STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2a, Open-label, Single and Multiple Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability, and Exploratory Treatment Effect of GBT440 in Adolescents with Sickle Cell Disease
Phase:	2b
Protocol No.:	GBT440-007
Protocol Date:	14June2018 Amendment 5
Analysis Plan Version and Date:	Part A and Part B: Version 1.0, 11January2019

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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

Prepared by:

PPD

PPD

PPD

MS

Global Blood Therapeutics, Inc.

PPD

Date

Reviewed by:

PPD

PPD

PPD

MS

PPD

PharPoint Research, Inc.

PPD

Date

Approved by:

PPD

PPD

PPD

PhD

Global Blood Therapeutics, Inc.

PPD

Date

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL 2
TABLE OF CONTENTS 3
LIST OF TABLES 4
1. GLOSSARY OF ABBREVIATIONS 5
2. INTRODUCTION AND STUDY OVERVIEW 6
3. OBJECTIVES 7
3.1. Part A Objectives 7
3.2. Part B Objectives 7
3.3. Part C Objectives 8
4. DEFINITIONS AND TERMINOLOGY 8
5. STUDY ENDPOINTS 10
5.1. Part A Endpoints 10
5.2. Part B Endpoints 10
5.3. Part C Endpoints 11
6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING 11
6.1. Sample Size Considerations 11
6.2. Handling of Data 12
6.2.1. Visit Windows 12
6.2.2. Missing Start and Stop Dates for Prior and Concomitant Medication 12
6.2.3. Missing Start and Stop Dates for Adverse Events 13
7. ANALYSIS POPULATIONS 13
7.1. Efficacy Evaluable Population 13
7.2. Safety Population 13
7.3. PK Population 13
8. STATISTICAL METHODS 13
8.1. Subject Disposition, Demographic and Baseline Characteristics 14
8.1.1. Subjects Disposition 14
8.1.2. Demographic and Baseline Characteristics 14
8.1.3. Baseline Sickle Cell Disease Characteristics 14
8.1.4. Other Medical History 14
8.2. Efficacy Analysis 14

8.2.1. Analysis of the Primary Efficacy Endpoint 14
8.2.2. Analysis of the Secondary Efficacy Endpoints 15
8.3. Safety 15
8.3.1. Summary of Exposure 15
8.3.2. Adverse Events 15
8.3.3. Concomitant Medications 16
8.3.4. Clinical Laboratory Data 16
8.3.5. Vital Signs and Physical Exam 17
8.3.6. 12-Lead Electrocardiogram 17
9. PROTOCOL DEVIATIONS 17
10. CHANGES IN THE PLANNED ANALYSES 17
11. TABLES, FIGURES, AND LISTINGS 18
11.1. Tables Part A 18
11.2. Listings Part A 19
11.3. Tables Part B 20
11.4. Listings Part B 22

LIST OF TABLES

Table 1: Nominal Analysis Visit Windows for PRO Measures 12

1. GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CRF	Case Report Form
Cmax	Maximum Blood Concentration
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data and Safety Monitoring Board
HU	Hydroxyurea
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PT	Preferred Term
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCD	Sickle Cell Disease
SCDSM	Sickle Cell Disease Severity Measure
SD	Standard Deviation
SOC	System Organ Class
TAMM	Time-Averaged Mean of the Maximum
TCD	Transcranial Doppler
TEAE	Treatment-Emergent Adverse Event
TSS	Total Symptom Score
WHO	World Health Organization

2. INTRODUCTION AND STUDY OVERVIEW

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and data displays to be included in the interim Clinical Study Report (CSR) for Protocol GBT440-007. The SAP will describe the analyses for Part A and Part B of the study only.

This SAP was developed in accordance with the ICH E9 guideline. All decisions regarding final interim analysis, as defined in this SAP, will be made prior to database snapshot. Further information can be found in the protocol.

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 CSR.

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

Study Overview:

This study is a multicenter, open-label study to evaluate the safety, PK and efficacy of GBT440 in pediatric participants with SCD.

This study consists of three parts, Part A, Part B and Part C:

Part A is a single dose PK study of GBT440 in pediatric participants with SCD aged 6 to 17 years. This study will involve 2 cohorts in this age range, Cohort 1 (12 to 17 years) and Cohort 2 (6 to 11 years)

Part B is a multiple dose, safety, PK and efficacy study of GBT440 in pediatric participants with SCD aged 12 to 17 years, inclusive.

Prior to proceeding from the 900 mg dose to the 1500 mg dose in Part B, the following data reviews will be conducted:

A review of the PK data from at least 8 pediatric participants enrolled in Part B of Study GBT440-007, following at least 15 days of dosing with GBT440 900 mg.

DSMB review of safety data from at least 8 pediatric participants enrolled in Part B of Study GBT440-007, following the completion of 28 days of dosing with GBT440 900 mg to confirm acceptable safety and tolerability.

DSMB review safety data from the first 6 adult participants 1500 mg dose level from Group 1 of Study GBT440-031 (HOPE study), following at least 28 days of dosing with study drug to confirm acceptable safety and tolerability.

Part C will assess the safety, tolerability and PK, as well as the hematological effects and the effect on TCD flow velocity of GBT440 in pediatric participants with SCD who are 4 to 17 years of age.

Up to 50 pediatric participants will be enrolled.

- At least 30 participants must have a TCD velocity ≥140 cm/sec and <200 cm/sec upon Screening AND
- At least 20 participants must be between 4 to 11 years of age

To further characterize a potential effect on TCD data for those participants who have a TCD velocity ≥140 cm/sec and <200 cm/sec upon screening, approximately 20 participants may be added with a TCD velocity of ≥140 cm/sec and <200 cm/sec, depending on the emerging data. In this event, Part C will contain up to 70 pediatric participants.

3. OBJECTIVES

3.1. Part A Objectives

Primary Objective:

To characterize the PK of GBT440 in plasma and whole blood following a single dose in pediatric participants with SCD

Secondary Objective:

To evaluate the safety and tolerability of GBT440 following a single dose in pediatric participants with SCD

3.2. Part B Objectives

Primary Objective:

The primary objective is to assess the efficacy of GBT440 in pediatric participants with SCD as measured by improvement in anemia

Secondary Objectives:

- To provide data on the ePRO measurement in establishing the longitudinal measurement properties of the PRO
- To evaluate the effect of GBT440 on clinical measures of hemolysis
- To characterize the PK of GBT440 in plasma, whole blood and red blood cells (RBCs) following multiple doses in pediatric participants with SCD
- To evaluate the safety and tolerability of GBT440 following multiple doses in pediatric participants with SCD
- To evaluate the effect of GBT440 on cerebral hemodynamics as assessed by transcranial Doppler (TCD) ultrasonography
- To evaluate the effects of GBT440 on SCD symptom exacerbation and total symptom score (TSS) from PRO measurement

3.3. Part C Objectives

Primary Objective:

To evaluate the effect of GBT440 on cerebral hemodynamics in pediatric participants with SCD with elevated or conditional TCD low velocity as assessed by transcranial Doppler (TCD) ultrasonography

Secondary Objectives:

- To evaluate the effect of GBT440 on clinical measures of anemia and hemolysis
- To characterize the PK of GBT440 in plasma, whole blood and red blood cells (RBCs) following multiple doses in pediatric participants with SCD
- To evaluate the safety and tolerability of GBT440 following multiple doses in pediatric participants with SCD

4. DEFINITIONS AND TERMINOLOGY

Study Day

Study Day is defined relative to initiation of treatment, i.e., Day 1. Thus, the study day of an event is calculated as:

Study Day = event date –Day 1 date + 1.

Day 1 is the date that study drug is first initiated.

Study Visit

Study Visit is the nominal visit as recorded on the CRF.

Baseline

For all endpoints where both Screening and Day 1 pre-dose assessments are collected, baseline is defined as average of all assessments prior to the first dose. If there is an unscheduled visit prior to first dose, this unscheduled assessment will also be included in the baseline calculation. For PRO endpoints specific to SCD, e.g. TSS, the Baseline value is the average of the non-missing scores during the 28 to 35-day Screening period (Part B).

