A Phase 3, Multicenter, Randomized, Double-Blind, Placebo--Controlled Trial to Evaluate the Efficacy of Voxelotor for the Treatment of Leg Ulcers in Patients with Sickle Cell Disease

Statistical Analysis Plan for Protocol GBT440-042 (C5341026) (SAP)

Version: <4>

DATE: **16-DEC-2024**

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1. VERSION HISTORY

Table 1. Summary of Changes

Version/ Date	Associated Protocol Amendment	Rationale	Specific Changes
4/ 16-Dec-2024	Protocol Amendment 3 22 December 2023	Update for the final CSR	Section 2: Added a sentence about dose pause and study termination. Section 2.3.2: • Replaced the open label treatment period with the open label treatment extension period • Clarified the analysis period Section 2.3.3: Clarified the baseline definition for labs and vital signs Section 3.4.2: Added baseline disease characteristics, sickle cell disease genotype and Hydroxyurea use. Section 3.5.1: Clarified MedDRA version Section 3.5.3: Removed the neurological examination. Section 4: Clarified analysis population. Section 6.4: Modified Section title and added safety subgroup analysis Section 6.6: • Added a sentence for Open-label treatment extension period • Updated the wordings to SCD-related and non-SCD related events. • Added listing of SCD and non-SCD related non-TEAEs. • Modified vital signs will be evaluated through end of study visit.
3/ 02-Jul-2024	Protocol Amendment 3 22 December 2023	**Update to Section headers to reflect endpoints and provide clarity for the analysis.**	Section 3.1: Added the definition of target ulcers. Section 3.3: Added PGI-C and CGI-C questionnaire.

			Section 6.3 CCI [redacted] • Added the analysis for the raw score of PROMIS endpoints. • Modified the analysis for PGI-C and CGI-C. Appendix 1: Added three exploratory endpoints. Appendix 2.1: Added a footnote of visit windowing to clarify the Day 1 leg ulcer assessment.
2/ 26-Jan-2024	Protocol Amendment 3 22 December 2023	Updated to match protocol amendment 3.	• Sections 2.2, 3.3 and 6.3 and Appendix 1 - Removed detail wordings on PROMIS measures • Section 2.3 - Updated Figure 1 Study schema

		Update to Section headers to reflect endpoints and provide clarity for the analysis.	• Section 2.2 – Added exploratory endpoints. • Section 2.3.2 - Added more detail on the scenario for subjects who have the initial skin re-epithelialization confirmed at Week 12 • Section 3.1- Added a definition of the target ulcer(s). • Section 3.3 - Changed 'Other' to 'Exploratory' in the Section title and added details on healing at Week 12 and Week 24 and modified hemolytic parameter.

			• Section 3.4.1- Added details on stratification factors. • Section 3.4.2 - Added country and site in the baseline variables to be summarized. • Section 3.5.2 - Added Total proteins and Phosphorus in the Serum Chemistry laboratory assessment in Table 2. • Section 5.2.1- Added details on proportion difference • Section 5.2.2.1 - Removed stratification factors and removed a sentence of difference in LS means as it is mentioned in Sections 6.2 and 6.3. • Section 5.2.3- Modified wordings for the stratified Cox regression model. • Section 5.2.4 – Updated Appendix 4 from 4.2 • Section 6.1- Removed Appendix 4.1. • Sections 6.2 and 6.3 - Added details on the MMRM and Cox regression model, added 'from baseline' to clarify the endpoint, modified description of covariates, added MMRM analysis for PROMIS and VAS exploratory endpoints and removed the sentence 'Note that…' as it is not needed. • Section 6.4 - Added Sections 6.4.1 and 6.4.2 for the subgroup analysis of primary and secondary endpoints, secondary endpoints for the subgroup analysis and age group and country in the subgroup analysis and added forest plot for the subgroup analysis and p-values will not be provided.

			• Section 6.5 - Added site and region in the baseline summary table and actuall exposure to study drug will be summarized. • Section 6.6.1 - Added SCD- related AEs in the reporting and removed safety database as the table are based on clinical database. • Section 6.6.2 - Revised lab unit to SI, removed the approach of handling extreme lab values, removed treatment-emergent graded abnormal AEs and shift table for one grade or more from baseline and added Hy's Law and E-DISH plot. • Section 8 – Updated the reference for stratified Cox model and removed reference #7 as not needed. • Appendix 1 – Added subgroup analysis and LS means for PRO PROMIS and VAS endpoints in the analysis type and more details in the main analysis model. • Appendix 2 - Added safety endpoints and modified visit windows and visit windows for laboratory assessments. • Appendix 3- Added PROMIS T-score conversion table. • Appendix 4 – Removed Appendix 4.1 and modified Appendix 4.2 to 4. • Appendix 5 – Added IRT, SI and TESAE and removed CDARS, HR, QT and QTcF from the table.

2. INTRODUCTION

This SAP provides the detailed methodology for summary and statistical analyses of the data collected in Study GBT440-042 for the final CSR after last subject last visit (LSLV). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment. Statistical analyses will be performed using cleaned case report form (CRF) data as well as non-CRF data (i.e., blood samples data and banked biospecimens).

The administration of the study intervention was voluntarily paused by the Sponsor on 10 May 2024 due to the overall number of deaths observed in the study. The decision was made by the sponsor to terminate the study on 25 September 2024 and the LSLV was on 22 October 2024.

2.1. Modifications to the Analysis Plan Described in the Protocol

Not applicable.

