Statistical Analysis Plan

Protocol GBT440-026

A Phase II open label study to evaluate the effect of GBT440 on hypoxemia in subjects with Idiopathic Pulmonary Fibrosis (IPF) who are using supplemental oxygen at rest (ZEPHYR)

Protocol Date: Version / Date: 2.0 /05 /June 2017

Analysis Plan Version and Date: 1.0, Date: 15Nov2017

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

This Statistical Analysis Plan has been prepared in accordance with team reviewers' specifications.

Prepared by:

Sandra Dixon, MS
Associate Director, Biostatistics
Global Blood Therapeutics, Inc.

15 Nov 2017
Date

Reviewed by:

Kalyani Kothapalli, MS
Principal Biostatistician
Statistics and Data Corporation

15 NOV 2017
Date

1 TABLE OF CONTENTS

2 INTRODUCTION

This statistical analysis plan (SAP) was prepared in accordance with Protocol GBT440-026, dated 5June2017 (Amendment 2), and was generated prior to locking the study database. This SAP specifies the safety analyses to be performed for an abbreviated report. Planned pharmacokinetic (PK) analyses will be described in a separate analysis plan.

2.1 Overview of Study Design

This is an open label study that will be conducted in two parts. Together, Parts A and B will provide safety and efficacy data across the two GBT440 doses that are expected to improve oxygen saturation in the enrolled subjects.

Approximately up to 32 eligible subjects will be enrolled in the study.

- In Part A, up to approximately 16 eligible IPF subjects will receive 900 mg of GBT440 administered orally as 3 × 300 mg capsules or tablets once daily for 90 days.
- In Part B, up to approximately 16 eligible IPF subjects will receive 1500 mg of GBT440 administered orally as 5 × 300 mg capsules or tablets once daily for 90 days.

The screening period for each subject commences when the subject undergoes the first study-specific screening assessment and must be completed and tests evaluated before dosing (Day 1). Subjects may be rescreened up to 2 times, if deemed appropriate by the Principal Investigator. The rescreening visit should not occur sooner than 10 calendar days after the failed screening visit.

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

- Treatment period (90 days): Subjects in Part A will receive 900 mg (3 × 300 mg) and subjects in Part B will receive 1500 mg (5 × 300 mg) capsules or tablets daily
- Safety follow up (30 days): Safety will be assessed for at least 5 half-lives after the last dose of GBT440 in both Parts A and B

2.2 Primary Objective

To evaluate the effect of GBT440 on oxygen saturation at rest, breathing room air, on Days 30 and 90 compared to baseline.

2.3 Secondary Objectives

- To evaluate the effect of GBT440 on the requirement for supplemental O_2 at rest and post-exercise at Days 30 and 90 compared to baseline

- To evaluate the effect of GBT440 on resting and post-exercise Alveolar-arterial O_2 tension difference [P(A-a)O_2] at Days 30 and 90 compared to baseline
- To evaluate the effect of GBT440 on six-minute walk distance (6MWD) at Days 30 and 90 compared to baseline
- To evaluate the effect of GBT440 on IPF-related symptoms, using patient reported outcomes (PROs), at Days 30 and 90 compared to baseline
- To evaluate pulmonary function at Day 90 compared to baseline
- To evaluate the safety and tolerability of 900 mg and 1500 mg GBT440 dosed daily for 90 days
- To evaluate the PK of GBT440

2.4 Exploratory Objectives

- To evaluate the effect of GBT440 on the need for any O2 while at rest at Days 30 and 90 compared to baseline
- To compare the change in O_2 requirement between the two O_2 flow rate allocation groups
- To evaluate the effect of GBT440 on extent of activity during daily living at Days 30 and 90 compared to baseline

3 STUDY ENDPOINTS

Endpoints described below are for the safety summaries only.

3.1 Safety Endpoints

The safety outcome measures for this study are the frequency and severity of treatment-emergent adverse events and tolerability of GBT440 administered daily orally for 90 days.

4 DETERMINATION OF SAMPLE SIZE

Sample size is not based on statistical power. The study will enroll up to approximately 32 subjects; up to approximately 16 subjects in Part A and up to approximately 16 subjects in Part B.

5 METHOD OF STUDY DRUG ASSIGNMENT

All subjects who are dosed will receive either 900 mg or 1500 mg of GBT440 administered orally daily for up to 90 days.

6 ANALYSIS POPULATION

Safety Population: All subjects who receive any amount of study drug will be included in the Safety population. The Safety population will be the primary population for all safety data presented.