Change from Baseline

Change from baseline to follow-up visit will be calculated as the baseline measurement subtracted from the follow-up measurement for all assessments. 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%

Duration of Exposure to Study Drug

Duration of exposure to study drug is defined as the number of weeks from Day 1 to the last date of dosing of Study drug which excludes days where treatment was entirely missed or intermittently stopped as recorded in the CRF. Duration of study drug exposure is calculated as follows:

$$\frac{\sum_{i=1}^{n}[End\ Date\ of\ Dose_i - Start\ Date\ of\ Dose_i + 1] \times I_{Dose_i}}{7},$$

where n is the number of dose modifications during the study and

$$I_{Dose_i} = \begin{cases} 0, if\ treatment\ dose\ i = 0\ mg \\ 1, if\ treatment\ dose\ i\ \neq 0\ mg \end{cases}.$$

Total Symptom Score (TSS)

For each participant, the TSS will be computed as follows: The Baseline TSS is the average of the scores during the 35 Screening period, i.e. the sum of non-missing TSS scores divided by the number of non-missing diary entries. Participants in Part B must complete a minimum of 14 days during Screening with ePRO to be enrolled in the study. During the treatment period when there is at least or 75% compliance during a 4-week period, the TSS is the average score for each 4-week period on treatment. The 4-week periods are Weeks 1-4 (Study Day 1-28), Weeks 5-8 (Study Day 29-56), Weeks 9-12 (Study Day 57-84), Weeks 13-16 (Study Day 85-112), Weeks 17-20 (Study Day 113-140), Weeks 21-24 (Study Day 141-168), and Weeks 25-28 (Study Days 169-196). If lack of compliance is due to missed diary entries or participant dropout, the TSS will be set to missing for that 4-week period or that 4-week period and beyond, respectively.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study drug. This definition includes medications started prior to the initiation of study drug, but continuing concurrently with study drug.

Prior Medications

Prior medications are those medications taken prior to the initiation of study drug.

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after initiation of study drug (having been absent pre-treatment), or an AE that existed pre-treatment and worsened on treatment (relative to the pre-treatment state) through 28 days after study drug discontinuation. AEs occurring on Day 1 are assumed to be treatment-emergent.

5. STUDY ENDPOINTS

5.1. Part A Endpoints

Primary Endpoint:

- C_{max}, area AUC from time 0 to the time of the last quantifiable concentration ($AUC_{0\text{-}last}$) and $AUC_{0\text{-}inf}$ of GBT440 in whole blood

Secondary Endpoints:

- C_{max}, $AUC_{0\text{-}last}$ and AUC0-$_{inf}$ of GBT440 in plasma and RBC
- The time that C_{max} was observed (t_{max}), terminal elimination half-life ($T_{1/2}$) in RBC, whole blood and plasma, and percent Hb occupancy

Safety Endpoints:

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)
- Clinical laboratory tests, physical examination findings, vital signs and ECGs

5.2. Part B Endpoints

Primary Endpoint:

- Change from baseline to Week 24 in Hb

Secondary Endpoint:

- Proportion of days with SCD symptom exacerbation during the first 24 weeks of treatment.
- Change from Baseline to Weeks 21–24 in the (SCDSM) TSS
- Change from baseline to 12 and 24 weeks in LDH, indirect bilirubin and reticulocyte count
- GBT440 PK (C_{max}, AUC0-$_{last}$, $AUC_{0\text{-}inf}$, $AUC_{0\text{-}24}$, $T_{1/2}$, accumulation ratio, blood/plasma ratio, RBC/plasma ratio, if appropriate) and percent Hb occupancy
- Change from baseline to 12 and 24 weeks in cerebral blood flow as measured by the TAMM TCD velocity

Safety Endpoints:

- TEAEs and SAEs
- Clinical laboratory tests, physical examination findings, vital signs and ECGs

5.3. Part C Endpoints

Primary Endpoint:

- Change from baseline to 48 Weeks in cerebral blood flow as measured by the TAMM TCD velocity

Secondary Endpoints:

- Change from baseline to Weeks 24 and 48 in Hb, LDH, indirect bilirubin and reticulocyte count
- Change from baseline to 24 weeks in cerebral blood flow as measured by the TAMM TCD velocity
- GBT440 PK (C_{max}, AUC0-$_{last}$, AUC0-inf, AUC0-$_{24}$, $T_{1/2}$, accumulation ratio, blood/plasma ratio, RBC/plasma ratio, if appropriate) and percent Hb occupancy

Safety Endpoints:

- TEAEs and SAEs
- Clinical laboratory tests, physical examination findings, vital signs and ECGs

6. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

6.1. Sample Size Considerations

Part A: A cohort size of up to approximately 6 participants for each age group: 6 to 11 and 12 to 17 is based on a typical size for a single-dose PK study and is intended to balance the desire to minimize exposure of pediatric participants to a novel compound at this stage of GBT440's development with the need to obtain PK, safety and tolerability data. No formal power or sample size calculations were performed to determine the cohort size.

Part B: Approximately 12 participants at 900 mg were selected to determine preliminary safety, tolerability, PK, laboratory effects and treatment response of GBT440 in pediatric participants with SCD. The number of participants may be increased to approximately 36 to further characterize the effect of multiple doses of GBT440. Upon a favorable review by the DSMB, dosing of a minimum of 6 participants at 1500 mg may commence (dependent on how many participants were enrolled at 900 mg, i.e. not to exceed a total study size of approximately 36).

For the endpoint of change from baseline to Week 24 in Hb, power calculations assume normally distributed data, a mean treatment effect (change from baseline) of 0.8 g/dL, with a standard deviation (SD) of 0.6 g/dL. For a two-sided alpha = 0.05 and N = 12, power exceeds 90% with a paired t-test to reject the null hypothesis of equality of post-treatment and baseline Hb means. The estimates of 0.8 g/dL and 0.6 g/dL for the mean and SD, respectively, are based on available Day 90 data from Cohorts 16 and (partial data) 17 from the GBT440-001 study.

Part C: Up to 50 pediatric participants who are 4 to 17 years of age with SCD will be enrolled. For the primary efficacy endpoint, change from baseline in TAMM TCD velocity at Week 48, a sample size of 30 participants achieves greater than 95% power to detect a mean difference of 15 cm/sec with an estimated sample standard deviation of 22 cm/sec using a paired t-test (two-sided) with a significance level (alpha) of 0.10.

6.2. Handling of Data

6.2.1. Visit Windows

Visit windows will be defined for Part B PRO measures. PRO measures include ePRO Screening and ePRO SCDSM.

Table 1: Nominal Analysis Visit Windows for PRO Measures

Nominal Visit Time	Study Day Range for Statistical Analysis
Screening	[-28, -1]
Week 4	[1, 28]
Week 8	[29, 56]
Week 12	[57, 84]
Week 16	[85, 112]
Week 20	[113, 140]
Week 24	[141, 168]
Week 28	[169, 196]

Note: ePRO SCDSM is measured every day from the first day of screening to Week 28 post first dose. Participants must complete a minimum of 14 days during Screening.

6.2.2. Missing Start and Stop Dates for Prior and Concomitant 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 treatment start date then the concomitant medication start date will be imputed as the treatment start date.

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 treatment start date then the concomitant medication start date will be imputed as the treatment start date.

For missing stop day only: Day only 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).

6.2.3. Missing Start and Stop Dates for Adverse Events

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 treatment start date then the adverse event start date will be imputed as the day prior to the treatment start date.

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

7. ANALYSIS POPULATIONS

7.1. Efficacy Evaluable Population

All participants who received any amount of study drug will be included in the Efficacy Evaluable population (EE). All efficacy analyses will be based on the EE population.

7.2. Safety Population

All participants who received any amount of study drug will be included in the Safety population. All safety analyses will be based on the Safety population. The Safety Population is defined as all subjects who receive at least one dose of study medication. This population will be used in the assessment and reporting of safety data.

