sign assessments

[a] All screening evaluations must be completed and reviewed prior to Day 1 (Visit 2) to confirm the subject meets all eligibility criteria prior to randomization to the treatment period. In cases when the screening 6MWT is done more than 7 days prior to Visit 2, it must be repeated, up and through Day 1, prior to any Day 1 assessments.

[b] All subjects who discontinue study or study drug prior to study completion, and who are unwilling or unable to complete the remaining scheduled visits, should return to the study site to complete all Day 45 (Visit 8) assessments (refer to Protocol Section 6).

[c] Written informed consent must be obtained and documented prior to performing any study-specific screening procedure.

[d] Demographics, medical history and baseline conditions obtained at screening should be reviewed again at this visit and any changes since screening updated in the eCRF.

[e] Includes evaluation of the head, eyes, ears, nose and throat and cardiovascular, respiratory, musculoskeletal, gastrointestinal, neurological, dermatologic systems. No rectal or pelvic examination is required. Record any observed abnormalities in the eCRF. At subsequent visits record new or worsened clinically significant findings on the eCRF

[f] Perform a limited, symptom-directed examination as clinically indicated. Record new or worsened clinically significant findings in the eCRF.

[g] Includes heart rate, respiratory rate, systolic and diastolic blood pressure and temperature measured whilst in a semi-recumbent or supine position and resting for at least 5 minutes.

[h] Performed while the subject is seated and resting for at least 5 minutes.

[i] Perform 12-lead ECG in triplicate; three separate tracings with approximately 1 minute between each tracing, after resting in a semi-recumbent or supine position for at least 5 minutes.

[j] After informed consent but prior to randomization only serious adverse events (SAEs) resulting from a protocol-mandated intervention should be reported. After randomization all adverse events will be reported until study completion (Day 58).

[k] Performed for all female patients who are not post-menopausal or surgically sterile

[l] If a urine pregnancy test is positive the result must be confirmed with a serum pregnancy test.

[m] PK blood samples during the treatment period should be collected on Days 1 and 28: pre-dose, and 2 hours post dose (+/- 15 minutes); Day 2: 24 hours (+/- 2 hours) after the Day-1 dose *and* prior to receiving the Day-2 dose; Days 8 & 15: pre-dose only. Also see Protocol Section 5.6.

[n] Instructions for per-protocol performance of the 6-minute walk (and Borg dyspnea scale) and cardio-pulmonary exercise tests are provided in the procedure manual. Note: The baseline 6MWT performed during screening must be performed within 7 days of the Day-1 visit.

[o] An unblinded study pharmacist will prepare daily doses of study drug, dispensed into 30 mL high-density polyethylene (HDPE) bottles. Each bottle (or dose) is packaged individually with 3 capsules of active or placebo or both specific to each subject's assigned treatment group. Subjects who have their dose modified during the study must return to the site to have the modified dose of study drug dispensed by the unblinded pharmacist.

[p] Subjects should not administer study drug on the morning of these study visits. Study drug will be administered by the study staff after completion of all pre-dose assessments.

[q] The SGRQ, ATAQ, and UCSD questionnaires and cough VAS should be self-administered by the subject, using the paper forms provided by the Sponsor prior to all other non-PRO assessments and before the patient receives any disease-status information during that assessment. ATAQ questionnaires should be administered to subjects enrolled in Part b of the study.

[r] The End of Study Questionnaire should be administered to subjects enrolled in Part B of the study.

6. Study Treatments

The study drug is GBT440 300 mg capsules or placebo.

Subjects randomized to the following treatment groups in Part A will receive:

- GBT440 900 mg -- 3 GBT440 300 mg capsules
- GBT440 600 mg -- 2 GBT440 300 mg capsules and 1 placebo capsule.
- Placebo -- 3 placebo capsules.

Subjects randomized to the following treatment groups in Part B will receive:

- GBT440 1500 mg -- 5 GBT440 300 mg capsules
- GBT440 600 mg -- 2 GBT440 300 mg capsules and 3 placebo capsules.
- Placebo -- 5 placebo capsules.

Study drug is to be dosed orally once daily for a total of 28 days.

6.1 Method of Assigning Subjects to Treatment Groups

Subject randomization will be carried out centrally through an IxRS. Eligible subjects in Part A will be randomized 1:1:1 to receive 900 mg GBT440, 600 mg GBT440, or Placebo. Eligible subjects in Part B will be randomized 3:1:1 to receive 1500 mg GBT440, 600 mg GBT440, or placebo respectively.

The randomization will be stratified by background IPF therapy (pirfenidone/nintedanib or no pirfenidone/nintedanib) use at the time of entry into the study.

6.2 Dose Modifications and Adjustments

Modification of study drug dosing may be considered if, in the opinion of the study Investigator, an AE may be related to study drug and it would be unsafe for the subject to continue receiving their current dose of study drug.

Dose adjustments may be initiated by the Investigator based on their assessment of the associated AE severity and overall subject safety and in discussion with the Sponsor's Medical Director.