2.2. Study Objectives and Endpoints

Type	Objective	Endpoint
Primary	**Primary**	**Primary**
Efficacy	Characterize the effect of voxelotor and SOC (standard of care) compared to placebo and SOC on leg ulcer healing in participants ≥ 12 years of age with SCD by Week 12	The proportion of participants achieving resolution of the target ulcer(s), CCI [redacted] during the 12-week Randomized Treatment Period. CCI [redacted]
Secondary	**Secondary**	**Secondary**
Efficacy	Characterize the effect of voxelotor and SOC compared to placebo and SOC on secondary endpoints	• Time (in days) to resolution of target ulcer(s) up to Week 12 • Change in total surface area(s) of target ulcer(s) at Week 12 • Incidence of new ulcers by Week 12
Exploratory	**Exploratory**	**Exploratory**
Efficacy	Characterize the effect of voxelotor and SOC compared to placebo and SOC on exploratory endpoints	• Proportion of participants achieving resolution of target ulcer(s) by Week 24 • Time (in days) to resolution of target ulcer(s) up to Week 24 • Change from baseline in total surface area of target ulcer(s) over time up to Week 24

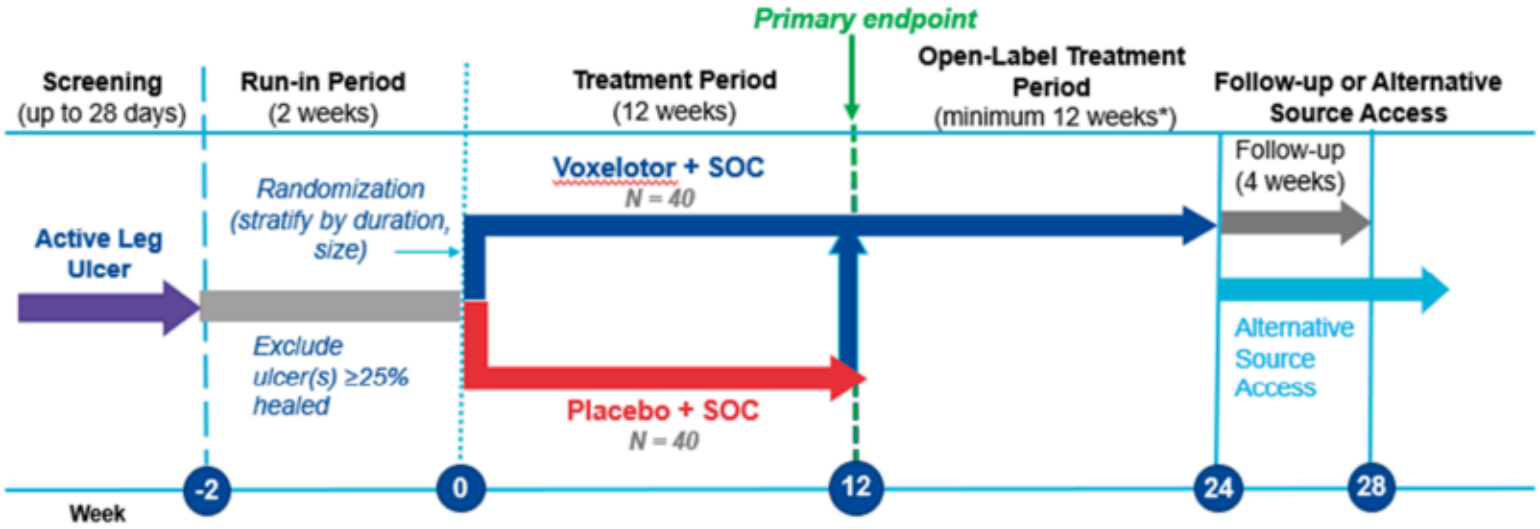
Type	Objective	Endpoint
		• Correlation between change in Hb and target ulcer(s) healing at Week 12 and Week 24 • Correlation between change in hemolytic parameters (% reticulocytes, indirect bilirubin, LDH) and target ulcer(s) healing at Week 12 and Week 24 • Health-related quality of life (HRQOL) using patient-reported outcome (PRO) measures, when available (pending translation and cultural validation requirements) o Change from baseline in PRO HRQOL measures: PROMIS-37 v2.0 Pediatric Profile/PROMIS-43 v2.1 at Week 12 and Week 24 o Change from baseline in pain level linked to target ulcer(s) assessed by VAS at Week 12 and Week 24 o Patient Global Impression of Change (PGI-C) score at Week 12 and Week 24 • Clinician Global Impression of Change (CGI-C) score at Week 12 and Week 24
Safety	Assess the safety and tolerability of voxelotor compared to placebo	• AEs • Clinical laboratory tests • Physical examinations • Vital signs • Other clinical measures (eg. discontinuation due to AEs, dose reductions)

2.3. Study Design

This study is a Phase 3, multicenter, randomized, placebo-controlled study to evaluate the efficacy of voxelotor and SOC for the treatment of leg ulcers in participants with SCD. The study is divided into 5 study periods: Screening, Run-in, Randomized Treatment, Open-label Treatment, and Follow-up/End of Study (EOS).

The study will be conducted in approximately 80 eligible participants at approximately 20 global clinical trial sites. Participants in this study will have safety and efficacy assessments performed at the investigative clinic per the protocol Schedule of Assessments. The overall study design is illustrated in the Study Schema provided in Figure 1. Study Schema

Figure 1. Study Schema



Abbreviations: SOC, standard of care

* Participants who have completed 12 weeks in the Open-label Treatment Period may continue to receive voxelotor as long as they continue to receive clinical benefit that outweighs risk as determined by the Investigator or until the participant has access to voxelotor from an alternative source (eg, through a clinical OLE study sponsored by Pfizer, commercialization of the product, or a managed access program). Participants who do not plan to continue to receive voxelotor from an alternative source should continue to the follow-up period after completing 12 weeks in the Open-label Treatment Period.

