STATISTICAL ANALYSIS PLAN

Study Title:	An Open-Label Extension Study of Voxelotor Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials
Phase:	Open-label Extension
Protocol Number:	GBT440-038 (C5341023), Amendment 4
Protocol Date	15 June 2023
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
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Prepared By:	PPD MS

CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

Prepared by: PPD

26 Jul 2024 13:29:042-0400

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

Date

Approved by:

PPD

26 Jul 2024 13:31:016-0400

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

Date

PPD

26 Jul 2024 22:42:029-0400

PPD , PhD
PPD
Pfizer, Inc.

Date

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1. GLOSSARY OF ABBREVIATIONS

Abbreviation	Description
ACS	acute chest syndrome
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below the limit of quantification
BMI	body mass index
CRF	case report form
CTCAE	Common Terminology Criteria for Adverse Events
GBT	Global Blood Therapeutics
Hb	hemoglobin
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
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
n	number of participants
NCI	National Cancer Institute
OLE	open-label extension
PK	pharmacokinetic
PT	Preferred Term
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SD	standard deviation
SI	International System of Units
SOC	System Organ Class
TEAE	treatment-emergent adverse event
WBC	white blood cell
WHO	World Health Organization

2. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses of data from Study GBT440-038 (C5341023).

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

2.1 Study Overview

This multicenter, nonrandomized, global open-label extension (OLE) study is designed to assess the safety of, and sickle cell disease (SCD)-related complications with, long-term treatment with voxelotor in pediatric participants with SCD. The study will be conducted globally and will be available to eligible participants from Global Blood Therapeutics (GBT)/Pfizer-sponsored voxelotor clinical studies. Participants must have completed participation in their originating clinical study and must meet the entry criteria for this study to be eligible for enrollment.

2.2 Study Measurement and Visit Schedule

Please refer to the study protocol, Appendix A and Appendix B, for the schedule of assessments.

3. STUDY OBJECTIVES

The objective of this OLE is to assess the safety of, and SCD-related complications with, long-term treatment with voxelotor in participants who have completed treatment in a GBT/Pfizer-sponsored voxelotor clinical study, based on the following parameters:

- Adverse events (AEs), clinical laboratory tests, physical examinations, and other clinical measures
- Frequency of SCD-related complications

In addition, this study will assess predose whole blood and plasma concentrations of voxelotor, in a subset of participants receiving a modified dose of voxelotor as dispersible tablets at selected sites.

4. STUDY ENDPOINTS

Safety:

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

Sickle Cell Disease-Related Complications:

- Frequency of SCD-related complications

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).

Change from Day 1

Change from Day 1 to follow-up visit will be calculated as Day 1 subtracted from the follow-up measurement for all assessments. Percent change from Day 1 values to post-Day 1 values will be calculated using the following formula where applicable:

([post-Day 1 value – Day 1 value] / Day 1 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

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.

Red blood cell (RBC) transfusions are collected on a separate CRF.

Treatment-Emergent Adverse Event

A 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.

6. GENERAL STATISTICAL CONSIDERATIONS

6.1 Sample Size Considerations

The total sample size for this study will not exceed total enrollment in the originating GBT/Pfizer-sponsored voxelotor clinical studies.

In addition, the collection of voxelotor predose whole blood and plasma concentrations in participants receiving a modified dose of voxelotor dispersible tablets will be conducted in approximately 20 participants at selected sites.

6.2 Handling of Missing or Partial Dates

6.2.1 Missing Start Dates for 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 treatment start date.

6.3 Analysis Timing

The final study analysis will be based on complete data from the study and performed after all enrolled participants have completed the study or discontinued early (i.e., last participant's last visit has occurred), and all corresponding data have been entered into the database, reviewed, and verified and the database is locked.

Prior to the final study analysis, interim data from this open-label extension study may be summarized as necessary (e.g., interim safety data summarized to support regulatory applications or health authority requests). The data included for the interim analyses will depend on the purpose. If performed, the interim analyses will be descriptive and no formal hypothesis testing performed.

7. ANALYSIS POPULATIONS

7.1 Safety Population

The Safety Population is defined as all participants who receive at least one dose of study drug.

7.2 Pharmacokinetic Population

The pharmacokinetic (PK) population is defined as all participants who take at least 1 dose of voxelotor and in whom at least 1 concentration value is reported.

8. STATISTICAL METHODS

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

Continuous variables will be descriptively summarized using number of participants (n), mean, standard deviation (SD), median, minimum, and maximum. Categorical variables will be descriptively summarized by presenting the number (frequency) and percentage in each category. All statistical analyses conducted will be descriptive and no formal statistical tests are planned.

Additionally, for the subset of participants receiving the modified dose of voxelotor in dispersible tablet in this study, separate summaries will be provided for selected CRF data (e.g., TEAEs).