The Investigator, in discussion with the Sponsor's Medical Director, may choose to:

- Change dosing frequency, to one capsule 3 times per day
- Reduce the total daily dose

A reduction in dose should be by one active study drug capsule. Dose reductions will require the subject to return to the study site for the unblinded pharmacist to dispense new study drug capsules. Subjects in Part A will continue to take 3 capsules per day. Subjects in Part B will continue to take 5 capsules per day.

A second dose reduction by one active study drug capsule may be initiated if deemed necessary by the Investigator and based on a safety assessment of the subject. The timing of the second dose reduction will be based on the Investigator's clinical assessment and in discussion with the Sponsor's Medical Director.

The Investigator must make every effort to restart the dosing regimen assigned to the subject at randomization when, in the investigator's opinion, it is safe to do so.

6.3 Blinding and Unblinding

An independent biostatistician who is not otherwise involved in the trial will generate the randomized study drug assignment list for Part A of the study. The subject, study team, Investigators, and study staff will be blinded during the randomization process and throughout the duration of the study. The Sponsor and CRO statistician will be unblinded to the treatment assignments when a minimum of 18 treated subjects in Part A complete at least 28 days of study. Sponsor representatives not involved in the conduct of the study will have access to unblinded treatment data throughout the conduct of the study.

The CRO statistician will generate the randomized study drug assignment list for Part B of the study. The Investigators, study staff, and CRO data manager will remain blinded to treatment assignments in Part B of the study. The Sponsor and CRO statistician will not be blinded to treatment assignments in Part B of the study.

The randomization lists will reside on a secure server to which members of the study team will not have access until the study is unblinded per the protocol.

If at any time during the study a decision about a subject's medical condition requires knowledge of the treatment assignment, the study blind may be broken (through the interactive response system [IxRS]) for that specific subject only. If, in the opinion of the Investigator, there is no impact on subject safety, the Investigator is encouraged to contact the Sponsor's Medical Director prior to unblinding. The reason for unblinding must be documented in the appropriate section of the case report form (eCRF).

The SMC must be informed by the Sponsor's Medical Director of any case of unblinding. Additionally, the SMC may unblind any individual treatment assignment for further safety evaluation at their discretion.

7. Sample Size and Power Considerations

The sample size in this study was not selected based on statistical considerations but to determine preliminary safety, tolerability, PK, laboratory and clinical effects of GBT440 in IPF subjects.

The study will enroll approximately 33 subjects: approximately 18 subjects in Part A and approximately 15 subjects in Part B.

8. Data Preparation

All reported study data will be recorded on the eCRFs supplied by Worldwide Clinical Trials (WCT) using eClincialOS™, version 2016.5.0. All data collected on the eCRF will be mapped from the clinical database to the appropriate Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) domains (Implementation Guide version 3.2). Analysis datasets will be mapped to the CDISC analysis data model (ADaM) using the ADaM Implementation Guide (version 1.1) for all data presented in summary tables and figures. Listings will generated from SDTM domains or ADaM datasets as appropriate.

The final analyses for this study will be carried out after the following have occurred:

- All data management requirements are met according to WCT standard operating procedures, including data entry, performance of edit and validation checks, documentation and resolution of data queries, and database lock with written authorization provided by appropriate WCT and Sponsor personnel;
- Protocol deviations have been identified and status defined (major/minor deviations); and
- Analysis populations have been determined

9. Analysis Populations

9.1 Safety Population

All subjects who receive any amount of study drug will be included in the Safety population. Subjects will be analyzed based on study drug received. This is the primary population for all safety analyses performed for this study.

9.2 Efficacy-Evaluable Population

All randomized subjects who received at least 14 days of study drug treatment will be included in the Efficacy-Evaluable population. The Efficacy-Evaluable population will be used for analysis of all secondary and exploratory efficacy endpoints, and subjects will be analyzed as treated.

9.3 PK Population

All subjects who receive investigational treatment and provide adequate data to evaluate the relevant PK parameter will be included in the PK population. The PK population will not be used for analyses described in this statistical analysis plan (SAP).

10. General Statistical Considerations

10.1 Missing or Inconclusive Data Handling

If only a partial date is available and is required for a calculation of whether a medication is concomitant or an AE is treatment-emergent, the following standards will be applied:

10.1.1 Start dates (e.g., AE onset date or start date of medication)

- For missing start day only - Day will be imputed as the first day of the month (i.e., 1) with the following exception: if the partial date falls in the same month and year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.
- For missing start day and month - Day and month will be imputed as the first day of the year (i.e., 1 January) with the following exception: if the partial date falls in the same year as the date being used in the calculation (e.g., first dose date, informed consent date), then the partial date will be imputed to equal the date being used for the calculation.

10.1.2 Stop dates (e.g., AE resolution date or stop date of medication)

- For missing stop day only - Day will be imputed as the last day of the month (i.e., 28, 29, 30, or 31)
- For missing stop day and month - Day and month will be imputed as the last day of the year (i.e., 31 December)

Any partial dates will be displayed in data listings without imputation of missing days and/or months (e.g., MAR2011, 2009). No other imputation of missing data will be performed.