7.3. PK Population

All participants who receive any amount of study drug and who provide PK data from at least one post dose sample in plasma will be included in the PK population. Additional details are provided in a separate plan.

8. STATISTICAL METHODS

The interim data analysis will be performed at the time of the database snapshot.

Statistical programming and analyses will be performed using SAS® Version 9.4 or higher.

Select Part A summaries will be presented for the 600 mg dose level by age group (6-11 years and 12-17 years) and Overall voxelotor (both age groups).

Part B summaries will be presented by dose level (900 mg and 1500 mg).

Continuous variables will be descriptively summarized using number of participants (n), mean, standard deviation (SD), median, minimum, maximum, and, as appropriate, geometric mean. Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category.

8.1. Subject Disposition, Demographic and Baseline Characteristics

8.1.1. Subjects Disposition

Participant disposition will be presented in terms of the numbers and percentages of participants who completed the treatment and discontinued from treatment. The reasons for early treatment discontinuation will be presented. Similar results will be presented for subjects who discontinue study.

Screen failures along with the reasons for screen failure will be listed only.

8.1.2. Demographic and Baseline Characteristics

The demographic variables collected in this study include age (years) at Screening, sex, race, and ethnicity and will be summarized descriptively. Height (cm), weight (kg) and BMI (kg/m^3) at Screening will be presented using descriptive statistics. Participants who record more than one race will be grouped into a single category denoted as multi-racial.

8.1.3. Baseline Sickle Cell Disease Characteristics

Number of VOCs including the number of VOCs requiring hospitalization and the number of blood transfusion during the previous 12 months will be summarized categorically.

Additional summaries including the number and percentage of participants who currently use HU, who have each genotype (HbSS or HbSBO) and who experienced a sickle cell complication prior to study enrollment will be presented. Baseline lab values including Hb, HbF (Part B only), and reticulocyte count will be summarized using descriptive statistics.

In Part B, prior HU results including most recent labs prior to initiation of HU, maximum tolerated dose of HU and lab results one month post MTD of HU will be provided in a listing.

8.1.4. Other Medical History

Other medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA), version 20.0 coding dictionary.

8.2. Efficacy Analysis

All efficacy data in Part B will be summarized using the EE population.

8.2.1. Analysis of the Primary Efficacy Endpoint

Change from baseline in hemoglobin to Week 24 will be summarized descriptively. The changes from baseline will be presented including the (absolute) values at each visit. Additionally, a responder endpoint defined as an increase in Hb >1 g/dL compared to Baseline, will be summarized descriptively at Week 12 through Week 24. No imputation will be performed for this endpoint.

8.2.2. Analysis of the Secondary Efficacy Endpoints

Change from baseline to each of the 4 week periods (Section 4, TSS definition) for the sickle cell disease severity measure (SCDSM) TSS, will be summarized. If SCDSM compliance is less than 75% for a 4-week period, the proportion will be considered missing.

Hematology parameters (reticulocyte count, indirect bilirubin, and LDH) and cerebral blood flow as measured by TAMM TCD velocity will be summarized at each visit for observed values and changes (absolute and percent) from baseline using appropriate descriptive statistics. If indirect bilirubin is missing and direct and total bilirubin are collected, indirect can be calculated as:

8.3. Safety

All safety analyses will be conducted using the Safety Population.

8.3.1. Summary of Exposure

Study drug administration in Part B will be summarized with number and percentage of participants receiving from 1 to the maximum number of doses by treatment group. Similarly, the duration of study drug exposure will be summarized with descriptive statistics.

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

8.3.2. Adverse Events

Adverse events reported for participants 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 20.0.

TEAE summary tables in both Part A and Part B will exclude sickle cell disease (SCD) related events defined as preferred terms of: combined acute chest syndrome and pneumonia, sickle cell anemia with crisis, osteonecrosis, and priapism. Additional select TEAE tables (Part B only) will summarize SCD related events which only include the preferred terms of acute chest syndrome and pneumonia (combined), sickle cell anemia with crisis, osteonecrosis, and priapism.

An overall summary will be presented which includes the number of TEAEs and the number and percentage of participants who experienced at least one TEAE. This summary will also include TEAEs Grade 3 or greater, TEAEs possibly/probably related to study drug, TEAEs leading to study drug reduction, TEAs leading to discontinuation of study drug, serious adverse events (SAEs), and deaths.

Additional summaries of TEAEs will be provided showing the number and percentage of participants who experienced at least one TEAE. These summaries will be presented by system organ class (SOC), preferred term (PT) and maximum severity. If a participant reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC for

that participant. As with the PT, if a participant reports multiple conditions within the same SOC, that SOC will only be counted once for that participant. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all participants within each SOC.

The occurrence of TEAEs possibly/probably related to GBT440 will be tabulated by SOC, PT and maximum severity. Serious adverse events will be presented by system organ class (SOC), preferred term (PT) and maximum severity.

Adverse events recorded in the eCRF which began prior to first dose of study drug will not be included in the summary tables.

8.3.3. 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.

8.3.4. Clinical Laboratory Data

All hematology and chemistry laboratory assessments were performed by local laboratories.

The following protocol-specified clinical laboratory findings will be summarized using descriptive statistics by dose level.

1. Hematology:
    a. Hemoglobin
    b. Neutrophils (absolute and %)
    c. Platelets
    d. Reticulocyte %
    e. WBC
2. Chemistry and Liver Function Tests:
    a. Alkaline phosphatase
    b. ALT
    c. AST
    d. Potassium
    e. Indirect bilirubin
    f. Total bilirubin
    g. Serum Erythropeietin

Change from baseline and the percent change from baseline will be summarized for the above laboratory results. Analyte units will be converted to SI units.

Participant listings of laboratory data will include a separate listing for clinically significant laboratory results. Urinalysis, coagulation and pregnancy results will be listed only.

8.3.5. Vital Signs and Physical Exam

Part A vital signs and physical exam data will be listed only.

Part B vital signs, including systolic and diastolic blood pressure, heart rate, and weight will be summarized using continuous descriptive statistics at each visit and time point by dose level. Change from baseline will also be summarized for each post-baseline visit.

8.3.6. 12-Lead Electrocardiogram

Heart rate, PR interval, QRS interval, QT interval, RR interval, and QTcF (Fridericia's) interval will be summarized along with the change from baseline using descriptive statistics at each visit in Part B. The average of the 3 ECGs collected will be used in the summary tables.

Additionally, in both Part A and Part B, the number and percentage of participants with QTcF $\leq$ 450 ms, >450 ms to $\leq$ 480 ms, >480 ms to $\leq$ 500 ms, and >500 ms at baseline and as the maximum post-baseline measurement will be summarized. The number and percentage of participants with maximum increase from baseline where increase in QTcF $\leq$ 30 ms, > 30 ms to 60 ms and> 60 ms also will be summarized. If the QTcF interval was not collected, the interval will be calculated using the following formula:

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

9. PROTOCOL DEVIATIONS

Protocol deviations as assessed by the study team will be displayed in a data listing and sorted by treatment group, subject number, and then by date (where applicable) within each subject number. The type of deviation along with a description and any additional comments about the deviation will be listed.

10. CHANGES IN THE PLANNED ANALYSES

The secondary endpoint, proportion of days with SCD symptom exacerbation during the first 24 weeks of treatment, will not be summarized. The definition for this variable is not defined at the time of the analysis.

11. TABLES, FIGURES, AND LISTINGS

Key planned summary tables and listings are provided below. Additional listings and tables may be included in final CSR and table/listing numbers may change.