7 ANALYTIC DEFINITIONS

Definitions of terms used for the calculation of derived variables and general terms used for the analyses are provided in this section.

7.1 Study Day

Study Day 1 corresponds to the date of the first dose of any study drug.

Unless otherwise specified, the timing of all study-related events, assessments, and interventions will be calculated relative to Study Day 1. For events, assessments, and interventions after Study Day 1, study day represents the elapsed number of days from Study Day 1, inclusive:

Study Day *n* = (Date of assessment – Date of Study Day 1) + 1 day

Study Day -1 will be the day before Study Day 1, and in general for assessments prior to Study Day 1, study day is defined as:

Study Day *n* = (Date of assessment – Date of Study Day 1)

For listings (such as for adverse events) that include the derivation of "days since last dose," this is defined as event date – date of last dose. Events that occur on the same day as the last dose of study drug will therefore be described as occurring zero days from the last dose of study drug.

7.2 Baseline

Unless otherwise specified, the baseline value for a given variable is defined as the last measurement for the variable prior to the first dose of GBT 440. For variables where multiple assessments prior to first dose are collected, the average of those assessments is calculated for the baseline value (eg, vital signs).

8 STATISTICAL METHODS

8.1 General Considerations

Data will be summarized using descriptive statistics. Continuous variables will be summarized using mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be summarized by presenting the number (frequency) and percentage in each category. Minimum and maximum will be presented to the same decimal places as the collected data; means and medians will be presented to one additional decimal place than reported in the collected data. Standard deviations will be presented to two additional decimal places than reported in the collected data.

Change from baseline to post-baseline values will be calculated by subtracting the post-baseline value from the baseline value. The percentage change from baseline values to post-baseline values will be calculated using the following formula:

$$([\text{post-baseline value} - \text{baseline value}] / \text{baseline value}) \times 100\%$$

Data will be summarized by dose level (900 mg, 1500 mg) and all GBT440.

Individual subject data recorded on the electronic case report forms (eCRFs) presented in summary table will be presented in subject listings.

8.2 Subject Disposition

The following subject disposition information will be summarized in the Safety population except otherwise noted.

- Number of treated subjects (Safety Population)
- Number of subjects who completed study treatment (did not permanently withdraw treatment as indicated on study drug administration eCRF)
- Number of subjects who discontinued study treatment
- Number of subjects who completed study
- Number of subject who discontinued from study
- Primary reason for study discontinuation (withdrawal of consent, discretion of the investigator, lost to follow-up, or other)

Other subject listings will include a listing of inclusion and exclusion criteria violations.

8.3 Demographic and Baseline Characteristics

8.3.1 Demographic and Baseline Characteristics

The demographic variables collected in this study include age, sex, race, and ethnicity. Subjects who record more than one race will be grouped into a single category denoted as multi-racial. Additionally, the number (%) of subjects who are on background pirfenidone, nintedanib, or either on pirfenidone or nintedanib and the number (%) of subjects whose baseline flow rate was ≤ 4 L/min O2 or > 4 L/min O2, will be presented.

Age (years) will be summarized using continuous descriptive statistics. Age will be reported in years as per the eCRF.

Demographic variables will be summarized for the Safety population.

8.3.2 Targeted and Other Medical History

Targeted medical history events will be summarized (n, percent) by the event type for the Safety population. The targeted medical history events that will be summarized are as follows:

- Cancer history
- Inflammatory/autoimmune disease
- Primary hypertension (including grade of severity and medication taken)
- Pulmonary rehabilitation
- Gastroesophageal reflux (including medication taken)
- Sleep disordered breathing/sleep apnea (including CPAP, surgeries, medication taken)
- Pulmonary embolism (including medication taken)
- Lactose intolerance (including medication taken)

Disorders recorded on the other medical history eCRF will be mapped to a preferred term (PT) and a system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA, Version 20.0). Other medical history events will be summarized by SOC and PT for the Safety population. If a subject has more than one event within a SOC, the subject will be counted only once in that SOC. If a subject has more than one event that codes to the same PT, the subject will be counted only once for that PT.

8.3.3 Prior and Concomitant Medications

All prior and concomitant medications will be coded using WHO Drug Dictionary Enhanced March 2017. Concomitant medications are defined as medications with start date or end date on or after the date of first dose and start date before the date of the last dose + 30 days or are ongoing at the time of first dose. Prior medications are defined as medications with a stop date before the date of first dose of study drug.