No imputation methods will be used for analysis of missing efficacy data in this study.

10.2 Definition of Baseline

For all endpoints, baseline is defined as the last non-missing measure or the average of the non-missing measures before the first dose of study drug. Change from baseline to follow-up visit will be calculated as the baseline measurement subtracted from the follow-up measurement for all assessments with the exception of the CPET endpoints. The first measurements for CPET endpoints occur at Study Day 2. The change from Day 2 to Day 29 will be calculated as the Day-2 measurement subtracted from the Day-29 measurement for all CPET endpoints.

The percent change from baseline values to post-baseline values will be calculated using the following formula where applicable:

([post-baseline value – baseline value] / baseline value) × 100%

10.3 Data Analysis Conventions

Analyses for SMC meetings, interim analyses, and final data analysis will be performed by Statistics & Data Corporation (SDC). The final data analyses will be performed after Part B of the study is completed and the database has been locked. Data from Parts A and B of the study will be pooled across the common treatment arms (GBT440 600 mg and placebo arms). Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. All study data will be listed by subject, study drug,

and visit (as applicable) based on randomized and treated subjects unless otherwise specified. Summary statistics will be presented by treatment group including all GBT440, and will include a total column where appropriate.

Study visits will be referred to in all tables and listings as the visit name corresponding to the planned study visit.

Summaries for continuous and ordinal variables will include the number of observations (n), arithmetic mean, standard deviation (SD), median, minimum, and maximum). Minima and maxima will be reported with the same precision as the raw values; means and medians will be presented to one additional decimal place than reported in the raw values. Standard deviations will be presented to two additional decimal places than reported in the raw values. Summaries for discrete variables will include frequency counts and percentages. All percentages will be rounded to one decimal place (i.e., XX.X%).

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. All p values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999".

All summary tables will be supported with subject listings.

10.4 Adjustments for Multiplicity

As this is a phase 2 study for which there is no pre-determined power to show a difference to a control, there will be no multiplicity adjustments in this study.

11. Disposition of Subjects

Subject disposition will be presented in terms of the numbers and percentages of subjects who were randomized and completed study treatment, completed the study, and discontinued from the study. Subjects who are not discontinued from the study will be considered study completers. The number of subjects in the Safety and Efficacy-Evaluable populations will be displayed by study drug, and percentages will be calculated using subjects in the Safety population as the denominator.

The number and percentage of subjects prematurely discontinued from the study and the reasons for study discontinuation will be summarized by treatment group for all subjects in the Safety population. The reasons for study discontinuation that will be summarized include: subject withdrawal of consent, discretion of the investigator, SMC recommendation, subject is lost to follow up, and other.

Other subject listings will include a listing of inclusion and exclusion criteria violations, a listing of major protocol deviations, and a listing of screen failures with the reasons for screen failure.

12. Demographic and Baseline Characteristics

The demographic variables collected in this study include age, gender, race, and ethnicity. Subjects who record more than one race will be grouped into a single category denoted as multiple. Additionally, the number and percentage of subjects in each treatment group who are on background pirfenidone or nintedanib will be included. Demographic variables will be summarized for the Safety population.

Age (years) will be summarized by study drug, using continuous descriptive statistics. Age will be reported in years and calculated using the following formula:

Age = ((consent date – date of birth) / 365.25) truncated as an integer

The number and percentage of subjects will be presented by treatment group, all GBT440, and all subjects.

The subject listing will include all demographic variables including the non-childbearing potential for female subjects.

13. Targeted Medical History, Other Medical History, and Concomitant Medications

13.1 Targeted Medical History

Medical history events identified as targeted medical history will be summarized with the number and percent of subjects in each treatment group, and for all GBT 440 subjects, who experienced each event. The targeted medical history events that will be summarized are as follows:

- Cancer (including cancer therapies and procedures)
- Inflammatory/Autoimmune Disorders
- Primary Hypertension (including grade of severity and medications taken)
- Pulmonary Rehabilitation
- Gastroesophageal Reflux (including medications taken)
- Sleep-Disordered Breathing/Sleep Apnea (including use of non-invasive ventilation, surgeries, and medications taken)
- Pulmonary Embolism (including medications taken)
- Lactose Intolerance (including medications taken)

Other medical history will be summarized using discrete summary statistics and will be presented by study drug at the subject and event level by System Organ Class (SOC) and Preferred Term (PT) using the Safety population. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. Other medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA), version 19.0.

All medical history data will be listed.

13.2 Prior and Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (Enhanced B2, March, 2016) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical (ATC) 4 classification) and preferred name. Medications with missing ATC codes will be classified as "uncoded".

Concomitant medications are defined as those medications having been taken 1) prior to initiation of study drug administration and continuing for any period of time following the first administration of study drug or 2) at any time following the first administration of study drug and within 30 days of last dose.