11.1. Tables Part A

Item	Title
Table 14.1.1.a	Demographics and Baseline Characteristics
Table 14.1.2.a	Baseline Sickle Cell Disease Characteristics
Table 14.1.3.a	Other Medical History
Table 14.1.4.a	Participant Follow-up and Termination from Study
Table 14.1.5.a	Concomitant Medications
Table 14.3.1.1.a	Overview of Treatment-Emergent Adverse Events and Serious Adverse Events
Table 14.3.1.2.a	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Table 14.3.2.1.a	Summary of Hematology and Change from Baseline
Table 14.3.2.2.a	Summary of Serum Chemistry and Change from Baseline
Table 14.3.2.3.a	Summary of Liver Function Tests and Change from Baseline
Table 14.3.3.a	Corrected QT Interval (Fridericia) Maximum Post-Baseline and Maximum Increase from Baseline Categories

11.2. Listings Part A

Item	Title
Listing 16.2.1.a	Eligibility and Enrollment for Screen Failures
Listing 16.2.2.a	Protocol Deviations for Safety Population
Listing 16.2.3.a	Demographics for Safety Population
Listing 16.2.4.a	Baseline Characteristics for Safety Population
Listing 16.2.5.a	Sickle Cell Disease History for Safety Population
Listing 16.2.6.a	Sickle Cell Disease Complications for Safety Population
Listing 16.2.7.a	Participant Follow-Up and Termination from Study for Safety Population
Listing 16.2.8.a	Prior and Concomitant Medications for Safety Population
Listing 16.2.9.a	Adverse Events for Safety Population
Listing 16.2.10.a	Study Drug Administration for Safety Population
Listing 16.2.11.1.a	Clinically Significant Laboratory Results for Safety Population
Listing 16.2.11.2.a	Coagulation Results for Safety Population
Listing 16.2.11.3.a	Urinalysis Results for Safety Population
Listing 16.2.11.4.a	Pregnancy Results for Safety Population
Listing 16.2.12.a	Vital Signs for Safety Population
Listing 16.2.13.a	Electrocardiogram for Safety Population
Listing 16.2.14.a	Physical Examinations for Safety Population

11.3. Tables Part B

Item	Title
Table 14.1.1.b	Eligibility and Enrollment
Table 14.1.2.b	Demographics and Baseline Characteristics
Table 14.1.3.b	Baseline Sickle Cell Disease Characteristics
Table 14.1.4.b	Other Medical History
Table 14.1.5.b	Participant Follow-up and Termination from Study
Table 14.1.6.b	Concomitant Medications
Table 14.1.7.b	Study Drug Exposure
Table 14.2.1.1.b	Summary of Hemoglobin and Measures of Hemolysis
Table 14.2.1.2.b	Hemoglobin Responders
Table 14.2.2.b	Summary of TCD Velocity and Change from Baseline
Table 14.2.3.b	Summary of Sickle Cell Disease Measure Total Symptom Score and Change from Baseline
Table 14.3.1.1.b	Overview of Treatment-Emergent Adverse Events and Serious Adverse Events
Table 14.3.1.2.1.b	Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Table 14.3.1.2.2.b	SCD Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Table 14.3.1.3.1.b	Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity
Table 14.3.1.3.2.b	SCD Related Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity
Table 14.3.1.4.b	Treatment-Emergent Adverse Events by Preferred Term
Table 14.3.1.5.b	Treatment-Emergent Adverse Events Related to Study Drug by Preferred Term
Table 14.3.1.6.1.b	Serious Adverse Events by System Organ Class and Preferred Term and Maximum Severity
Table 14.3.1.6.2.b	SCD Related Serious Adverse Events by System Organ Class and Preferred Term and Maximum Severity
Table 14.3.2.1.b	Summary of Hematology and Change from Baseline

Item	Title
Table 14.3.2.2.b	Summary of Serum Chemistry and Change from Baseline
Table 14.3.2.3.b	Summary of Liver Function Tests and Change from Baseline
Table 14.3.2.4.b	Summary of Serum Erythropoietin and Change from Baseline
Table 14.3.3.b	Summary of Vital Sign and Weight
Table 14.3.4.1.b	Summary of Electrocardiograms
Table 14.3.4.2.b	Corrected QT Interval (Fridericia) Maximum Post-Baseline and Maximum Increase from Baseline Categories

11.4. Listings Part B

Item	Title
Listing 16.2.1.b	Eligibility and Enrollment for Screen Failures
Listing 16.2.2.b	Protocol Deviations for Safety Population
Listing 16.2.3.b	Demographics for Safety Population
Listing 16.2.4.b	Baseline Characteristics for Safety Population
Listing 16.2.5.b	Sickle Cell Disease History for Safety Population
Listing 16.2.6.b	Sickle Cell Disease Complications for Safety Population
Listing 16.2.7.b	Hu History for Safety Population
Listing 16.2.8.1.b	Adverse Events for Safety Population
Listing 16.2.8.2. b	Serious Adverse Events for Safety Population
Listing 16.2.9.1.b	Clinically Significant Laboratory Results for Safety Population
Listing 16.2.9.2.b	Coagulation Results for Safety Population
Listing 16.2.9.3.b	Urinalysis Results for Safety Population
Listing 16.2.9.4.b	Pregnancy Results for Safety Population
Listing 16.2.9.5.b	Pregnancy Results for Safety Population

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2a, Open-label, Single and Multiple Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Treatment Effect of GBT440 in Pediatric Participants with Sickle Cell Disease
Phase:	2a
Protocol No.:	GBT440-007
Protocol Date:	28 April 2021, Amendment 7
Analysis Plan and Date:	Part C (Final Data), 2 November 2022

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

Prepared by:

PPD

02-Nov-2022 | 14:18 PDT

PPD MS
PPD
Date

Global Blood Therapeutics, Inc.

Reviewed by:

PPD

03-Nov-2022 | 11:10 EDT

PPD MStat
PPD
Date

PharPoint Research, Inc.

Approved by:

PPD

03-Nov-2022 | 08:14 PDT

PPD , PhD PPD
PPD
Date

Global Blood Therapeutics, Inc.

.

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL 2
TABLE OF CONTENTS 3
1. GLOSSARY OF ABBREVIATIONS 5
2. INTRODUCTION AND STUDY OVERVIEW 6
2.1. Objectives 6
2.2. Part C (Multiple Dose) 6
2.2.1. Primary Objective 6
2.2.2. Secondary Objective 6
3. ENDPOINTS 8
3.1. Endpoints for Part C 8
3.1.1. Primary Endpoint 8
3.1.2. Secondary Endpoints 8
3.1.3. Safety Endpoints 8
4. DEFINITIONS AND TERMINOLOGY 8
5. GENERAL STATISTICAL CONSIDERATIONS 10
5.1. Sample Size Considerations 10
5.2. Handling of Missing or Partial Dates 10
5.2.1. Missing Start and Stop Dates for Prior and Concomitant Medication 10
5.2.2. Missing Start and Stop Dates for Adverse Events 10
6. ANALYSIS POPULATIONS 10
6.1. Efficacy Evaluable Population 10
6.2. Safety Population 10
6.3. PK Population 11
7. STATISTICAL METHODS 11
7.1. Subject Disposition, Demographic and Baseline Characteristics 11
7.1.1. Subject Disposition 11
7.1.2. Demographic and Baseline Characteristics 11
7.1.3. Baseline Sickle Cell Disease Characteristics 11
7.1.4. Medical History Excluding Sickle Cell History 11
7.2. Efficacy Analysis 12
7.3. Safety 12

7.3.1. Summary of Exposure 12
7.3.2. Adverse Events 13
7.3.3. Concomitant Medications 14
7.3.4. Clinical Laboratory Data 14
7.3.5. Vital Signs and Physical Exam 15
7.3.6. 12-Lead Electrocardiogram 15
8. PROTOCOL DEVIATIONS 15

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CRF	Case Report Form
Cmin	Trough Concentration
Cmax	Maximum Concentration
CTCAE	Common Terminology Criteria for Adverse Events
HU	Hydroxyurea
ICH	International Conference on Harmonisation
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PT	Preferred Term
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCD	Sickle Cell Disease
SD	Standard Deviation
SOC	System Organ Class
TAMM	Time-Averaged Mean of the Maximum
TCD	Transcranial Doppler
TEAE	Treatment-Emergent Adverse Event
WHO	World Health Organization

2. INTRODUCTION AND STUDY OVERVIEW

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses of final data from GBT44-007 Part C.