2.3.1. Sample Size Determination

Approximately 80 participants will be enrolled in the study. Participants will be randomized in a 1:1 ratio to receive treatment with voxelotor 1500 mg or placebo for 12 weeks. The primary endpoint will be measured by the proportion of participants achieving resolution of the target ulcer(s), CCI [redacted] during the 12-week Randomized Treatment Period. CCI [redacted]

For the primary endpoint, the sample size of 80 participants (40 participants per treatment group) provides approximately 90% power to detect a 35% absolute difference between treatment groups (voxelotor 1500 mg + SOC versus placebo + SOC) in proportion of participants experiencing resolution of the target ulcer(s) by Week 12. Calculations were based on a two-sided alpha = 5% test of the difference in two binomial proportions (Normal approximation).

2.3.2. Treatment Group and Reporting Period for Analysis

In the study schematic in Figure 1. Study Schema, the study period and treatment groups to be included in the primary and open-label analysis.

Efficacy and Safety: Primary analysis (Randomized Treatment Period):

- Treatment groups:
  1. Voxelotor: participants randomized to voxelotor.
  2. Placebo: participants randomized to placebo.
- Reporting Period:
  - From Day 1 through Week 12 for subjects who either do not achieve confirmed re-epithelialization or achieve it before or at Week 12 visit.
  - From Day 1 through Week 14 for subjects who have the initial skin re-epithelialization confirmed at Week 12 and then the 14-week visit will be used to confirm resolution.

  Day 1 is defined as the date of randomization. The last day (i.e. Week 12 visit or Week 14) of randomized treatment period is defined as the last day entered on the disposition page for end of randomized treatment period.

Efficacy: Open-label analysis (Open-Label Treatment Period):

- Treatment groups:
  1. Voxelotor: participants randomized to voxelotor who received at least one dose of voxelotor.

2. Delayed voxelotor: participants randomized to placebo during Randomized Treatment Period (through Week 12) and who received at least one dose of voxelotor on or after the Week 12 visit.

3. Total: participants who received at least one dose of voxelotor.

- Reporting Period:
  - After Week 12 (one day after Week 12 visit) through Week 24 for subjects who either do not achieve confirmed re-epithelialization or achieved it before or at Week 12 visit.
  - After Week 14 (one day after Week 14 visit) through Week 24 for subjects who have the initial skin re-epithelialization confirmed at Week 12 and then the 14-week visit will be used to confirm resolution.

Safety: Open-label analysis (Open-Label Treatment Extension Period which is combining the entire Open-Label Treatment Period and the Follow-up Period):

- Treatment groups:

1. Voxelotor: participants randomized to voxelotor and received at least one dose of voxelotor.

2. Delayed voxelotor: participants randomized to placebo and who did not receive voxelotor during Randomized Treatment Period (through Week 12) and who received at least one dose of voxelotor on during the open-label period (or after the Week 12).

3. Total: participants who received at least one dose of voxelotor.

- Reporting Period:
  - After Week 12 (one day after Week 12 visit) through end of study for subjects who either do not achieve confirmed re-epithelialization or achieved it before or at Week 12 visit.
  - After Week 14 (one day after Week 14 visit) through end of study for subjects who have the initial skin re-epithelialization confirmed at Week 12 and then the 14-week visit will be used to confirm resolution.

2.3.3. Definitions and Terminology

Study Drug

The term study drug refers to either voxelotor or placebo.

Baseline Value

Baseline for all assessments other than laboratory or vital sign parameters, will be defined as the last available pre-treatment value taken on or before the day of randomization and will be used for summary of baseline characteristics and change from baseline analyses, as appropriate.

Baseline for a given laboratory parameter will be defined as the average of all non-missing laboratory values on or prior to the randomization Date.

Baseline for a given vital sign parameter will be defined as the average of all non-missing vital sign value on or prior to randomization Date.

Study Day

Study Day is defined relative to the date of randomization.

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

Study Day = Event Date – Day 1 date + 1.

For study assessments or events that occur before the date of randomization, study day is calculated as:

Study Day = Event Date – Day 1 date.

Study Visit

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

Change from Baseline

Change from baseline for a given endpoint is defined as the Study Day value minus the Baseline value.

On-treatment period:

On-treatment period is defined as the time from the first dose of study drug through minimum of 28 days + last dose of study drug and the date of study completion/discontinuation.

Extent of exposure to study drug

Extent of exposure to study drug is defined as the number of weeks from initiation of study drug to the end of study drug treatment. Extent of exposure is calculated as follows:

$$\frac{(End\ of\ Treatment\ Date - Start\ Date\ of\ Dosing + 1)}{7}.$$

Actual exposure to study drug

Actual exposure to study drug is defined as the number of weeks from initiation of study drug 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

$$I_{Dose_i} = \begin{cases} 0, \text{if treatment dose i} = 0\ \text{mg} \\ 1, \text{if treatment dose i} \neq 0\ \text{mg} \end{cases}, i = 1,2, \ldots, n.$$

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

The proportion of participants achieving resolution of the target ulcer(s), CCI [redacted] during the 12-week Randomized Treatment Period. CCI [redacted]

For participants with more than one target ulcer, all target ulcers must be confirmed resolved in order for the participant to be considered a responder.

A target ulcer can be defined as following criteria:

CCI [redacted]

- Size: > 2 cm^2 at any visit, prior to randomization (Visits 1, 2, and 3, using central reader measurement)

If the ulcer does not meet the criteria above, it will not be used as the target ulcer for the efficacy analysis.

3.2. Secondary Endpoint(s)

- Time (in days) to resolution of target ulcer(s) up to Week 12

Time to resolution of target ulcer(s) is defined as

Date of resolution – Date of randomization +1,

where the date of resolution is defined as the first time of the observed ulcer was resolved. For participants with more than one target ulcer, time to resolution of target

ulcer(s) is defined as time to the last target ulcer confirmed resolved. For participants who do not have the last target ulcer confirmed resolved by Week 12 or who are discontinued from study, the time to resolution will be censored.