14. Study Drug Administration, Extent of Exposure, and Dosing Compliance

14.1 Study Drug Administration

The number and percent of subjects who completed study administration will be summarized with the number and percentage of subjects in each treatment group and for all GBT440 using the Safety population. A subject will be defined to have "Completed Study Drug Administration" if the subject has a record for study drug administration corresponding to the Day-28 visit (Visit 6) and a response of "No" has been entered for the question, "Was study drug permanently discontinued?" on the Study Drug CRF for the same visit.

The number and percentage of subjects who permanently discontinued study drug, and the reason for discontinuation (adverse event (AE) or other) will be summarized by study drug and for all GBT440. The number and percentage of subjects who missed at least 1 dose of study drug, had at least 1 dose reduction, or had at least 1 dose interruption will be summarized by study drug and for all GBT440. The summary will include the number and percentage of subjects who had a dose reduction or dose interruption due to an adverse event. Additionally, the number and percentage of subjects grouped by number of doses missed, number of dose reductions, and number of dose interruptions will be summarized by study drug and all GBT440.

14.2 Extent of Exposure

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

Extent of Exposure (days) = (Date of last dose – date of first dose [Day 1]) + 1 – (Number of Missed Doses + Number of Days with Dose Interruption)

Extent of exposure (days) will be summarized with continuous descriptive statistics using the Safety population.

14.3 Dosing Compliance

Dosing compliance will be calculated using the following:

$$\text{Dosing Compliance (\%)} = \frac{\text{Sum of the Actual Days Dosed (days)}}{\text{Sum of Expected Days Dosed}} \times 100\%$$

The actual days dosed is defined as the sum of the days a subject was dosed. The number of expected days dosed that will be used for calculating dosing compliance will be calculated as (date of last dose – date of Day1 dosing +1) for all subjects, regardless of study completion status.

Dosing compliance will be summarized with continuous descriptive statistics for each treatment group, using the Safety population.

Study drug administration (including extent of exposure and dosing compliance) will be listed for all subjects who received at least 1 dose of study drug.

15. Primary Analysis

The primary endpoint in this study is treatment-emergent adverse events and tolerability. All safety analyses will be conducted using the Safety population.

15.1 Analyses of Treatment-emergent Adverse Events and Serious Adverse Events

TEAEs are defined as any event that occurs or worsens on or after the first dose of study drug and within 30 days after the last dose. Adverse events recorded in the eCRF which began prior to first dose of study drug will not be included in the summary tables but will be included in the AE data listings.

Adverse events reported for subjects participating in this study will be graded using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. All AEs will be coded using the using MedDRA, version 19.0.

An overall summary will be presented that includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE, by study drug and all GBT440. This summary will also include the number of Grade 3 or greater TEAEs, the number and percentage of subjects with at least 1 TEAE ≥ Grade 3, the number of possibly/probably related TEAEs, the number and percentage of subjects with at least 1 possibly/probably related TEAE, the number of serious adverse events (SAEs), the number and percentage of subjects with at least 1 SAE, the number of TEAEs leading to study drug discontinuation, the number and percentage of subjects who discontinued study drug due to TEAEs, and the number and percentage of deaths.

Additional summaries of TEAEs by study drug and all GBT440 will include the following:

- Incidence of TEAEs by SOC and PT

- Incidence of TEAEs by SOC and PT by antifibrotic use
- Incidence of TEAEs of Special Interest by SOC and PT
  - (If less than 5 events occur in each treatment group, then only a listing will be created)
- Incidence of TEAEs by SOC, PT, and Maximum Severity
- Incidence of TEAEs by SOC, PT, and Maximum Severity by antifibrotic use
- Incidence of TEAEs Resulting in Discontinuation of Study Drug
- Incidence of TEAEs Possibly/Probably Related to Study Drug
  - (If less than 5 events occur in each treatment group, then only listing will be created)
- Incidence of SAEs

All summaries will be provided showing the number and percentage of subjects who experienced at least one TEAE. TEAEs will be summarized using discrete summary statistics (number and percentage of subjects) and will be presented by study drug and total GBT 440 by SOC and PT. If a subject reports the same PT multiple times within the same SOC, that PT will only be reported once within that SOC. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be reported once. Summaries will list SOC in ascending alphabetical order, and PTs will be listed in order of descending frequency for all GBT440 subjects within each SOC.

Separate subject listings of AEs will be provided for all AEs, TEAEs Resulting in Discontinuation of Drug, SAEs, and Deaths.

15.2 Analyses of Other Safety Measures

15.2.1 Physical Examination

The physical examination results, height (cm), weight (kg), and body mass index (BMI) (kg/m^2) will be summarized by study drug and all GBT 440 using summary statistics (number of subjects, mean, standard deviation, median, minimum, and maximum) by each applicable visit (Screening [Baseline], and Day 28,) in the Safety population. Height will be summarized only for Screening, and the screening height will be used for the calculation of BMI at Day 28. Weight collected at visits other than those specified in the protocol will be included in the summary for completeness. A subject listing of all physical exam results will be generated.