Where applicable, the statistical analysis methods presented in this document supersede the statistical analysis methods described in the study protocol.

Study Overview:

GBT440-007 is a multicenter, open-label study to evaluate the safety, PK and efficacy of voxelotor in pediatric subjects with SCD.

This study consists of 4 parts, Part A, Part B, Part C and Part D. The planned analysis of the final data from Part C (ages 4 to 17 years) is described in this SAP.

Part C assesses the safety, tolerability and PK, as well as the hematological effects and the effect on transcranial doppler (TCD) flow velocity of voxelotor in pediatric subjects with SCD who are 4 to 17 years of age.

Up to 50 pediatric subjects will be enrolled in Part C.

- At least 30 subjects must have a TCD velocity ≥ 140 and < 200 cm/sec by nonimaging TCD (≥ 125 and < 185 cm/sec by imaging transcranial Doppler [TCDi]) upon Screening AND
- At least 20 subjects must be between 4 to 11 years of age

To further characterize a potential effect on TCD data for those subjects who have a TCD velocity ≥ 140 and < 170 cm/sec by nonimaging TCD (≥ 125 and < 155 cm/sec by TCDi) upon screening, approximately 20 subjects may be added with a TCD velocity that falls within this range, depending on the emerging data. In this event, Part C will contain up to 70 pediatric subjects.

2.1. Objectives

2.2. Part C (Multiple Dose)

2.2.1. Primary Objective

- To evaluate the effect of voxelotor on cerebral hemodynamics in pediatric subjects with SCD with elevated or conditional TCD flow velocity as assessed by TCD ultrasonography

2.2.2. Secondary Objective

- To evaluate the effect of voxelotor on clinical measures of anemia and hemolysis
- To characterize the PK of voxelotor in plasma, whole blood and RBCs following multiple doses in pediatric subjects with SCD

- To evaluate the safety and tolerability of voxelotor following multiple doses in pediatric subjects with SCD
- To evaluate the proportion of subjects with normal TCD flow velocity (< 170 cm/sec by nonimaging TCD or < 155 cm/sec by TCDi) at 48 weeks
- To evaluate the effect of voxelotor on the incidence of stroke and vaso-occlusive crisis (VOC)

3. ENDPOINTS

3.1. Endpoints for Part C

3.1.1. Primary Endpoint

- Change from baseline to 48 weeks in cerebral blood flow as measured by the TAMM TCD velocity

3.1.2. Secondary Endpoints

- Change from baseline to Weeks 24 and 48 in Hb, LDH, indirect bilirubin, and reticulocyte count
- Change from baseline to 24 weeks in cerebral blood flow as measured by the TAMM TCD velocity
- Time to initial Hb response, defined as change from baseline in Hb > 1g/dL
- Whole blood and plasma voxelotor PK (C_{min}, C_{max}, AUC), plasma $t_{1/2}$, and percent Hb occupancy
- Proportion of subjects with normal TCD flow velocity (< 170 cm/sec by nonimagining TCD or < 155 cm/sec by TCDi) at 48 weeks
- Incidence of stroke and VOC during the study

3.1.3. Safety Endpoints

- TEAEs and SAEs
- Clinical laboratory tests, vital signs, and ECGs

4. DEFINITIONS AND TERMINOLOGY

Study Day

Study Day is defined relative to initiation of treatment, i.e., Day 1. Thus, the study day of an event is calculated as:

Study Day = event date – Day 1 date + 1.

Study Visit

Study Visit is the nominal visit as recorded on the CRF.

Baseline

For all endpoints where both Screening and Day 1 pre-dose assessments are collected, baseline is defined as average of all assessments prior to the first dose. If there is an unscheduled visit prior to first dose, this unscheduled assessment will also be included in the baseline calculation.

Change from Baseline

Change from baseline to follow-up visit will be calculated as the baseline measurement subtracted from the follow-up measurement for all assessments. 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%

Exposure to Study Drug

Duration of exposure to study drug is defined as the number of weeks from Day 1 to the last date of dosing of Study drug. The derivation is as follows:

(Last dose date - First dose date + 1)/7

Actual exposure to study drug is defined as the number of weeks from Day 1 to the last date of dosing of Study drug which excludes days where treatment was entirely missed or intermittently stopped as recorded in the CRF. The derivation is as follows:

(Last dose date - First dose date - Number of days study drug was not taken +1)/7

Prior Medications

Prior medications are those medications taken prior to the initiation of study drug.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study drug. This definition includes medications started prior to the initiation of study drug, but continuing concurrently with study drug.

RBC transfusions are collected as concomitant medications.

Hemoglobin Response

An Hb response is defined as an increase in Hb > 1 g/dL from Baseline to each week of interest.

Annualized Incidence Rate

Annualized incidence rate = (total number of events recorded over the treatment period) / (total person years)

Total person-years = sum of subject treatment period in years, which covers the time from first dose to last dose

Treatment-emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an AE that emerges on or after initiation of study drug (having been absent pre-treatment), or an AE that existed pre-treatment and worsened on treatment (relative to the pre-treatment state) through 28 days after study drug discontinuation. AEs occurring on Day 1 are assumed to be treatment-emergent.

5. GENERAL STATISTICAL CONSIDERATIONS

5.1. Sample Size Considerations

Part C: Up to 50 pediatric subjects who are 4 to 17 years of age with SCD will be enrolled. For the primary efficacy endpoint, change from baseline in TAMM TCD velocity at Week 48, a sample size of 30 subjects achieves greater than 95% power to detect a mean difference of 15 cm/sec with an estimated sample standard deviation of 22 cm/sec using a paired t-test (2-sided) with a significance level (alpha) of 0.10.

5.2. Handling of Missing or Partial Dates

5.2.1. Missing Start and Stop Dates for Prior and Concomitant 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 treatment start date then the concomitant medication start date will be imputed as the treatment start date.

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 treatment start date then the concomitant medication start date will be imputed as the treatment start date.

For missing stop day only: day only 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).

5.2.2. Missing Start and Stop Dates for Adverse Events

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 treatment start date then the adverse event start date will be imputed as the treatment start date.

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

6. ANALYSIS POPULATIONS

6.1. Efficacy Evaluable Population

All subjects who received at least one dose of study drug will be included in the Efficacy Evaluable population (EE). The EE population will be the primary population for the efficacy analyses.

6.2. Safety Population

The Safety Population is defined as all subjects who receive at least one dose of study drug. This population will be used in the assessment and reporting of safety data.

6.3. PK Population

All subjects who receive any amount of study drug and who provide PK data from at least one post dose sample in plasma will be included in the PK population. Additional details are provided in a separate plan.

7. STATISTICAL METHODS

Statistical analyses will be performed using SAS® Version 9.4 or higher.

Data summaries will be presented as: 4-11 years, 12-17 years and overall (4-17 years) age groups.

Continuous variables will be descriptively summarized using number of subjects (n), mean, standard deviation (SD), median, quartiles, minimum, maximum, and, as appropriate, 95% confidence intervals. Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category.

7.1. Subject Disposition, Demographic and Baseline Characteristics

7.1.1. Subject Disposition

Subject disposition will be presented in terms of the numbers and percentages of subjects who completed the treatment and discontinued from treatment. The reasons for early treatment discontinuation will be presented. Similar results will be presented for subjects who discontinue study.

7.1.2. Demographic and Baseline Characteristics

The demographic variables collected in this study include age (years) at Screening, sex, race, and ethnicity and will be summarized descriptively. Height (cm), weight (kg) and BMI (kg/m^2) at Screening will be presented using descriptive statistics. Subjects who record more than one race will be grouped into a single category denoted as multi-racial.

7.1.3. Baseline Sickle Cell Disease Characteristics

Number of VOCs including the number of VOCs requiring hospitalization and the number of blood transfusion during the previous 12 months will be summarized categorically.

