STATISTICAL ANALYSIS PLAN

Study Title:	AN OPEN-LABEL EXTENSION STUDY OF VOXELOTOR (GBT440) ADMINISTERED ORALLY TO PARTICIPANTS WITH SICKLE CELL DISEASE WHO HAVE PARTICIPATED IN VOXELOTOR CLINICAL TRIALS
Development Phase:	Open-Label Extension
Protocol Number:	GBT440-034 (C5341022)
Protocol Date:	18 December 2023 (Amendment 3)
Investigational Product:	Voxelotor (GBT440 / PF-06759497)
Sponsor:	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc. 181 Oyster Point Boulevard South San Francisco, CA 94080 United States of America
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CONFIDENTIAL AND PROPRIETARY INFORMATION

STATISTICAL ANALYSIS PLAN REVIEW AND APPROVAL

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1. GLOSSARY OF ABBREVIATIONS

CRF	case report form
CSR	clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
ECG	electrocardiogram
EOS	end of study
EOT	end of treatment
HU	hydroxyurea
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
OLE	open-label extension
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SOC	System Organ Class
TEAE	treatment-emergent adverse event
VOC	vaso-occlusive crisis
WHO	World Health Organization

2. INTRODUCTION

The objective of Study GBT440-034 (C5341022) is to assess the long-term safety and treatment effect of voxelotor in participants with sickle cell disease (SCD) who have completed treatment in Study GBT440-031.

This statistical analysis plan (SAP) provides details of the planned analyses and statistical methods for Study GBT440-034 final clinical study report (CSR). Where this document differs from the high-level analysis plan described in the study protocol, the methodology described in this SAP is considered the latest and supersedes the corresponding section(s) in the protocol.

2.1. Study Design

Study GBT440-034 is a multicenter, global, open-label extension (OLE) study available to participants who were previously enrolled and treated in Study GBT440-031. Participants must meet the entry criteria for this study to be eligible for enrollment.

All participants enrolled in GBT440-034, regardless of treatment received in the parent study GBT440-031 (i.e., placebo, voxelotor 900 mg, or voxelotor 1500 mg), receive treatment with voxelotor 1500 mg once daily (the highest dose deemed safe for continued assessment based on GBT440-031).

All participants in Study GBT440-034 have scheduled study visits with assessments at Day 1, Week 12, Week 24, and Week 48, and then every 24 weeks thereafter. Participants who were treated with placebo or voxelotor 900 mg in Study GBT440-031 have additional study visits with assessments at Week 4 and Week 8.

Participants may receive voxelotor in GBT440-034 as long as they continue to receive clinical benefit which outweighs risk as determined by the Investigator and/or until the participant has access to voxelotor from an alternative source (i.e., commercialization or through a managed access program).

Additional details and background information are provided in the study protocol.

2.2. Study Endpoints

2.2.1. Safety

Safety endpoints include adverse events, clinical laboratory tests, physical examinations, and other clinical measures.

2.2.2. Sickle Cell Disease (SCD)-Related Complications

Frequency of SCD-related complications of long-term dosing with voxelotor. SCD-related complications include adverse events with preferred terms of acute chest syndrome, hepatic sequestration, leg ulcers, osteonecrosis, pneumonia, priapism, pulmonary hypertension, retinopathy, scleral icterus, sickle cell anaemia with crisis, splenic sequestration, and stroke.

2.2.3. Treatment Effect (Durability of Hematologic Effect)

Hemolytic anemia as measured by hematological laboratory parameters (e.g., hemoglobin, reticulocytes, and unconjugated bilirubin).

2.3. Determination of Sample Size

The sample size for this study will not exceed the total enrollment of the parent study GBT440-031 (i.e., will not exceed 274 participants).

2.4. Analysis Timing

The final 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 were summarized as necessary (e.g., interim safety data summarized to support regulatory applications and health authority requests). The data included for the interim analyses were dependent on the purpose of the regulatory submission. When performed, interim analyses were descriptive with no formal hypothesis testing performed.

3. GENERAL CONSIDERATIONS

3.1. Definitions and Terminology

Baseline Value

Baseline value is defined as the last available value (including from Week 72, End of Treatment [EOT], or End of Study [EOS] visits in the parent study GBT440-031) collected on or prior to first dose in GBT440-034, and will be used for summary of change from GBT440-034 baseline analyses, as appropriate. If multiple records exist in the GBT440-034 database, all laboratory records prior to treatment initiation in GBT440-034 will be averaged and used as the baseline value.