15.2.2 Vital Signs and Pulse Oximetry

Vital signs, including systolic blood pressure (SBP [millimeters of mercury (mmHg)]), diastolic blood pressure (DBP [mmHg]), heart rate (HR [beats per minute (bpm)]), respiratory rate (RR [bpm]), body temperature (degrees Celsius), and SpO_2 (%), will be summarized with continuous descriptive statistics at each visit by study drug and for all GBT 440 subjects in the Safety population. Change from baseline and percent change from baseline to each post-baseline visit also will be summarized.

15.2.3 Electrocardiogram (ECG)

HR (bpm), PR interval (milliseconds [ms]), QRS interval (ms), QT interval (ms), and QT interval with Fridericia's correction (QTcF [ms]) will be summarized using descriptive statistics by study drug and all GBT440 by visit in the Safety population. When all electrocardiogram (ECG) parameters, except for the QTcF interval, are collected at the site, the QTcF interval will be calculated using the following formula:

$QTcF = QT / (60/HR)^{1/3}$

Change from baseline to each post-baseline visit also will be summarized by study drug and all GBT 440. ECG triplicates will be averaged for summary tables. Each triplicate and the average of triplicates will be provided in a subject listing for Baseline, Day 8, Day 15, Day 28, Day 45, and Day 58.

Additionally, the number and percentage of subjects with QTcF > 450 ms, > 480 ms, and > 500 ms at baseline and as the maximum post-baseline measurement will be summarized. The number and percentage of subjects with maximum increase from baseline where increase in QTcF > 30 ms and > 60 ms will be included in the summary.

A subject listing of ECG parameters will include each triplicate and the average of triplicates for each visit.

15.2.4 Clinical Laboratory Results

Clinical laboratory data including serum chemistry, liver function tests, serum hematology, serum erythropoietin, coagulation panel, and urinalysis are collected at specified visits. The quantitative variables will be summarized by study drug and all GT440 with continuous descriptive statistics for each visit in the Safety population. Urinalysis results will be presented only as a subject listing. Change from baseline and the percent change from baseline will also be summarized by study drug and all GBT 440. Units for laboratory results will be converted from reported units to SI units in the SDTM datasets. Reported results and units will be used for the summary tables.

Subject listings of laboratory data will include a separate listing for clinically significant laboratory values in addition to subject listings of all laboratory values. Listings will be presented with reported units and SI units. Pregnancy test results for both serum and urinalysis sampling will be provided in a separate listing.

16. Secondary Analyses of 6-Minute Walk Test

The 6-Minute Walk Test is a multiple period assessment that includes a resting period (first minute before the walking portion), the 6-minute walking period, and a post-walking period that includes results at each minute for 2 minutes upon completion of walking. End of exercise is defined as last SpO_2 immediately at end of 6MWT (not including the post-walking period). Blood pressure is collected at rest

and at each minute post walking. The distance walked (meters) is recorded at the end of the walking period.

Results of the 6-Minute Walk test (6MWT) will be summarized by study drug and all GBT440 at the following visits: Baseline (Screening or repeat at Day 1 if applicable), Day 15, Day 28, and Day 58. The number and percentage of subjects in each treatment group and all GBT 440 who completed the 6MWT, experienced myocardial infarction (MI) or unstable angina in the previous 30 days before the 6MWT, and utilized oxygen during the 6MWT will be summarized. Summary statistics (N, mean, SD, median, min, and max) will be displayed for systolic and diastolic blood pressure collected at rest and at each minute post-walking.

Subject listings will be provided for all 6MWT data collected on the eCRF.

Summary statistics for resting SpO_2, SpO_2 at end of the 6MWT (last available result) and lowest SpO_2 collected during the 6MWT will be summarized at each visit by study drug and all GBT440 in the Efficacy-Evaluable population. Summary statistics for the change and percent change from baseline to Day 15, Day 28, and Day 58 also will be displayed.

Analysis of covariance models (ANCOVA) will be used to analyze the effect of treatment on the change from baseline and the percent change from baseline for each secondary endpoint with baseline value as a covariate. Least squares (LS) means and SEs will be displayed for the change and percent change from baseline in each treatment group and for all GBT440.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

17. Exploratory Analyses

17.1 6-Minute Walk Test

Summary statistics for the distance walked (meters) during the 6MWT, time to the first $SpO_2 < 88\%$, and AUC of SpO_2 will be summarized by study drug and all GBT 440, and visit in the Efficacy-Evaluable population. The change and percent change from baseline to Day 15, Day 28, and Day 58 in distance walked also will be summarized and displayed.

The AUC of SpO_2 measurements will be calculated for each subject's data at baseline, Day 15, Day 28, and Day 58. The AUC will be estimated using the trapezoid rule for data collected on the eCRF as follows:

$$\text{AUC}=\left\{\sum_{t=1}^{n}\frac{1}{2}[(\text{Time}_t-\text{Time}_{t-1})\times(\text{SpO2}_t+\text{SpO2}_{t-1})]\right\}$$

where n is the is the number of measurements of SpO_2 collected during the 6MWT, t is the elapsed time in minutes (nominal time) and SpO_2 is the measurement of SpO_2 level at the respective timepoint, and Time is the timepoint. If a SpO_2 measurement is missing during the 6MWT, then that timepoint is removed from the calculation, such that the AUC is calculated using the trapezoid rule from the 2 timepoints surrounding the missing SpO_2 measurement.