- Change from baseline in total surface area of target ulcer(s) at Week 12
- Incidence of new ulcers by Week 12

3.3. Exploratory Endpoint(s)

Protocol specified exploratory efficacy endpoints include:

- Proportion of participants achieving resolution of target ulcer(s) by Week 24
- Time (in days) to resolution of target ulcer(s) up to Week 24
- Change from baseline in total surface area of target ulcer(s) over time up to Week 24
- Correlation between change in Hb and target ulcer(s) healing at Weeks 12 and 24

  Healing at Week 12 and 24 is defined as achieving confirmed re-epithelialization by Week 12 and Week 24 which is defined as participants achieving resolution of the target ulcer(s), CCI [redacted] during the 12-week Randomized Treatment Period and during the 24-week treatment period, respectively. CCI [redacted]
- Correlation between change in hemolytic parameter (% reticulocytes, indirect bilirubin, LDH) and target ulcer(s) healing at Weeks 12 and 24
- Change from baseline in PRO HRQOL measures: PROMIS-37 v2.0 Pediatric Profile/PROMIS-43 v2.1 at Weeks 12 and 24
- Change from baseline in pain level linked to target ulcer(s) assessed by VAS at Weeks 12 and 24
- PGI-C score at Weeks 12 and 24

  PGI-C questionnaire includes 7 responses which are 1) very much improved, 2) much improved, 3) minimal improved, 4) no change, 5) minimal worse, 6) much worse and 7) very much worse.
- CGI-C score at Weeks 12 and 24

CGI-C questionnaire includes 7 responses which are 1) very much improved, 2) much improved, 3) minimal improved, 4) no change, 5) minimal worse, 6) much worse and 7) very much worse.

3.4. Baseline Variables

Randomized Treatment Period:

- Voxelotor: Baseline period is defined as Day 1 of the study.
- Placebo: Baseline period is defined as Day 1 of the study.

Open-Label Treatment Period:

- Voxelotor: Baseline period is defined as Day 1 of the study.
- Delayed voxelotor: Baseline period is defined as Day 1 of the study.

3.4.1. Stratification Variable

Stratification factors (variables) are defined as followed:

- Ulcer size: total target ulcer surface area (ie, sum of all target ulcer surface areas) at baseline visit (Day 1).

  CCI [redacted]
- Duration of ulcer(s): longest duration of any individual target ulcer(s) present at baseline visit (Day 1).

  CCI [redacted]

CCI [redacted]

Note that the stratification variables will be derived based on the baseline visit (Day 1) in the clinical database. If the derived stratification variables are not matched with IRT stratified randomization factors, the derived stratification variables from clinical database will be used for the analysis. If duration of ulcer(s) or ulcer size not are available in the clinical database, the data from IRT will be used for the analysis.

3.4.2. Other Baseline Variables to be Summarized

- Demographic characteristics include gender, race, ethnicity, geographical region, country, site, and age at Screening visit.
- Baseline disease characteristics (including number of target leg ulcer(s), total surface area of target leg ulcer(s), and maximum duration of target leg ulcer(s))

- Physical examination at Screening include height (cm), weight (kg) and BMI (kg/m^2)=weight (kg)/[height (m)]^2
- Sickle cell disease genotype
- Hydroxyurea use

3.5. Safety Endpoints

3.5.1. Adverse Events

MedDRA will be used to code all AEs (non-serious and serious) with respect to system organ class and preferred term (PT) using most current version of the MedDRA dictionary.

TEAE is defined as an AE that occurs or worsens during the on-treatment period as defined in Section 2.3.3.

3.5.2. Laboratory Data

The following safety laboratory tests (Table 2) will be collected. Analyses for banked biospecimens are out of scope for this SAP.

Table 2. Protocol-Required Safety Laboratory Assessments

Hematology	Serum Chemistry
• RBCs • Hematocrit • Hemoglobin • Platelet • White blood cells with differential (basophils, eosinophils, neutrophils, monocytes, and lymphocytes) • % and absolute reticulocytes • RBC distribution width • Mean corpuscular volume • Mean corpuscular hemoglobin concentration • HbSS, HbS/β0 thalassemia test (at Screening only for medical diagnosis of SCD, if diagnosis is not documented in medical chart)	• ALT • Albumin • Alkaline phosphatase (ALP) • AST • Bicarbonate • Blood urea nitrogen • Chloride • Calcium • Creatinine • Glucose • LDH • Sodium • Potassium • Bilirubin (total, direct, and indirect) • Total proteins • Phosphorus

3.5.3. Other Safety Endpoints

- Complete physical examination and brief physical examination: if any finding on the physical examination is considered by the investigator to be 'clinically significant', the event is to be recorded as medical history or an AE, as appropriate.

- Vital Signs: vital sign parameters include blood pressure, heart rate, and temperature.

4. ANALYSIS SETS (POPULATIONS FOR ANALYSIS)

For purposes of analysis, two main analysis populations are defined for this study as below.

Population	Description
ITT Population	All randomized participants according to the treatment group to which they were randomized, regardless of the treatment received
Safety-Evaluable Population	All randomized participants who received at least one dose of study drug, regardless of the group to which they were randomized

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

The hypothesis testing for the primary endpoint is to compare the proportion of participants achieving resolution of the target ulcer(s) by Week 12 in voxelotor vs. placebo group as follows:

$$H_0: p_v = p_c \text{ vs. } H_1: p_v \neq p_c,$$

where p_v and p_c are the proportion of participants achieving resolution of the target ulcer(s) by Week 12 in voxelotor and placebo group, respectively.

CCI

[redacted]

5.2. General Methods

5.2.1. Analyses for Binary Endpoints

The exact CMH[5,6] general association test will be used for binary endpoints. The estimated proportions with 95% CI by treatment group, the estimated proportion difference (voxelotor vs. placebo) with 95% CI and the p-value will be provided.

Descriptive statistics including the number of participants (N) and percentage (%) will be provided by treatment group.