Additional summaries including the number and percentage of subjects who currently use HU, who have each genotype (HbSS or HbS β^0 thal) and who experienced a sickle cell complication prior to study enrollment will be presented. Baseline lab values including Hb, HbF, reticulocyte count and Baseline TCD will be summarized using descriptive statistics.

7.1.4. Medical History Excluding Sickle Cell History

Medical history excluding sickle cell history will be summarized by System Organ Class (SOC) and Preferred Term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA), coding dictionary (current version).

7.2. Efficacy Analysis

Efficacy data will be summarized using the EE population.

The primary endpoint for Part C is change from baseline to 48 weeks in cerebral blood flow as measured by the TAMM TCD velocity.

TCD flow velocity will be summarized descriptively at Week 24 and Week 48 for observed values and absolute changes. TCD is presented as TCD (non-imaging) in the summary table. TCDi (imaging) has been normalized to TCD (non-imaging) by adding 15 cm/sec.

The proportion of subjects with normal TCD flow velocity (< 170 cm/sec by nonimaging TCD or < 155 cm/sec by TCDi) at 48 weeks will be summarized descriptively for the overall population and by Baseline TCD category (Normal, Conditional).

Hb response, defined as an increase in Hb > 1 g/dL, will be summarized descriptively at Week 24 and Week 48. Subjects who drop-out early or do not have a Week 24 or Week 48 visit, are not included in the analysis for Hb response at each of the respective visits. Additional response assessment at each visit will be summarized descriptively. No missing data imputation or adjustment for RBC transfusion will be performed for this endpoint.

Additionally, Hb response at Week 24 and Week 48 will be summarized using the treated population. All subjects treated will be included in the denominator for Hb response.

For subjects who have had a Hb response at least 1 visit, the time to the first response will be summarized descriptively.

Hematology parameters (hemoglobin, reticulocyte count, indirect bilirubin, and LDH) and in addition to each visit for observed values and changes (absolute and percent) from baseline using appropriate descriptive statistics. If indirect bilirubin is missing and direct and total bilirubin are collected, indirect can be calculated as:

Indirect Bilirubin = Total Bilirubin – Direct Bilirubin.

To evaluate the effect of voxelotor on the incidence of stroke and vaso-occlusive crisis (VOC), the annualized incidence rate will be summarized and 95% CI provided.

Efficacy assessment will be summarized by subgroups defined by subjects' sex, baseline HU use, and 4-11 age group (4 to 7 years and 8 to 11 years). Efficacy assessments to be summarized by subgroup include Hb response and change from baseline for hematology parameters and TCD flow velocity.

7.3. Safety

All safety analyses will be conducted using the Safety Population.

7.3.1. Summary of Exposure

The duration of study drug exposure and actual study drug exposure will be summarized with descriptive statistics.

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

7.3.2. Adverse Events

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 MedDRA (current version).

All adverse events summaries described below will be presented for both non-SCD and SCD-related TEAEs.

Non-SCD-related TEAE summary tables will exclude sickle cell disease (SCD) related events defined as preferred terms of: acute chest syndrome, pneumonia, pneumonia necrotising, sickle cell anemia with crisis, osteonecrosis, and priapism. Additional TEAE tables will summarize the aforementioned SCD related events.

Overall summaries will be presented which includes the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE. The summaries will also include TEAEs Grade 3 or greater, TEAEs possibly/probably related to study drug, TEAEs leading to study drug reduction, TEAEs leading to study drug interruption, TEAEs leading to discontinuation of study drug, serious adverse events (SAEs) and SAEs possibly/probably related to study drug. TEAEs leading to deaths will be summarized together regardless if they are SCD-related as cause of death may include multiple TEAEs.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by system organ class (SOC), preferred term (PT) and maximum severity. If a subject reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC for that subject. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be counted once for that subject. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

The occurrence of TEAEs possibly/probably related to voxelotor will be tabulated by SOC, PT and maximum severity. Serious adverse events will be presented by system organ class (SOC), preferred term (PT) and maximum severity.

Grouped terms for rash and abdominal pain are summarized by PT.

Adverse events recorded in the eCRF which began prior to first dose of study drug will not be included in the TEAE summary tables.

7.3.3. Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (current version) and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical (ATC) 4 classification) and preferred name.

7.3.4. Clinical Laboratory Data

All hematology and chemistry laboratory assessments were performed by local laboratories.

The following protocol-specified clinical laboratory findings will be summarized using descriptive statistics.

1. Hematology:
    a. Hemoglobin
    b. Neutrophils (absolute and %)
    c. Platelets
    d. Reticulocyte count (percent)
    e. WBC

2. Chemistry and Liver Function Tests:
    a. Alkaline phosphatase
    b. ALT
    c. AST
    d. Lactate dehydrogenase (LDH)
    e. Potassium
    f. Indirect bilirubin
    g. Total bilirubin
    h. Serum erythropoietin

Change from baseline and the percent change from baseline will be summarized for the above laboratory results. Analyte units will be converted to SI units.

Subject listings of laboratory data will include a separate listing for clinically significant laboratory results. Urinalysis, coagulation and pregnancy results will be listed only.

7.3.5. Vital Signs and Physical Exam

Vital signs, including systolic and diastolic blood pressure, heart rate, respiratory rate, temperature, and weight will be summarized using continuous descriptive statistics at each visit and time point. Change from baseline will also be summarized for each post-baseline visit.

7.3.6. 12-Lead Electrocardiogram

Heart rate, PR interval, QRS interval, QT interval, RR interval, and QTcF (Fridericia's) interval will be summarized along with the change from baseline using descriptive statistics at each visit. The average of the 3 ECGs collected will be used in the summary tables.

Additionally, the number and percentage of subjects with QTcF $\leq$ 450 ms, >450 ms to $\leq$ 480 ms, >480 ms to $\leq$ 500 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 $\leq$ 30 ms, > 30 ms to 60 ms and> 60 ms also will be summarized. If the QTcF interval was not collected, the interval will be calculated using the following formula:

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

8. PROTOCOL DEVIATIONS

Important protocol deviations and COVID 19 related deviations will be displayed in a data listing and sorted by age group, subject number, and then by date (where applicable) within each subject number. The type of deviation along with a description and any additional comments about the deviation will be listed.

STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 2a, Open-label, Single and Multiple Dose Study to Evaluate the Pharmacokinetics, Safety, Tolerability and Treatment Effect of GBT440 in Pediatric Participants with Sickle Cell Disease
Phase:	2a
Protocol No.:	GBT440-007 (C5341020)
Protocol Date and Version:	28 April 2021, Amendment 7
Investigational Product:	Voxelotor (GBT440 / PF-06759497)
Study Sponsor:	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc. 181 Oyster Point Blvd. South San Francisco, CA 94080 United States of America
SAP Version:	Part D, Version 1.0
SAP Date:	03 October 2023

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

Prepared by:

REASON: I approve this document as author.

PPD

03 Oct 2023 13:46:007-0400

PPD MS
PPD

Date

Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc.

Reviewed by:

REASON: I approve this document.

PPD

03 Oct 2023 13:46:055-0400

PPD PhD
PPD

Date

Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc.

Approved by:

REASON: I approve this document.

PPD

03 Oct 2023 14:45:048-0400

PPD PhD
PPD

Date

Pfizer Inc.