Additional exploratory endpoints include the change from rest to end of 6MWT and change from rest to lowest SpO_2 . Both endpoints will be summarized by study drug and all GBT440.

ANCOVA models will be used to analyze the effect of treatment on the change from baseline for each exploratory endpoint with baseline value as a covariate. Least squares (LS) means and SEs will be displayed for the change from baseline in each treatment group and for all GBT440. Similar ANCOVA models will be constructed for percent change from baseline for AUC and distance walked.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

All exploratory efficacy data will be provided in subject listings.

17.2 Saint George's Respiratory Questionnaire

The Saint George's Respiratory Questionnaire (SGRQ) is completed at baseline (Day 1), Day 8, Day 15, Day 28, Day 45, and Day 58. The SGRQ is a component-based questionnaire with 3 component scores (Symptoms, Activity, and Impacts) and a total score for all components. The method of calculating all component scores and total score is detailed in the SGRQ manual provided in the Appendix to this SAP.

The questions and response weights used in the scoring algorithm are presented in Section 7 of the SGRQ manual. The responses to Questions 1-8 are used to calculate the Symptoms component score. The Symptoms questions are designed to assess subjects' perception of their respiratory problems over the preceding 3 months. The Activity component score is calculated from the responses to Questions 11 and 15, which measure disturbances to subjects' daily physical activity. The Impacts component score is calculated from the responses to Questions 9-10, 12-14, and 16-17. The Impacts component score assesses disturbances of psycho-social function resulting from subjects' respiratory problems. Subjects who are not receiving respiratory treatment are scored weight values corresponding to a

response of “False” for Question 14. A Total score that summarizes the impact of the disease on overall health status also is calculated. Each component score and the total score are expressed as a percentage of overall impairment where 100 represents the worst possible health status and 0 indicates the best possible health status. No imputation for missing values will be performed. The scoring algorithms account for unanswered questions.

Summary statistics for each component score and total score will be displayed by study drug and all GBT440, and by visit for the Efficacy-Evaluable population. The change from baseline to each post-baseline visit also will be summarized. Self-described current health status (very poor, poor, fair, good, or very good) at each visit will be summarized with the number and percent of subjects in each category. Additionally, subjects receiving respiratory treatment and those who reported other activities stopped by respiratory problems at each visit will be summarized with the number and percent of subjects by study drug and overall.

ANCOVA models will be used to analyze the effect of treatment on the change from baseline with baseline value as a covariate. Least squares (LS) means and SEs will be displayed for the change from baseline in each treatment group and for all GBT440.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

Component scores and total score, self-described health status, receiving respiratory treatment, and other activities stopped by respiratory problems will be provided in a subject listing of SGRQ results.

17.3 UCSD Shortness of Breath Questionnaire

The UCSD Shortness of Breath Questionnaire is completed at Baseline (Day 1), Day 8, Day 15, Day 28, Day 45, and Day 58. The questionnaire is comprised of 24 questions each scored on a scale of 0 to 5. Total score ranges from 0 to 120 where higher scores indicate worse severity due to shortness of breath. Scores for each question answered will be summed to provide a total score. Missing responses are not included in the calculation of the total score.

Summary statistics for the UCSD Shortness of Breath Questionnaire total score will be displayed by study drug and all GBT440, and by visit for the Efficacy-Evaluable population using actual data collected at the site. The change and percent change from baseline to each post-baseline visit also will be summarized and displayed.

ANCOVA models will be used to analyze the effect of treatment on the change from baseline with baseline value as a covariate. Least squares (LS) means and SEs will be displayed for the change from baseline in each treatment group and for all GBT440.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

Total scores will be provided in a subject listing of UCSD Shortness of Breath Questionnaire results.

17.4 Borg Dyspnea Score during the 6-Minute Walk Test

The Borg dyspnea score will be assessed as the subject performs the 6MWT at the beginning of the rest period, at minute 3 during the walking period, at post-walking minute 1, and at post-walking minute 2. The Borg dyspnea score ranges from 0 to 10 with 0 being no breathing difficulty and 10 being maximal breathing difficulty. Summary statistics for the Borg dyspnea score will be presented by study drug and all GBT440 for each visit and timepoint for the Efficacy-Evaluable population. Summary statistics for the change from baseline to Day 15, Day 28, and Day 58 will also be summarized.

ANCOVA models will be used to analyze the effect of treatment on the change from baseline with baseline value as a covariate. Least squares (LS) means and SEs will be displayed for the change from baseline in each treatment group and for all GBT440.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

Borg dyspnea scores will be provided in subject listings of the 6MWT for each visit and timepoint.