5.2.2. Analyses for Continuous Endpoints

5.2.2.1. Mixed Model Repeated Measures (MMRM)

The MMRM model will be used for the specific endpoint and will include fixed effects terms for:

- Treatment group (as a categorical variable);
- Scheduled visit time point (as an ordered categorical variable);

- Interaction between treatment group and scheduled visit time point.

The restricted maximum likelihood (REML) estimation method will be used with an unstructured covariance matrix to describe the correlation among different visits from the same participant. If there are convergence issues with the model, the following structures will be considered in the order listed below until convergence is obtained:

1. Spatial Power (SP);
2. Autoregressive-1 (AR(1));
3. Compound Symmetry (CS).

The Kenward-Roger[2] degrees of freedom will be used.

The model adjusted estimates for the endpoint for each treatment group at each specified time point will be provided using the least squares (LS) means and their 95% confidence intervals (CIs).

Descriptive statistics including the number of participants (N), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be provided.

5.2.3. Analyses for Time-to Event Endpoints

Time-to event endpoint will also be summarized using the Kaplan-Meier method (product-limit estimates) and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time. The median, quartiles, and probabilities of an event at particular points in time will be estimated by the Kaplan-Meier method. Confidence intervals for medians and quartiles are based on the Brookmeyer-Crowley method. Confidence intervals for the estimated probability of an event at a particular time point will be generated using the Greenwood formula.

A stratified log-rank test with stratification factors will be performed to test for differences between the voxelotor and placebo treatment groups.

A stratified Cox regression model[3] with treatment group as the covariate will be used to estimate the treatment group hazard ratio (voxelotor vs. placebo) and the corresponding two-sided 95% confidence interval.

Counts and percentages of subjects who experienced the event as well as the counts and percentages of subjects who were censored and the type of censoring (eg, death or missing data) will be reported for each of the treatment groups.

5.2.4. Correlation Analysis Between Continuous and Binary Endpoints

CCI [redacted] Pearson[4] correlation with one dichotomous variable will be used CCI [redacted].

5.3. Methods to Manage Missing Data

Guidelines regarding how missing data will be handled are described below.

5.3.1. Status of Target Study Ulcer(s)

Participants who are lost to follow-up or otherwise drop out of the study without confirmation of resolution of all target study ulcer(s) prior to Week 12, will be classified as non-responders for purposes of the primary analysis.

5.3.2. Imputation of Incomplete Dates

An incomplete date is any date for which either the day, month or year is unknown, but all three fields are not unknown. An incomplete date occurs when the exact date an event occurred or ended cannot be obtained from a subject. For many of the analyses, a complete date is necessary to determine if the event should be included in the analysis (i.e., if the event is treatment-emergent) or to establish the duration of an event. In such cases, incomplete dates will be imputed as follows.

For concomitant medications, the case report form permits the start date to have an unknown day and/or month.

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.

Stop dates for concomitant medications

- 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).

For adverse events, the case report form permits the date to have an unknown day. If day is missing, then a question on the case report form asks whether the event started prior to the first dose.

Start dates for adverse events where the event occurs prior to the first dose

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.

Start dates for adverse events where the event is not prior to the first dose

For missing start day only – 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. Otherwise, the day will be imputed as the first day of the month (i.e., 1) as long as the imputed date does not occur before the treatment start date.

Stop Dates for Adverse Events

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 study drug exposure, the case report form permits the date to have an unknown day. However, due to daily dosing, partial dates will not be imputed. Any partial dates will be displayed in data listings without imputation of missing days and/or months.

6. ANALYSES AND SUMMARIES

Analyses based on ITT participants will be grouped according to the treatment assigned at randomization and for Safety-Evaluable populations, participants will be grouped according to the actual study drug taken.

6.1. Primary Endpoint

The proportion of participants achieving resolution of the target ulcer(s) by Week 12.

Population: ITT population as described in Section 4.

Primary analysis:

The exact CMH[5,6] test as described in Section 5.2.1 stratified by stratification factors of target ulcer size and duration with imputation rules outlined in Section 5.3 will be used.

6.2. Secondary Endpoints

1. Endpoint: Time (in days) to resolution of target ulcer(s) up to Week 12

Population: ITT Population as described in Section 4.

Analysis:

The analysis as described in Section 5.2.3 consists of a stratified log-rank test to test the difference in this endpoint between the voxelotor and placebo groups, where the stratification factors are target ulcer size and duration, will be performed and the p-value for log-rank test will be reported. A stratified Cox regression model with the strata

including target ulcer size (categorical) and target ulcer duration (categorical) and the treatment group as the covariate will be used to estimate the hazard ratio (voxelotor vs. placebo) and the corresponding two-sided 95% confidence interval.

2. Endpoint: Change from baseline in total surface area of target ulcer(s) at Week 12

Population: ITT Population as described in Section 4.

Analysis:

MMRM analysis as described in Section 5.2.2.1 will be used with target ulcer size (categorical) and target ulcer duration (categorical) as covariates and the change from baseline in total surface area of target ulcer(s) at Week 12 as a response variable. The LS means difference (voxelotor vs. placebo) with 95% CI and p-value for LS mean difference at Week 12 will be provided.

3. Endpoint: Incidence of new ulcers by Week 12

Population: ITT Population as described in Section 4.

Analysis:

The exact CMH general association test as described in Section 5.2.1 with imputation rules outlined in Section 5.3 will be used.

Voxelotor will be compared to placebo while stratifying for the stratification factors of target ulcer size and duration.

6.3. Exploratory Efficacy Endpoints

Endpoint: The proportion of participants achieving resolution of the target ulcer(s) by Week 24

Population: ITT population as described in Section 4.

Analysis: Descriptive statistics including the number of participants (N) and percentage (%) will be provided by Voxelotor and delayed Voxelotor groups.

Endpoint: Time (in days) to resolution of target ulcer(s) up to Week 24

Population: ITT population as described in Section 4.

Analysis: Number of participants (N) who achieved resolution of target ulcer, median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be provided by Voxelotor and Delayed Voxelotor groups.