Prior Study Drug

Prior study drug (or prior study treatment) refers to the study drug (i.e., placebo, voxelotor 900 mg, or voxelotor 1500 mg) received during the parent study GBT440-031. All participants receive open-label voxelotor as study drug during GBT440-034.

Study Day

Study Day is defined relative to the date of GBT440-034 informed consent.

For study assessments or events that occur on or after the date of informed consent, study day is calculated as:

Study Day = Event Date – Informed Consent Date + 1.

Study Year

Study Year is defined relative to the date of GBT440-034 informed consent, and refers to study year within Study GBT440-034 only. Study year is calculated as:

Study Year = ceiling(Study Day/365.25).

Treatment Day

Treatment Day is defined relative to the date of GBT440-034 first dose.

For study assessments that occur on or after the date of first dose, treatment day is calculated as:

Treatment Day = Assessment Date – First Dose Date + 1.

For study assessments that occur before the date of first dose, treatment day is calculated as:

Treatment Day = Event Date – First Dose Date.

Treatment-Emergent Adverse Event

Treatment-emergent adverse events (TEAEs) are defined as adverse events with onset on or after the date of informed consent until 28 days after last dose of study drug. Note: For this study, informed consent date is used (rather than first dose date) as the majority of participants were previously treated with voxelotor in the parent study GBT440-031.

Study Completion

Completion of study is specified on the EOS case report form (CRF). Participants are considered to have completed the study if they end study participation to transition to voxelotor from an alternative source (i.e., commercialization or through a managed access program). Participants who end study participation for any other reason (e.g., adverse event, withdrawal of consent, lost to follow-up, study terminated by sponsor) are considered to have discontinued the study early.

Treatment Completion

Completion of treatment is specified on the EOT CRF. Participants are considered to have completed treatment if they end study drug treatment to transition to voxelotor from an alternative source. Participants who end study treatment for any other reason (e.g., adverse event, withdrawal of consent, lost to follow-up, study terminated by sponsor) are considered to have discontinued study treatment early.

3.2. Visit Windows

For summaries by timepoint (e.g., laboratory values and vital signs), analysis visit windows will be used to classify assessments based on the actual treatment day of the measurement regardless of the original nominal visit label. This includes assessments collected at Unscheduled or EOS visits. Target study days, the protocol-specified study day windows, and the analysis visit windows are shown in Table 1.

Table 1: Analysis Windows

Timepoint	Target Study Day (relative to first dose)	Visit Window per Protocol (treatment days)	Window for Statistical Analysis (treatment days)
Baseline	1	--	Last value[a] taken on or prior to date of first dose in GBT440-034
Week 4	28	[23, 33]	[2, 42]
Week 8	56	[51, 61]	[43, 70]

Timepoint	Target Study Day (relative to first dose)	Visit Window per Protocol (treatment days)	Window for Statistical Analysis (treatment days)
Week 12	84	[79, 89]	[71, 126]
Week 24	168	[158, 178]	[127, 252]
Week 48	336	[326, 346]	[253, 420]
Week 72	504	[494, 514]	[421, 588]
Week 96	672	[662, 682]	[589, 756]
Week 120	840	[830, 850]	[757, 924]
Week 144	1008	[998, 1018]	[925, 1092]
Week 168	1176	[1166 , 1186]	[1093, 1260]
Week 192	1344	[1334 , 1354]	[1261, 1428]
< Continues with 24-week intervals >			

Note: If multiple measurements fall within the statistical analysis window, the average of the measurements will be used.
[a] Including Week 72, End of Treatment, or End of Study laboratory values collected in Study GBT440-031.

Note that per the protocol Schedule of Assessments, laboratory assessments and vital signs are collected at visits up to Week 48. After Week 48, laboratory assessments are collected per standard of care for clinical management with the following exception: for participants enrolled outside of the US and Europe, hemoglobin and clinical measures of hemolysis (% reticulocytes, absolute reticulocytes, and bilirubin [total, direct, and indirect]) are collected after Week 48 at 24-week intervals (see Section 5.4.3).

4. ANALYSIS POPULATIONS

4.1. Enrolled Population

All participants with signed informed consent will be considered enrolled in the study.

Enrollment by country and study site, subject disposition, and protocol deviations will be summarized for the enrolled population.

4.2. Safety Population

The safety population includes all enrolled participants who received treatment with study drug (voxelotor) during Study GBT440-034.