17.5 Cough Visual Analog Scale

The Cough VAS is completed at Baseline (Day 1), Day 8, Day 15, Day 28, Day 45, and Day 58. The VAS is scored from 0 to 100 where 0 represents no symptom and 100 represents the worst symptom.

Summary statistics for the Cough VAS will be displayed by study drug and all GBT440, and by visit for the Efficacy-Evaluable population using actual data collected at the site. The change from baseline to each post-baseline visit also will be summarized.

ANCOVA models will be used to analyze the effect of treatment on the change from baseline with baseline value as a covariate. Least squares (LS) means and SEs will be displayed for the change from baseline in each treatment group and for all GBT440.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

17.6 A Tool to Assess Quality of Life (ATAQ)

For Part B of the study only, the ATAQ questionnaires (ATAQ Symptoms and ATAQ Impacts) will be self-administered at Baseline (Day 1), Day 8, Day 15, Day 28, Day 45, and Day 58 to assess subjects' disease symptoms across three domains (dyspnea, cough, and energy level), impact on quality of life across 4 domains (dyspnea, cough, energy level, and global impact), and a set of questions pertaining to oxygen use.

17.6.1 ATAQ Symptoms Domains

The ATAQ Symptoms questionnaire contains 3 domains (dyspnea, cough, and energy level). The dyspnea domain (Questions 1-12) assesses subjects' ability to perform physical activities in the previous 24 hours. Responses are measured using a Likert scale (0-4) as applicable to subjects who completed the activities assessed. Subjects who found the assessed activity for Questions 1, 2, 4-10, and 12 too difficult to perform due to their disease symptoms receive a score of 5 for the question, and subjects who did not complete the activity for other reasons receive no score. The cough domain (Questions 13-18) measures subjects' cough symptoms in the previous 24 hours, and the energy level domain (Questions 19-23) measures subjects' energy level in the previous 24 hours. Responses to questions within the cough and energy level symptoms domains measured on a Likert scale (0-4).

Questions 19, 20, and 21 require reverse mapping for scoring and will be mapped as follows:

- 0 mapped to 4
- 1 mapped to 3
- 2 mapped to 2
- 3 mapped to 1
- 4 mapped to 0

Each domain score ranges from 0 to 100%. Higher scores indicate worse health status in terms of subjects' symptoms. The Symptoms total score is an average of the domain scores. Details of the scoring algorithm are provided in the Appendix to the SAP.

17.6.2 ATAQ Impacts Domains

All questions within the Impact domains are assessed using a Likert scale (0-4). The impact of disease is assessed through subjects' recall of events during the previous week. Each domain (dyspnea, cough, energy level, and global impact) is scored on a scale of 0 to 100%, where 100% indicates worse health status in terms of the impact of disease on subjects' quality of life. The dyspnea domain is defined for Questions 1-6. The cough domain is defined for Questions 7-11. The energy domain is defined for Questions 13-14. The global impact domain is defined for Questions 12 and 15-21. The Impacts total score is an average of the ATAQ Impacts domain scores. The same reverse mapping as described in the previous section is required for Questions 3, 17, 18, 19, 20, and 21.

Scoring for both ATAQ questionnaires will be based only on observed data. No imputation for missing values will be used to calculate ATAQ scores.

17.6.3 Analysis of ATAQ Data

Summary statistics for each ATAQ domain will be displayed by study drug and all GBT440, and by visit for the Efficacy-Evaluable population. The change from baseline to each post-baseline visit also will be summarized.

ANCOVA models will be used to analyze the effect of treatment on the change from baseline with baseline value as a covariate. Least squares (LS) means and SEs will be displayed for the change from baseline in each treatment group and for all GBT440.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

Responses to questions regarding supplemental oxygen use will be summarized with the number and percentage of subjects in each treatment group and for all GBT440 at each visit. Flow rates of oxygen during sleep, during physical activity, and during rest also be summarized with continuous descriptive statistics if at least 2 subjects in each treatment group are on supplemental oxygen. The change from baseline to each post-baseline visit in flow rates will be included as applicable.

17.7 Cardiopulmonary Exercise Testing (CPET)

Cardiopulmonary exercise testing (CPET) parameters are computed using data collected on the CRF from all treated subjects at Day 2 and Day 29. The following CPET parameters by stage include:

Stage	CPET Parameters
Rest	HR, Extime, VCO_2, VO_2, RER, SpO_2, Art_O_2, Art_O_2Sat, Art_CO_2, Lactate
VentThrsh	HR, Extime, VCO_2, RER, SpO_2, Art_O_2, Art_O_2Sat, Art_CO_2, Lactate, VENT/ VO_2
LactThrsh	HR, Extime, VCO_2, VO_2, RER, SpO_2, Art_O_2, Art_O_2Sat, Art_CO_2, Lactate, Watts
Max	HR, Extime, VCO_2, VO_2, RER, SpO_2, Art_O_2, Art_O_2Sat, Art_CO_2, Lactate, Watts