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL 2
TABLE OF CONTENTS 3
1. GLOSSARY OF ABBREVIATIONS 5
2. INTRODUCTION AND STUDY OVERVIEW 7
3. STUDY OBJECTIVES FOR PART D 7
3.1. Primary 7
3.2. Secondary 7
3.3. Exploratory 7
4. ENDPOINTS FOR PART D 8
4.1. Primary 8
4.2. Secondary 8
4.3. Exploratory 8
4.4. Safety 8
5. DEFINITIONS AND TERMINOLOGY 8
6. GENERAL STATISTICAL CONSIDERATIONS 10
6.1. Sample Size Considerations 10
6.2. Handling of Missing or Partial Dates 10
6.2.1. Missing Start Dates for Prior and Concomitant Medication 10
6.2.2. Missing Start Dates for Adverse Events 10
7. ANALYSIS POPULATIONS 10
7.1. Efficacy Evaluable Population 10
7.2. Safety Population 10
7.3. PK Population 10
8. STATISTICAL METHODS 11
8.1. Subject Disposition, Demographic and Baseline Characteristics 11
8.1.1. Subject Disposition 11
8.1.2. Demographic and Baseline Characteristics 11
8.1.3. Baseline Sickle Cell Disease Characteristics 11
8.1.4. Medical History Excluding Sickle Cell History 11
8.2. Efficacy Analysis 12
8.3. Safety 12

8.3.1. Summary of Exposure 12
8.3.2. Adverse Events 13
8.3.3. Concomitant Medications 13
8.3.4. Clinical Laboratory Data 13
8.3.5. Vital Signs and Physical Exam 14
8.3.6. 12-Lead Electrocardiogram 14
9. PROTOCOL DEVIATIONS 14

1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
AE	Adverse Event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	area under the concentration-time curve
BMI	Body Mass Index
CI	Confidence Interval
cm	Centimeter
CRF	Case Report Form
Cmax	Maximum Blood Concentration
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
eCRF	electronic case report form
EE	Efficacy Evaluable
g/dL	gram per deciliter
Hb	Hemoglobin
HbF	hemoglobin – fetal
HbS β^0 thal	sickle hemoglobin (S) and one beta thalassemia gene (β^0 thal)
HbSS	sickle hemoglobin with two sickle cell genes (SS)
HU	Hydroxyurea
kg	Kilogram
kg/m^2	kilogram per meter squared
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
n	number of subjects
NCI	National Cancer Institute
PK	Pharmacokinetic(s)
PT	Preferred Term
RBC	Red Blood Cells
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan

Abbreviation	Description
SAS®	Statistical Analysis Software
SCD	Sickle Cell Disease
SD	Standard Deviation
SI	Systeme International
SOC	System Organ Class
$t_{1/2}$	terminal elimination half-life
TEAE	Treatment-Emergent Adverse Event
VOC	vaso-occlusive crisis
WBC	white blood cell
WHO	World Health Organization

2. INTRODUCTION AND STUDY OVERVIEW

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses of data from GBT440-007 Part D.

Where applicable, the statistical analysis methods presented in this document will supersede the statistical analysis methods described in the study protocol.

Study Overview:

GBT440-007 is a multicenter, open-label study to evaluate the safety, pharmacokinetics (PK) and efficacy of voxelotor in pediatric subjects with Sickle Cell Disease (SCD).

This study consists of 4 parts, Part A, Part B, Part C, and Part D. The planned analyses of data from Part D are described in this SAP.

Part D assesses the safety, tolerability, and PK, as well as the hematological effects of voxelotor in pediatric subjects with SCD who are 6 months to < 4 years of age. Approximately 30 pediatric subjects will be enrolled into Part D.

3. STUDY OBJECTIVES FOR PART D

3.1. Primary

- To evaluate the safety and tolerability of voxelotor in pediatric subjects with SCD aged 6 months to < 4 years

3.2. Secondary

- To characterize the PK of voxelotor in plasma, whole blood, and red blood cells (RBCs) in pediatric subjects with SCD aged 6 months to < 4 years
- To evaluate the effect of voxelotor on clinical measures of anemia and hemolysis in pediatric subjects with SCD aged 6 months to < 4 years
- To evaluate the effect of voxelotor on the incidence of stroke and vaso-occlusive crisis (VOC) in pediatric subjects with SCD aged 6 months to < 4 years

3.3. Exploratory

- To evaluate the effect of voxelotor on growth and development pediatric subjects with SCD aged 6 months to < 4 years

4. ENDPOINTS FOR PART D

4.1. Primary

- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs)

4.2. Secondary

- Whole blood and plasma voxelotor PK (maximum blood concentration [C_{max}], area under the concentration-time curve [AUC], terminal elimination half-life [$t_{1/2}$], if appropriate) and percent hemoglobin (Hb) occupancy
- Change from baseline to Week 24 and Week 48 in Hb, lactate dehydrogenase (LDH), indirect bilirubin, and reticulocyte count
- Time to initial Hb response, with Hb response defined as change from baseline in Hb > 1g/dL
  - Time to initial Hb response is defined as time from first dose of study treatment to first occurrence of change from baseline in Hb > 1g/dL
- Incidence of stroke and VOC during the study
- In addition to the protocol-specified secondary endpoints, Hb response (defined as a change from baseline in Hb > 1g/dL) will be assessed at both Week 24 and Week 48.

4.3. Exploratory

- Growth and development as assessed by change from baseline to Weeks 24 and 48 in height, weight, and head circumference

4.4. Safety

- Clinical laboratory tests and vital signs

5. DEFINITIONS AND TERMINOLOGY

Study Day

Study Day is defined relative to initiation of treatment, i.e., Day 1. Thus, the study day of an event is calculated as:

Study Day = event date – Day 1 date + 1.

Study Visit

Study Visit is the nominal visit as recorded on the Case Report Form (CRF).

Baseline

For all endpoints where both Screening and Day 1 pre-dose assessments are collected, baseline is defined as average of all assessments prior to the first dose. If there is an unscheduled visit prior to first dose, this unscheduled assessment will also be included in the baseline calculation.

Change from Baseline

Change from baseline to follow-up visit will be calculated as the baseline measurement subtracted from the follow-up measurement for all assessments. Percent change from baseline values to post-baseline values will be calculated using the following formula where applicable:

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

Exposure to Study Drug

Duration of exposure to study drug is defined as the number of weeks from Day 1 to the last date of dosing of study drug. The derivation is as follows:

$$(\text{Last dose date} - \text{First dose date} + 1)/7$$

Actual exposure to study drug is defined as the number of weeks from Day 1 to the last date of dosing of study drug which excludes days where treatment was entirely missed or intermittently stopped as recorded in the CRF. The derivation is as follows:

$$(\text{Last dose date} - \text{First dose date} - \text{Number of days study drug was not taken} + 1)/7$$

Prior Medications

Prior medications are those medications taken prior to the initiation of study drug.

Concomitant Medications

Concomitant medications are those medications taken on or after the initiation of study drug. This definition includes medications started prior to the initiation of study drug, but continuing concurrently with study drug.

RBC transfusions are collected as concomitant medications.

Hemoglobin Response

Hb response is defined as an increase in Hb > 1 g/dL from Baseline and will be assessed at both Week 24 and Week 48.

Treatment-Emergent Adverse Event

A treatment-emergent adverse event (TEAE) is defined as an adverse event (AE) that emerges on or after initiation of study drug (having been absent pre-treatment), or an AE that existed pre-treatment and worsened on treatment (relative to the pre-treatment state) through 28 days after study drug discontinuation.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. Sample Size Considerations

Approximately 30 pediatric subjects with SCD who are 6 months to < 4 years of age will be enrolled in GBT440-007 Part D. The sample size was selected to provide descriptive assessment of safety, tolerability, and PK effects of voxelotor in this younger age group with no formal statistical assumptions.

6.2. Handling of Missing or Partial Dates

6.2.1. Missing Start Dates for Prior and Concomitant 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 treatment start date then the concomitant medication start date will be imputed as the treatment start date.

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 treatment start date then the concomitant medication start date will be imputed as the treatment start date.

6.2.2. Missing Start Dates for Adverse Events

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 treatment start date then the adverse event start date will be imputed as the day prior to the treatment start date.

7. ANALYSIS POPULATIONS

7.1. Efficacy Evaluable Population

All subjects who receive at least one dose of study drug will be included in the Efficacy Evaluable population (EE). All efficacy analyses will be based on the EE population.

In this study (GBT440-007 Part D), the EE population is the same as the Safety Population (see Section 7.2).