8.1 Participant Disposition, Demographic and Baseline Characteristics

8.1.1 Participant Disposition

The number of participants enrolled will be tabulated by originating study and prior treatment group, country, and study site. Participant disposition will be presented in terms of the numbers and percentages of participants who completed the study including reasons for study termination.

8.1.2 Demographic and Baseline Characteristics

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

Additional summaries include the number and percentage of participants who currently use hydroxyurea (HU), and who have each SCD genotype (homozygous hemoglobin SS [HbSS] or hemoglobin S beta^0 thalassemia [HbS β^0 thal]).

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 Safety

8.2.1 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 participants who permanently discontinued study drug, and the reason for discontinuation (AE or other) will be summarized as collected on the study drug administration CRF. The number and percentage of participants 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 participants who had a dose reduction or dose missed due to an adverse event or other reason. Additionally, the number and percentage of participants will be summarized in categories of number of missed doses and number of dose reductions.

8.2.2 Adverse Events

All AEs will be coded using MedDRA (current version). 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 5.0. For AEs not adequately addressed in the NCI CTCAE, version 5.0, protocol-specified criteria will be used.

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 SCD related events including but not limited to the preferred terms of: sickle cell anemia with crisis, acute chest syndrome (ACS), pneumonia, priapism, splenic sequestration, hepatic sequestration, stroke, leg ulcers, dactylitis, and osteonecrosis. 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 participants who experienced at least one TEAE. The summaries will also include TEAEs Grade 3 or greater, TEAE related to study drug, TEAEs leading to study drug reduction, TEAEs leading to study drug interruption, TEAEs leading to discontinuation of study drug, and 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 participants who experienced at least one TEAE. These summaries will be presented by MedDRA 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.

The occurrence of TEAEs assessed as related to voxelotor by the investigator will be tabulated by SOC, PT, and maximum severity. Serious adverse events will be presented by SOC, PT, and maximum severity.

Grouped terms for rash and abdominal pain will be summarized.

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

For the subset of participants receiving a modified dose of voxelotor as dispersible tablets in this study, AEs will be presented with participants grouped by the dosing form prior to the switch to the modified dose.

8.2.3 Frequency of Sickle Cell Disease–Related Complications

SCD-related complications over the course of the treatment period will be recorded as adverse events for each participant. SCD-related complications may include the following: sickle cell anemia with crisis, ACS, pneumonia, priapism, splenic sequestration, hepatic sequestration, stroke, leg ulcers, dactylitis, and osteonecrosis. SCD-related complications will be summarized in the SCD-related adverse event summaries as described in Section 8.2.2.

8.2.4 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) 2 classification, and preferred name.

8.2.5 Clinical Laboratory Assessments

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

1. Hematology:
    a. Hemoglobin (Hb)
    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. Potassium
    e. Indirect bilirubin
    f. Total bilirubin
    g. Lactate dehydrogenase (LDH)
    h. Serum Erythropoietin

Change from Day 1 and the percent change from Day 1 will be summarized for the above laboratory results. Analyte units will be converted to International System of Units (SI). The end-of-treatment assessments performed upon completion of the antecedent study may serve as the Day 1 assessments for Study GBT440-038.

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

If indirect bilirubin is missing and direct and total bilirubin are collected, indirect can be calculated as:

Indirect Bilirubin = Total Bilirubin – Direct Bilirubin.

8.2.6 Vital Signs and Physical Exam

Vital signs, including systolic and diastolic blood pressure, heart rate, height and weight will be summarized using descriptive statistics at each visit and time point. Change from Day 1 will also be summarized for each post-baseline visit.

8.3. Taste and Palatability Questionnaire

For the subset of participants receiving a new dosage form or switch to a higher dose (i.e., modified dose of voxelotor as dispersible tablets), taste and palatability questionnaires collected on day of switch to the modified dose and 2 consecutive visits will be summarized using descriptive statistics.

8.4. Pharmacokinetics

Pre-dose voxelotor whole blood and plasma concentrations will be available for day of switch to modified dose, 14-day post switch, and 12-week post switch. The PK data will be reported for an individual participant with corresponding voxelotor pre-switch dose, pre-switch formulation, and post-switch voxelotor dose (and formulation) in a table. In addition, the PK data for day of switch, 14-day post-switch, and 12-week post-switch will be summarized (all data and by pre-dose formulation) using descriptive statistics (number of valid PK data, mean, SD, 95% Confidence Interval, median, min, max). Below the limit of quantitation (BLQ) concentrations will be treated as zero for the computation of descriptive statistics. Concentrations assigned a value of missing will be omitted from the calculation of descriptive statistics.

9. PROTOCOL DEVIATIONS

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