HR = Heart Rate (bpm)
Extime = Exercise time (elapsed time from start to end of stage)
VCO_2 = Carbon Dioxide Excretion (mls/min)
VO_2 = Oxygen Consumption (ml/min)
RER = Respiratory Exchange Ratio (VCO_2/VO_2)
SpO_2 = Oxygen Saturation (%)
Art_O_2 = Arterial Oxygen (mmHg)
Art_O_2Sat = Arterial Oxygen Saturation (%)
Art_CO_2 = Arterial Carbon Dioxide (mmHg)
Lactate = Lactate Concentration (mmol/L)
Watts = Exercise Output (Watts)
VentThrsh = Ventilatory Threshold
LactThrsh = Lactic Acid Threshold

Summary statistics for the CPET parameters at the following endpoints will be displayed by study drug and for all GBT440 by visit using the Efficacy-Evaluable population. Summary statistics for the change from Day 2 to Day 29 will be included in the summary.

Parameter	Endpoint
Exercise Time (Minutes)	Max – Rest
Watts	Max
VO_2 (ml/min/kg)	Max
SpO_2 (%)	Max – Rest
Arterial Oxygen (mmHg)	Max – Rest
Arterial Oxygen Saturation (%)	Max – Rest
Lactate (mmol/L)	Max – Rest
VO_2 (ml/min/kg)	VentThrsh / Max
Watts	VentThrsh / Max
Heart Rate (bpm)	Rest
Heart Rate (bpm)	Max – Rest
RER	Max
Arterial Carbon Dioxide (mmHg)	Max – Rest
Heart Rate (bpm)	VentThrsh – Rest
Exercise Time (Minutes)	VentThrsh – Rest
VENT/VO_2 (ml/min/kg)	VentThrsh
SpO_2 (%)	VentThrsh – Rest
Arterial Oxygen (mmHg)	VentThrsh – Rest
Arterial Carbon Dioxide (mmHg)	VentThrsh – Rest
Arterial Oxygen Saturation (%)	VentThrsh – Rest

VO_2 (ml/min) will be divided by the subject's last non-missing body weight measurement before each analysis timepoint (ie Day 2 or Day 29) to obtain VO_2 (ml/min/kg).

ANCOVA models will be used to analyze the effect of treatment on the change from Day 2 with the Day-2 value as a covariate. Least squares (LS) means and SEs will be displayed for the change from Day 2 in each treatment group and for all GBT440.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

17.8 Spirometry and DLco

Spirometry and DLco are assessed at Screening (Baseline), Day 28, and Day 58. Spirometry and DLco parameters include forced expiratory volume in 1 second (FEV1) actual (L) and predicted (%), FVC actual (L) and predicted (%), FEV1/FVC (actual and predicted), DLco actual (ml/mmHg/min), and DLco adjusted (%).

Summary statistics for the spirometry and DLco parameters will be displayed by study drug and all GBT440, and by visit for the Efficacy-Evaluable population. The change and percent change from baseline to each post-baseline visit also will be summarized.

Analysis of covariance models (ANCOVA) will be used to analyze the effect of treatment on the change from baseline and the percent change from baseline for each parameter with the baseline value as a covariate. Least squares (LS) means and SEs will be displayed for the change and percent change from baseline in each treatment group and for all GBT440.

LS means (95% CI) and p-values from the models will be used to make the following comparisons:

- GBT440 600 mg – Placebo
- GBT440-900 mg – Placebo
- GBT440-1500 mg – Placebo
- All GBT 440 – Placebo

17.9 End of Study Questionnaire

The End of Study Questionnaire is an 8-item survey to evaluate the subjects' experience while on the study including symptoms, changes in oxygen saturation and use. The questionnaire is a self-administered survey to be completed during the Day-58 visit. The survey is to be completed by subjects enrolled under Part B of the trial. All responses will be summarized with the number and percentage of subjects in the Safety population by study drug and all GBT440.

18. Interim Analyses

In Part A of the study, two unblinded interim analyses of the primary and secondary endpoints are planned: i) when approximately 9 subjects have completed their Day-28 study visit and ii) when approximately 18 subjects have completed their Day-15 study visit.

19. Changes from Protocol-Stated Analyses

Protocol	SAP Change	Rationale
Exploratory endpoint: Time to first SpO2 < 88% that is sustained for at least 10 seconds during the 6MWT at days 15 and 28.	Exploratory endpoint: Time to first SpO2 < 88% during the 6MWT at days 15 and 28.	Did not collect SpO2 in seconds on CRF therefore cannot confirm “at least 10 seconds” as per the protocol definition.
	Inclusion of additional exploratory endpoints: change from end of 6MWT to rest and change from lowest SpO2 to rest	Not specified in protocol.
Efficacy-Evaluable Population: All randomized subjects who received at least 15 days of study drug treatment will be included in the Efficacy-Evaluable population.	Efficacy-Evaluable Population: All randomized subjects who received at least 14 days of study drug treatment will be included in the Efficacy-Evaluable population.	Half of 28 days (complete dosing) is 14.

20. References

Not Applicable.

21. Appendices

Saint George’s Respiratory Questionnaire Manual

ATAQ Scoring Algorithm