Endpoint: Change from Baseline in total surface area of target ulcer(s) over time up to Week 24

Population: ITT population as described in Section 4.

Analysis: Descriptive statistics including the number of participants (N), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be provided by Voxelotor and Delayed Voxelotor groups.

Endpoint: Correlation between change from Baseline in Hb and target ulcer(s) healing at Week 12 and Week 24.

Population: ITT Population as described in Section 4.

Analysis: The point biserial correlation r_{pb} will be provided as described in Section 5.2.4 by treatment groups.

Endpoint:

- Correlation between change in hemolytic parameter, % reticulocytes and target ulcer(s) healing at Week 12 and Week 24
- Correlation between change in hemolytic parameter, indirect bilirubin and target ulcer(s) healing at Week 12 and Week 24
- Correlation between change in hemolytic parameter, LDH and target ulcer(s) healing at Week 12 and Week 24

Population: ITT Population as described in Section 4.

Analysis: The point biserial correlation r_{pb} will be provided as described in Section 5.2.4 by treatment groups.

Health-related quality of life (HRQOL) using patient-reported outcome (PRO) measures endpoints:

Endpoint: Change from baseline in PRO HRQOL measures: PROMIS-37 v2.0 Pediatric Profile/PROMIS-43 v2.1 at Week 12 and Week 24.

PROMIS-37 v2.0 Pediatric Profile domains included Physical Function Mobility, Anxiety, Depressive Symptoms, Fatigue, Peer Relationships, Pain Interference and Pain Intensity. PROMIS-43 v2.1 Adult Profile domains included Physical Functioning, Pain Interference, Sleep Disturbance, Fatigue, Anxiety, Depression, Ability to Participate in Social Roles and Activities and Pain Intensity.
The PROMIS-37 v2.0 and PROMIS-43 v2.1 raw score for each domain will be converted to T-score (see Appendix 3) except pain intensity domain in both PROMIS-37 v2.0 and

PROMIS-43 v2.1. All analysis will be based on both raw score and T-score by domain including pain intensity score.

Population: ITT Population as described in Section 4.

Analysis:

- MMRM analysis as described in Section 5.2.2.1 will be used with target ulcer size (categorical) and target ulcer duration (categorical) as covariates and the change from baseline in PROMIS domain T-score and raw score at Week 12 as a response variable. The p-value for LS means difference (voxelotor vs. placebo) at Week 12 will be provided for each of domains.

- Descriptive statistics including the number of participants (N), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be provided by treatment group at Weeks 12 and 24.

Endpoint: Change from baseline in pain level linked to target ulcer(s) assessed by VAS at Week 12 and Week 24

Population: ITT Population as described in Section 4.

Analysis:

- MMRM analysis as described in Section 5.2.2.1 will be used with target ulcer size (categorical) and target ulcer duration (categorical) as covariates and the change from baseline in pain level linked to target ulcer(s) assessed by VAS at Week 12 as a response variable. The p-value for LS means difference (voxelotor vs. placebo) at Week 12 will be provided.

- Descriptive statistics including the number of participants (N), mean, standard deviation (SD), median, first quartile (Q1), third quartile (Q3), minimum, and maximum will be provided by treatment group at Weeks 12 and 24.

Endpoint: Patient Global Impression of Change (PGI-C) score at Week 12 and Week 24

Population: ITT Population as described in Section 4.

Analysis: Descriptive statistics including the percentage of patients for each response will be provided by treatment group at Weeks 12 and 24.

Endpoint: Clinician Global Impression of Change (CGI-C) score at Week 12 and Week 24

Population: ITT Population as described in Section 4.

Analysis: Descriptive statistics including the number and percentage of patients for each response will be provided by treatment group at Weeks 12 and 24.

6.4. Subset Analyses

6.4.1. Subset analysis for efficacy endpoints

Efficacy subgroup analyses will be performed for the primary and secondary efficacy endpoints for the following subsets unless otherwise noted. The forest plots for all subset analysis by endpoint will be provided. P-values will not be provided for any subgroup analysis.

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3. Age group with <18 years of age and ≥ 18 years of age
4. Country (Nigeria, Kenya and Brazil)

6.4.1.1. Primary Endpoint

The proportion of participants achieving resolution of the target ulcer(s) by Week 12

Population: ITT population as described in Section 4

Analysis:

The proportion difference (voxelotor vs. placebo) and 95% CI will be provided by subgroup.

6.4.1.2. Secondary Endpoint

1. Endpoint: Time (in days) to resolution of target ulcer(s) up to Week 12

Population: ITT population as described in Section 4

Analysis:

A Cox regression model with the treatment group as a covariate will be used to estimate the hazard ratio (voxelotor vs. placebo) and the corresponding two-sided 95% CI by subgroup.

2. Endpoint: Change from baseline in total surface area of target ulcer(s) at Week 12

Population: ITT population as described in Section 4

Analysis:

MMRM analysis as described in Section 5.2.2.1 will be used and the change from baseline in total surface area of target ulcer(s) at Week 12 as a response variable. The LS means difference (voxelotor vs. placebo) with 95% CI for LS mean difference at Week 12 will be provided by subgroup.

3. Endpoint: Incidence of new ulcers by Week 12

Population: ITT population as described in Section 4

Analysis:

The proportion difference (voxelotor vs. placebo) and 95% CI will be provided by subgroups of age group and country only.

6.4.2. Subset analysis for safety endpoints

Safety subgroup analyses will be performed on safety analysis set for SCD-related TEAEs and TESAEs in the randomized treatment period on the following subgroups.