7.2. Safety Population

The Safety Population is defined as all subjects who receive at least one dose of study drug. This population will be used in the assessment and reporting of safety data.

7.3. PK Population

For the Population PK analysis, an individual will be defined as evaluable if both of the following criteria are satisfied:

1. Received at least 1 dose of voxelotor with associated dosing date and time

2. Has at least 1 measurable voxelotor concentration observation in plasma or whole blood with associated sampling time and dosing information

Details on PK analyses, as well as Hb occupancy, are provided in a separate analysis plan.

8. STATISTICAL METHODS

Statistical analyses will be performed using SAS® Version 9.4 or higher.

Continuous variables will be descriptively summarized using number of subjects (n), mean, standard deviation (SD), median, minimum, maximum, and, as appropriate, 95% confidence intervals (CIs). Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category.

In general, results for Part D will be presented by age group (6 months to < 2 years and 2 years to < 4 years) and overall, as appropriate.

8.1. Subject Disposition, Demographic and Baseline Characteristics

8.1.1. Subject Disposition

Subject disposition will be presented in terms of the numbers and percentages of subjects who completed the treatment and discontinued from treatment. The reasons for early treatment discontinuation will be presented. Similar summaries will be presented for subjects who discontinue study.

8.1.2. Demographic and Baseline Characteristics

The demographic variables collected in this study include age (months or years) at Screening, sex, race, and ethnicity and will be summarized descriptively. Height (cm), weight (kg), and BMI (kg/m^2) at Day 1 will be presented using descriptive statistics. Subjects who record more than one race will be grouped into a single category denoted as multi-racial.

8.1.3. Baseline Sickle Cell Disease Characteristics

Number of VOCs including the number of VOCs requiring hospitalization and the number of blood transfusions during the previous 12 months will be summarized categorically.

Additional summaries including the number and percentage of subjects who currently use HU, who have each genotype (homozygous hemoglobin SS [HbSS] or hemoglobin S $beta^0$ thalassemia [HbS β^0 thal]), and who experienced a sickle cell complication prior to study enrollment will be presented. Baseline lab values including Hb, hemoglobin – fetal (HbF), and reticulocyte count will be summarized using descriptive statistics.

8.1.4. Medical History Excluding Sickle Cell History

Medical history excluding sickle cell history will be summarized by System Organ Class (SOC) and Preferred Term (PT) according to Medical Dictionary for Regulatory Activities (MedDRA), coding dictionary (current version).

8.2. Efficacy Analysis

All efficacy data will be summarized using the EE population.

Hematology and hemolysis parameters (hemoglobin, reticulocyte count, indirect bilirubin, and LDH) will be summarized at Week 24 and Week 48 in addition to each visit for observed values and changes (absolute and percent, as appropriate) from baseline using appropriate descriptive statistics. If indirect bilirubin is missing and direct and total bilirubin are collected, indirect can be calculated as:

Indirect Bilirubin = Total Bilirubin – Direct Bilirubin.

Hb response, defined as an increase in Hb > 1 g/dL, will be summarized descriptively at Week 24 and Week 48 with 95% confidence intervals provided for the response rates. Subjects who drop-out early or do not have a Week 24 or Week 48 assessment, are not included in the analysis for Hb response. Additional response assessments at each visit will be summarized descriptively. No missing data imputation or adjustment for RBC transfusion will be performed for this endpoint.

Additionally, Hb response at Week 24 and Week 48 with 95% confidence intervals will be summarized using the treated population. All subjects treated will be included in the denominator for Hb response, and subjects without a Week 24 or Week 48 assessment will be counted as non-responders at each relevant timepoint.

For subjects who had a Hb response at least 1 visit, the time to the first response will be summarized descriptively (ie, median, first quartile, third quartile, and range).

The annualized incidence rates for VOC and stroke and the associated 95% CIs will be presented. Annualized rate is defined as the total number of events divided by total person years. Total person-years is defined as the sum of subject treatment period in years which covers the time from first dose to last dose. VOC is defined based on clinical review of adverse event MedDRA preferred terms (eg, sickle cell anemia with crisis, acute chest syndrome, and pneumonia).

Exploratory analysis for change from baseline to Weeks 24 and 48 in height, weight, and head circumference, will be summarized using continuous descriptive statistics at each visit.

8.3. Safety

All safety analyses will be conducted using the Safety Population.

8.3.1. Summary of Exposure

The duration of study drug exposure and actual study drug exposure will be summarized with descriptive statistics.

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

8.3.2. Adverse Events

Adverse events reported for subjects participating in this study were primarily graded for severity using the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. For adverse events not covered in the NCI-CTCAE, grading was performed per the criteria outlined in Table 13 of the protocol.

All adverse events will be coded using MedDRA (current version).

All adverse events summaries described below will be presented for both non-SCD and SCD-related TEAEs.

Non-SCD-related TEAE summary tables will exclude sickle cell disease (SCD) related events defined as preferred terms of: acute chest syndrome, pneumonia, sickle cell anemia with crisis, osteonecrosis, and priapism. Additional TEAE tables will summarize the aforementioned SCD related events.

Overall summaries will be presented which include the number of TEAEs and the number and percentage of subjects who experienced at least one TEAE. The summaries will also include TEAEs Grade 3 or greater, TEAEs possibly/probably related to study drug, TEAEs leading to study drug reduction, TEAEs leading to study drug interruption, TEAEs leading to discontinuation of study drug, and serious adverse events (SAEs). TEAEs leading to deaths will be summarized together regardless if they are SCD-related, as cause of death may include multiple TEAEs.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. These summaries will be presented by system organ class (SOC), preferred term (PT) and maximum severity. If a subject reports the same PT multiple times within the same SOC, that PT will only be counted once within that SOC for that subject. As with the PT, if a subject reports multiple conditions within the same SOC, that SOC will only be counted once for that subject. In the summary, SOC will be listed in ascending alphabetical order; PTs will be listed in order of descending frequency for all subjects within each SOC.

The occurrence of TEAEs possibly/probably related to voxelotor will be tabulated by system organ class (SOC), preferred term (PT), and maximum severity. Serious adverse events will be presented by system organ class (SOC), preferred term (PT), and maximum severity.

Grouped terms for rash and abdominal pain will be summarized.

Adverse events recorded in the electronic case report form (eCRF) which began prior to first dose of study drug will not be included in the summary tables.

8.3.3. Concomitant Medications

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary (current version) and summarized to the therapeutic drug class, Anatomical Therapeutic Chemical (ATC) 4 classification, and preferred name.

8.3.4. Clinical Laboratory Data

All hematology and chemistry laboratory assessments were performed by local laboratories.

The following protocol-specified clinical laboratory findings will be summarized using descriptive statistics.

1. Hematology:
    a. Hemoglobin
    b. Neutrophils (absolute and %)
    c. Platelets
    d. Reticulocyte count (percent and absolute reticulocyte)
    e. White blood cells (WBCs)
2. Chemistry and Liver Function Tests:
    a. Alkaline phosphatase
    b. Alanine aminotransferase (ALT)
    c. Aspartate aminotransferase (AST)
    d. Indirect bilirubin
    e. Total bilirubin
    f. Lactate dehydrogenase (LDH)
    g. Serum Erythropoietin

Change from baseline and the percent change from baseline will be summarized for the above laboratory results. Analyte units will be converted to International System of Units (SI) units.

Subject listings of laboratory data will include a separate listing for clinically significant laboratory results.

8.3.5. Vital Signs and Physical Exam

Vital signs, including systolic and diastolic blood pressure and heart rate, will be summarized using continuous descriptive statistics at each visit. Change from baseline will also be summarized for each post-baseline visit.

8.3.6. 12-Lead Electrocardiogram

Data from ECG assessments (collected at Screening only) will be listed.

9. PROTOCOL DEVIATIONS

Protocol deviations as assessed by the study team will be displayed in a data listing and sorted by subject number, and then by date (where applicable) within each subject number. The type of deviation along with a description and any additional comments about the deviation will be listed.