Prior and concomitamt medications will be listed only.

8.4 Safety Analysis

All safety analyses will be based on the Safety population.

8.4.1 Study Drug Administration

The following measures of overall extent of GBT 440 includes:

- Extent of exposure (days), defined as (date of last dose – date of first dose + 1)
- Number (%) of subjects with drug permanently discontinued
    - Reasons for discontinuation (Adverse event, Other)

- Number (%) of subjects with at least one dose missed
    - Number of subjects grouped by number of doses missed (0,1, etc.)
- Number (%) of subjects with at least one dose reduction
    - Number of subjects grouped by number of dose reductions (0,1, etc.)
    - Reasons for dose reduction (AE or Other)
- Number (%) of subjects with at least one dose interruption
    - Number of subjects grouped by number of dose interruptions (0,1, etc.)
    - Reasons for dose interruption (AE or Other)

8.4.2 Study Drug Compliance

Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses as follows.

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

The actual days dosed is defined as the sum of the days a subject was dosed. The number of expected days dosed (date of last dose – date of Day 1 +1) that will be used for calculating dosing compliance.

8.4.3 Adverse Events

Each reported AE term will be mapped to PT and SOC using the MedDRA Version 20.

Treatment-emergent 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. Treatment-emergent adverse events (TEAEs) will be summarized based on the number (%) of subjects experiencing events by SOC and PT. The denominator for the percentage will be based on the number of subjects in the Safety population (i.e., those that received at least one dose of study drug).

A subject reporting the same AE more than once will be counted only once when calculating incidence 1) within a given system organ class, and 2) within a given system organ class and preferred term combination. For such cases, the maximum CTCAE toxicity grade and strongest causal relationship to study treatment for the event will be used in the incidence calculations.

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. This summary will also include TEAEs ≥ Grade 3, TEAEs possibly/probably related to study drug, serious adverse events (SAEs), TEAEs leading to discontinuation of study drug, and deaths.

Summaries of the following TEAEs will be provided by SOC and PT:

- All TEAEs
- Treatment-related AEs
- TEAEs by maximum severity, table includes a summary of AEs grade 3 or higher
- Serious TEAEs (AE listing)
- TEAEs that led to dose modification or permanent discontinuation of GBT 440 (listing only)

Summaries presented by SOC and PT will be ordered alphabetically for SOC and descending frequency within SOC of PT based on the total GBT 440 group.

All AE data will be summarized for each dose level (900 mg, 1500mg).

8.4.4 Laboratory Data

Actual values and change from baselines for all laboratory parameters will be summarized using descriptive statistics (serum chemistry, liver function tests, hematology, and serum erythropoietin) using SI units. Coagulation results will be listed only. Baseline is defined as the Screening measurement taken before the first dose of GBT440 for most labs. Baseline serum erythropoietin is Day 1.

A listing of all clinically significant laboratory values will be provided. Pregnancy results at each visit will be listed without summary. Listings will be presented with reported units and SI units.

8.4.5 Vital Signs and Physical Examination

Actual value and change from baseline for vital sign and pulse oximetry results including blood pressure (SBP[mmHg], DBP[mmHg]), heart rate (bpm), respiratory rate (bpm), temperature (C), SpO2(%) and flow rate (L/min) will be summarized at each scheduled visit.

Physical examination results including height, weight, and BMI will be summarized by the absolute value and change from baseline at each scheduled visit during the study. Height will presented for Screening only. Baseline is the Screening visit.

Baseline for vital signs is defined as the average of Screening and Day 1 measurements taken before the first dose of GBT440.

8.4.6 12-Lead Electrocardiogram

HR (beats/min), PR interval (ms), QRS interval (ms), QT interval (ms), and QTc F interval (ms) will be summarized by the absolute value and change from baseline (Screening) at D90.

Additionally, the number and percentage of subjects with QTcF > 450 ms, >480 ms, and >500 ms at baseline and post-baseline measurement (Day 90 and Early Termination) will

be summarized by dose level and All GBT 440. The number and percentage of subjects with increase from baseline in QTcF of > 30ms and > 60 ms will also be summarized.

8.5 Pharmacokinetic Analyses

Planned PK will be described in a separate analysis plan. The results will be described in the CSR.

Safety population.

9 STATISTICAL/ANALYTICAL ISSUES

9.1 Handling of Dropouts or Missing Data

Missing data will not be estimated or carried forward for any of the other summaries.

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:

- 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.
- 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.