1) Malaria

   a. Subjects with at least one TEAE of Malaria by Week 12 (Yes, No)

   b. Subjects with at least one TEAE of Malaria by Week 24 (Yes, No)

2) Change from Baseline in Hemoglobin at Week 12 (< 0 g/dL, 0-1 g/dL, >1 g/dL)

3) Hemoglobin at Week 12 (< 7 g/dL, >=7 g/dL and <9 g/dL, >=9 g/dL)

4) Number of VOCs in the past 12 Months (0 VOCs, >=1 VOCs)

5) Number of VOCs in the past 12 Months (1 VOC, >=2 VOCs)

6) Country (Nigeria, Kenya, Brazil)

6.5. Baseline and Other Summaries and Analyses

6.5.1. Baseline Summaries

1. Demographic characteristics will be summarized by treatment group.

   Demographic and baseline characteristics such as age, sex, race, and baseline disease characteristics (including number of target leg ulcer(s), total surface area of target leg ulcer(s), and maximum duration of target leg ulcer(s))

2. Baseline physical measurements (including height and weight) will be summarized by treatment group.

3. The below will be summarized using number (%) of participants by treatment group:

   - Sickle cell disease genotype; and
   - Enrollment site, country and region.

4. General medical history will be summarized by treatment group.

5. Hydroxyurea use by treatment group.

6.5.2. Study Conduct and Participant Disposition

1. The below participant population will be summarized by treatment group.

    - ITT Population.

    - Safety-Evaluable Population.

2. Participant disposition (eg, discontinuation from study, reason for discontinuation, completed study, and ongoing) will be summarized by treatment group at Week 12 and 24.

3. Actual exposure to study drug will be summarized by treatment group at Week 12 and 24.

4. Important protocol deviations will be summarized by treatment group.

6.5.3. Concomitant Medications and Nondrug Treatments

The most current World Health Organization (WHO)-Drug coding dictionary will be used to classify concomitant medications.

The number (%) of participants who took each concomitant medication will be provided by treatment group.

6.6. Safety Summaries and Analyses

All safety analysis will be performed based on Safety-Evaluable Population as described in Section 4 and Open-Label Treatment Extension Period for Safety as described in Section 2.3.2.

6.6.1. Adverse Events

SCD-related adverse events, defined as MedDRA PTs of sickle cell anaemia with crisis, acute chest syndrome, pneumonia, priapism (male participants only), splenic or hepatic sequestrations, stroke, and osteonecrosis, are included in the summary. Non-SCD-related adverse events are all other adverse events. The TEAEs/TESAEs and treatment-related AEs/SAEs will be displayed by SCD-related and non-SCD-related.

The total number and percentage of subjects with TEAEs will be presented by system organ class and preferred term by treatment group. TEAEs will be presented by severity (CTCAE grade or protocol defined severity). TEAEs will be tabulated presenting the system organ class alphabetically and within each system the preferred term will be presented by treatment group. The total number and percentage of subjects discontinued from study due to AEs will by presented by treatment group.

The frequency of subjects who experience each TEAE or treatment-related AE will be determined as follows: A subject experiencing the same AE multiple times will only be counted once for the preferred term. Similarly, if a subject experiences multiple AEs within the same system organ class, that subject will be counted only once for that system. If changes in the severity of an AE are recorded in the eCRF, only the most severe incidence of the AE will be counted. If a subject experiences multiple occurrences of a TEAE, only the related event or the worst severity (analysis dependent), will be counted for each subject within each system organ class or preferred term for the summaries of treatment-related AEs.

Missing onset dates will be imputed as previously outlined in Section 5.3.2 as required to determine treatment-emergent events. Should an event have a missing severity or relationship to study medication, then the severity or relationship, respectively, will be classified as missing for summary tabulation purposes.

Listings of AEs leading to discontinuation of the study, SAEs and deaths, if any, will be provided.

Listing of all AEs, including AEs occurred after 28 days of the last treatment date.

Deaths and SAEs will be listed and incidence of SAEs (all causalities and treatment-related) will be summarized by system organ class and PT by treatment group.

Serious adverse events (SAEs) will be summarized with counts and percentage. SAE information will be reconciled between the clinical and safety databases prior to the database lock for database release.

6.6.2. Laboratory Data

All hematology and chemistry laboratory assessments were performed by a central laboratory. Laboratory data will be converted into SI for the analysis. The protocol-specified clinical laboratory (Table 2) findings will be summarized using descriptive statistics by treatment group, without any imputation.

Descriptive statistics will be presented for baseline, each evaluation post baseline, and change from baseline for each post baseline evaluation through 28 days after last dose date.

Laboratory abnormalities will be graded via the Common Terminology Criteria for Adverse Event (CTCAE) or protocol defined severity classification. Laboratory abnormality shifts from baseline will be summarized by treatment group and by reporting periods.

To assess liver injury, a listing of the participants potentially meeting Hy's Law criteria and E-DISH plots will be produced.

6.6.3. Vital Signs

Vital signs (body temperature, heart rate, and systolic/diastolic blood pressure) will be summarized using descriptive statistics for baseline and change from baseline for each post-baseline evaluation through 28 days after the last dose date.

7. INTERIM ANALYSES

No interim analysis is planned for this study.

8. REFERENCES

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APPENDICES

Appendix 1. Summary of Efficacy Analyses

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Main Analysis Model
Primary				
The status of participants achieving resolution of the target ulcer(s) by Week 12	Exact CMH test Descriptive summary statistics Subgroup analysis	ITT	Participants who are lost to follow-up or otherwise drop out of the study without confirmation of resolution of all target study ulcer(s) prior to Week 12, will be classified as non-responder.	Exact CMH test with stratification factors of target ulcer size and duration
Secondary				
Time (in days) to resolution of target ulcer(s) up to Week 12	Log-rank and Cox regression model Descriptive summary statistics Subgroup analysis	ITT	For participants who do not have the last target ulcer confirmed resolved by Week 12 or who are discontinued from study, the time to resolution will be censored	Kaplan-Meier method (product-limit estimates) and estimated survival curves will be displayed graphically when appropriate. Graphs will describe the number of participants at risk over time. A stratified log-rank test with stratification factors will be performed to test for differences between the voxelotor and placebo treatment groups
Change from baseline in total surface area of target ulcer(s) at Week 12	LS means (95%CI) LS means difference Descriptive summary statistics Subgroup analysis	ITT	NA	MMRM analysis will be used as described in Section 5.2.2.1 with the stratification factors including target ulcer size (categorical) and target ulcer duration (categorical) as covariates and. The p-value for LS means difference (voxelotor vs. placebo) at Week 12 will be provided.