The safety population will be the primary analysis population for this study.

Analyses will be presented for overall population, and by prior treatment group (i.e., placebo, voxelotor 900 mg, and voxelotor 1500 mg) based on treatment received in the parent study GBT440-031, as appropriate.

5. STATISTICAL METHODS

All statistical analyses will be descriptive in nature; no formal statistical tests are planned.

5.1. Summaries of Study Conduct

The number of participants enrolled will be tabulated by country and study site. Participant disposition (the number of participants treated, discontinuing the study early, and completing the study) will be tabulated. Reasons for early study drug discontinuation and study discontinuation will be summarized.

Any eligibility criteria deviations, other important protocol deviations (i.e, those categorized as 'critical' in severity), and protocol deviations related to COVID-19 will be tabulated and evaluated for potential impact on the interpretation of study results. Medication errors (e.g., administration of incorrect dosage or administration of expired study drug) per protocol amendment 3.0 (protocol Section 7.5) will be listed.

5.2. Summaries of Demographic and Baseline Characteristics, Medical History, and Concomitant Medications

Demographic and baseline characteristics (such as age at GBT440-034 enrollment, sex, race, ethnicity, sickle cell genotype, hydroxyurea (HU) use at GBT440-034 enrollment, and geographic region) will be summarized for the safety population.

Medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA) and summarized. Prior and concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary and summarized. For both MedDRA and WHO Drug Dictionary, the most current version at the time of analysis will be used.

Time on study, defined as time from informed consent date to the participant's end of study date, will also be tabulated.

5.3. Safety Analyses

Safety will be assessed through descriptive summaries of adverse events, clinical laboratory test results, electrocardiogram (ECG) findings, and vital signs. Safety summaries will be based on the safety population (Section 4.2).

5.3.1. Exposure to Study Drug and Adherence

Duration of exposure is defined based on the difference between the dates of the first and last dose of study drug, i.e.,

$$Duration\ of\ Exposure\ (weeks) = \frac{LastDoseDate - FirstDoseDate + 1}{7}$$

and will be summarized descriptively.

For each participant, the study drug adherence will be calculated based on the ratio of the number of tablets taken on study to the expected number of tablets from the first to the last dose date:

$$Study\ Drug\ Adherence\ (\%) = 100 \text{ x } \frac{Number\ of\ Tablets\ Taken}{Expected\ Number\ of\ Tablets}$$

Study drug adherence will be summarized descriptively.

In addition, the number of dose reductions per participant and the number of dose interruptions per participant will be summarized.

The number and percent of participants who transitioned from five tablets of voxelotor 300 mg daily to three tablets of voxelotor 500 mg daily during the study will be tabulated.

5.3.2. Adverse Events

Adverse events will be classified according to MedDRA; the most current version at the time of analysis will be used. Severity of adverse events will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03, when possible, or based on the protocol-specified grading for adverse events not covered in the NCI CTCAE.

Non-SCD-related adverse events and SCD-related adverse events will be summarized separately. SCD-related adverse events include sickle cell anaemia with crisis, acute chest syndrome, pneumonia, priapism, and osteonecrosis. All other adverse events will be considered non-SCD-related.

Summaries of TEAEs, defined as adverse events with an onset on or after the date of informed consent until 28 days after last dose of study drug, will be tabulated by MedDRA system organ class (SOC) and preferred term, as appropriate.

Summaries of TEAEs will be provided for the following categories:

- Non-SCD-related TEAEs
- Non-SCD-related TEAEs by study year
- Non-SCD-related TEAEs by maximum severity
- Non-SCD-related TEAEs assessed as related to study drug by the investigator
- Non-SCD-related TEAEs of rash (group term)
- Non-SCD-related TEAE of abdominal pain (group term)
- Non-SCD-related treatment-emergent serious adverse events (SAEs)
- Non-SCD-related treatment-emergent SAEs by study year
- Non-SCD-related treatment-emergent SAEs assessed as related to study drug by the investigator
- SCD-related TEAEs
- SCD-related TEAEs by study year
- SCD-related TEAEs by maximum severity
- SCD-related TEAEs assessed as related to study drug by the investigator

- SCD-related treatment-emergent SAEs
- SCD-related treatment-emergent SAEs by study year
- SCD-related treatment-emergent SAEs assessed as related to study drug by the investigator
- All TEAEs leading to study drug discontinuation
- All TEAEs leading to study drug dose modification (dose reduction or interruption)

Listings for all adverse events, adverse events leading to study drug discontinuation, SAEs, and deaths will be provided.

5.3.3. Clinical Laboratory Assessments

Laboratory abnormalities assessed by the Investigator as clinically significant will be recorded as adverse events.

For participants enrolled in the US and Europe, laboratory values were collected at regular timepoints per the Schedule of Assessments up to Week 48 and analyzed by a central laboratory. After Week 48, laboratory assessments were collected per standard of care for clinical management.

For participants enrolled outside of the US and Europe, laboratory values were collected at regular timepoints per the Schedule of Assessments up to Week 48 and analyzed by each individual site's local laboratory. After Week 48, laboratory assessments were collected per standard of care for clinical management, except for hemoglobin and clinical measures of hemolysis (% reticulocytes, absolute reticulocytes, and bilirubin [total, direct, and indirect]), which continued to be collected every 24 weeks per the Schedule of Assessments.

Descriptive summaries of laboratory parameters (e.g., hematology and serum chemistry) for all participants at baseline and each evaluation post baseline through Week 48, as well as changes from baseline over time, will be provided. If any of the results are below the limit of quantitation or above the limit of quantitation, then the numerical limit will be used in the descriptive summaries.

In addition, laboratory values for hemoglobin and clinical measures of hemolysis collected via local laboratories for participants outside of the US and Europe for all scheduled timepoints (including beyond Week 48) will be summarized descriptively.

Central laboratory values will be graded for selected parameters using the NCI CTCAE. Laboratory abnormality shifts from baseline grade to maximum grade post-baseline up to Week 48 will be tabulated. All assessments after study drug initiation until 28 days after discontinuation of study drug will be included in identifying the maximum grade post-baseline.

5.3.4. Electrocardiogram Assessments

ECGs (12-lead) were initially performed for GBT440-034 study participants who received placebo or voxelotor 900 mg in the parent study GBT440-031. However, based on results from Study GBT440-0115 (a dedicated thorough QT study in healthy participants in which no effects on QT were observed), ECG collection was no longer required in GBT440-034 as of 20 August 2019. The limited ECG data collected in this study will be provided in a listing.

5.3.5. Vital Signs

Descriptive summaries of vital signs (e.g., systolic blood pressure, diastolic blood pressure, and heart rate) at baseline and each evaluation post baseline to Week 48, as well as changes from baseline over time, will be generated.

5.4. SCD-Related Complications

5.4.1. Frequency of SCD-Related Complications

SCD-related complications include adverse events of acute chest syndrome, hepatic sequestration, leg ulcers, osteonecrosis, pneumonia, priapism, pulmonary hypertension, retinopathy, scleral icterus, sickle cell anaemia with crisis, splenic sequestration, and stroke.

The incidence and the annualized incidence rate of each SCD-related complication based on TEAEs, as well as the total of all SCD-related complications, will be computed. Annualized incidence rates will be estimated by dividing the total number of complications observed for all participants by the total assessment time for all participants, and 95% confidence intervals provided based on exact Poisson confidence limits.

5.4.2. Vaso-occlusive Crisis (VOCs)

Vaso-occlusive crises (VOCs) are as defined in protocol Section 7.1.6.1 and are a composite of acute painful crisis and acute chest syndrome events. The annualized incidence rate of on-treatment VOC events will be calculated and 95% confidence interval provided. VOC events with an onset date from informed consent to last dose date will be included in the summary.

5.4.3. Therapies Associated with Sickle Cell Disease

The incidence rate and reasons for on-treatment red blood cell (RBC) transfusions will be summarized. RBC transfusions with an onset date from informed consent to last dose date will be included in the summary.

Opioid usage will be identified based on reported concomitant medications. The number and percentage of participants reporting opioid use at baseline and post-baseline will be summarized.

5.5. Treatment Effect (Durability of Hematologic Effect)

Descriptive summaries of hemoglobin, indirect bilirubin, % reticulocytes, and absolute reticulocytes for all participants at GBT440-034 baseline and each evaluation post baseline through Week 48, as well as changes from baseline over time, will be provided. Laboratory assessments within 8 weeks post RBC transfusion, for any reason, will be imputed by the last laboratory value prior to the transfusion.

6. TABLES, LISTINGS, AND FIGURES

A separate document will provide mockups of the tables, listings, and figures that support the analyses proposed in this SAP.