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Main Analysis Model
Incidence of new ulcers by Week 12	Exact CMH test Descriptive summary statistics Subgroup analysis (age group and country)	ITT	NA	Exact CMH test with stratification factors of target ulcer size and duration
Exploratory				
The proportion of participants achieving resolution of the target ulcer(s) by Week 24	Descriptive summary statistics	ITT	NA	Descriptive statistics
Time (in days) to resolution of target ulcer(s) up to Week 24	Descriptive summary statistics	ITT	NA	Descriptive statistics
Change from Baseline in total surface area of target ulcer(s) over time up to Week 24	Descriptive summary statistics	ITT	NA	Descriptive statistics
Correlation between change in Hb and target ulcer(s) healing at Week 12 and Week 24	Point biserial correlation	ITT	NA	The point biserial correlation r_{pb}
Correlation between change in hemolytic parameters (% reticulocytes, indirect bilirubin, LDH) and target ulcer(s) healing at Week 12 and Week 24	Point biserial correlation	ITT	NA	The point biserial correlation r_{pb}

Endpoint	Analysis Type	Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Main Analysis Model
Change from baseline in PRO HRQOL measures: PROMIS-37 v2.0 Pediatric Profile/PROMIS-43 v2.1 at Week 12 and Week 24	LS means (95%CI) LS means difference Descriptive summary statistics	ITT	NA	Descriptive statistics MMRM analysis will be used as described in Section 5.2.2.1 with the stratification factors including target ulcer size (categorical) and target ulcer duration (categorical) as covariates.
Change from baseline in pain level linked to target ulcer(s) assessed by VAS at Week 12 and Week 24	LS means (95%CI) LS means difference Descriptive summary statistics	ITT	NA	Descriptive statistics MMRM analysis will be used as described in Section 5.2.2.1 the stratification factors including target ulcer size (categorical) and target ulcer duration (categorical) as covariates.
Patient Global Impression of Change (PGI-C) score at Week 12 and Week 24	Descriptive summary statistics	ITT	NA	Descriptive statistics
Clinician Global Impression of Change (CGI-C) score at Week 12 and Week 24	Descriptive summary statistics	ITT	NA	Descriptive statistics

Appendix 2. Data Derivation Details

Appendix 2.1. Definition and Use of Visit Windows in Reporting

Nominal analysis visit windows for the efficacy and safety endpoints will be defined below.

Nominal Visit Time	Target Study Day	Protocol Study Day Range	Study Day Range for Statistical Analysis
Day 1	1	[1, 1]	[1, 1]*
Week 2	14	[11, 17]	[2, 21]
Week 4	28	[25, 31]	[22, 35]
Week 6	42	[39, 45]	[36, 49]

Week 8	56	[53, 59]	[50, 63]
Week 10	70	[57, 63]	[64, 77]
Week 12	84	[81, 87]	[78, 91]
Week 14	98	[95, 101]	[92, 105]
Week 16	112	[109, 115]	[106, 119]
Week 18	126	[123, 129]	[120, 133]
Week 20	140	[137, 143]	[134, 147]
Week 22	154	[151, 157]	[148, 161]
Week 24	168	[165, 171]	[162, 175]
Week 28	196	[191, 201]	[176, 216]

*: For the leg ulcer Day 1 assessment, the windowing Day 1 visit is defined as [-1,1]

Nominal analysis visit windows for the laboratory assessments will be defined below.

Nominal Visit Time	Target Study Day	Protocol Study Day Range	Study Day Range for Statistical Analysis
Day 1	1	[1, 1]	[1, 1]
Week 12	84	[81, 87]	[2, 125]
Week 24	168	[165, 171]	[126, 216]

Appendix 2.2. Protocol Deviations that Related to Statistical Analyses/Populations

For the primary endpoint, the sample size of 80 participants (40 participants per treatment group) provides approximately 90% power to detect a 35% absolute difference between treatment groups (voxelotor 1500 mg + SOC versus placebo + SOC) in proportion of participants experiencing resolution of the target ulcer(s) by Week 12. Calculations were based on a two-sided alpha = 5% test of the difference in two binomial proportions (Normal approximation). If the drop out rate of 5% is assumed, the sample size should be 84 participants.

Appendix 3. Data Conversion

PROMIS-43 v2.1 Adult Profile T-score conversion table

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PROMIS-37 v2.0 Pediatric Profile T-score conversion table

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Appendix 5. List of Abbreviations

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate transferase
AR(1)	first order autoregressive
CGI-C	clinical global impression of change
CI	confidence interval
CMH	Cochran–Mantel–Haenszel
CRF	case report form
CS	compound symmetry
CSR	clinical study report
CTCAE	common terminology criteria for adverse event
EOS	end of study
HRQOL	health-related quality of life
IRT	interative response technology
ITT	intent-to-treat
LDH	lactate dehydrogenase
LS	least squared
MedDRA	medical dictionary for regulatory activities
MMRM	mixed model repeated measures
N/A	not applicable
OLE	open-label extension
PGI-C	patient global impression of change
PRO	patient-reported outcome
PROMIS	patient-reported outcomes measurement information system
PT	preferred term
Q1	first quartile
Q3	third quartile
REML	restricted maximum likelihood
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SCD	sickle cell disease
SD	standard deviation
SI	international system of units
SOC	standard of care
SOP	standard operating procedure
SP	spatial power
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
VAS	visual analogue scale

Abbreviation	Term
WBC	white blood cell
WHO	world health organization