CLINICAL STUDY PROTOCOL

Study Title	**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**
Short Title	**Resolution of Sickle Cell Leg Ulcers with Voxelotor (RESOLVE)**
Investigational Product	Voxelotor (GBT440)
IND Number	121691
Sponsor Legal Address	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 United States of America
Protocol Amendment 3.0	22 December 2023
Protocol Amendment 2.0	01 September 2022
Protocol Amendment 1.0	13 January 2022
Original Protocol	22 September 2020

CONFIDENTIAL

The information in this study protocol is strictly confidential and is available for review to Investigators, study center personnel, the ethics committee, and the health authorities. It will not be disclosed to third parties without written authorization from the Sponsor, except to obtain informed consent from persons receiving the study treatment. Once the protocol is signed, its terms are binding for all parties.

SUMMARY OF CHANGES

Amendment 3 (22 December 2023)

Overall Rationale for the Amendment:

- To incorporate changes previously implemented via protocol clarification memos
- To align the protocol with the Pfizer Protocol Template and Standard Operating Procedures
- Note: the changes below are not due to any increase in safety signals

Protocol Amendment Summary of Changes Table

Description of Change	Brief Rationale	Section Number and Name
Non-Substantial Modifications		
Removed name of Study Director	Name of Study Director is considered personal protected data	Title page
Removed Statement of Approval and Compliance	Statement of Approval and Compliance is considered personal protected data	Statement of Approval and Compliance
Added detailed guidance for reporting AEs	To support Study transition to Pfizer Pharmacovigilance processes and systems	7.2.1 Adverse Event Reporting (general)
Added language for reporting AEs and SAEs after the end of AE/SAE active collection period	To support Study transition to Pfizer Pharmacovigilance processes and systems	7.3 Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting
Revised language on reporting overdose	To align with Pfizer's safety reporting process	7.4 Reporting Overdose
Revised language regarding environmental and occupational exposure as well as exposure during pregnancy and breastfeeding	To support Study transition to Pfizer Pharmacovigilance processes and systems	7.4 Reporting Pregnancy (deleted section) 7.5 Environmental Exposure, Exposure During Pregnancy or Breastfeeding, Occupational Exposure, and Lack of Efficacy (new section)
Added language regarding the definition and reporting of medication errors	To support Study transition to Pfizer Pharmacovigilance processes and systems	7.6 Medication Errors (new section)
Added language regarding maximum amount of blood to be drawn for pediatric participants	To optimize pediatric blood draws	6.10 Laboratory Assessments Table 5

Description of Change	Brief Rationale	Section Number and Name
Updated the list of examples of moderate and strong CYP34A inducers	To provide up-to-date guidance to Investigators per the latest list of examples provided by the FDA and align with other voxelotor clinical study protocols	5.7.5 Prohibited Concomitant Medications
Extended the Visit 3/ Day 1 window by one additional calendar day at Visit 3	To allow additional time for enrollment in the event that central review and reporting of results to determine eligibility for randomization is not received in a timely manner. (Implemented via Protocol Clarification Letter #1 – 02 November 2022)	3.1 Study Design Appendix 1 Schedule of Assessments
Revised table footnote "n" to add: Urine pregnancy test will be performed at Baseline (Day 1), Week 6, Week 12, Week 18, and Week 24 in female participants who have experienced menarche.	Correction to align with text in Section 6.10, Laboratory Assessments (Implemented via Protocol Clarification Letter #2 – 15 February 2023)	Appendix 1 Schedule of Assessments
Added or revised language regarding access to medical monitor and regulatory obligations, dissemination of clinical study data, publication policy, data quality assurance, study/site start site and closure, data protection, and informed consent	To support Study transition to Pfizer Protocol Template and Standard Operating Procedures	11. Regulatory, Ethical, Legal, and Oversight Obligations (includes several new subsections) 14. Publication Policy
Added language and a new appendix for reporting and follow-up assessments for potential drug-induced liver injury (DILI) events	To support study transition to Pfizer Pharmacovigilance processes and systems	7.2.3 Abnormal Laboratory Values 10.4 Sponsor's Medically Qualified Individual (new section) Appendix 2 Liver Safety: Suggested actions and follow-up assessments and study drug rechallenge guidelines
Revised instructions for collection of blood samples for retesting.	Allows flexibility in the event that blood sample cannot be redrawn and submitted for	6.10 Laboratory Assessments Appendix 1 Schedule of Assessments

Description of Change	Brief Rationale	Section Number and Name
	testing within 7 days of the study visit.	
Updated the list of SCD-related AEs to include splenic or hepatic sequestrations, and stroke	To provide a broader definition of SCD-related AEs for safety analyses	7.2.5 Worsening of Sickle Cell Disease
Added clarifying language regarding leg ulcer photography and measurement process	To provide clarity to sites regarding process	6.7 Ulcer Assessments
Removed clarifying language on PROMIS measures	PROMIS data will be analyzed using the measures included in the original PROMIS instrument	Protocol Synopsis 2.3 Exploratory Objectives 3.1.3.3 Exploratory Endpoints 6.11 Patient-Reported Outcomes
Revised study schema to reference alternative access	Study drug may be provided through alternative access programs	Figure 1 Study Schema
Added language regarding eligibility review process	To provide clarity to sites regarding process	6.3 Eligibility Assessment, Inclusion/Exclusion Review
Added language regarding digital photography review process	To provide clarity regarding efficacy analysis of leg ulcers	8.4 Efficacy Analysis
Minor administrative changes were made to correct typographical errors or to emphasize subtle points	Improve internal consistency with the protocol.	Throughout the protocol

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Description
AE	adverse event
AF	assent form
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CFR	Code of Federal Regulations
CGI-C	Clinician Global Impression of Change
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug-induced liver injury
ECC	emergency contact card
eCRF	electronic case report form
EDB	exposure during breastfeeding
EDC	electronic data capture
EDP	exposure during pregnancy
eGFR	estimated glomerular filtration rate
EOS	end of study
EU	European Union
EudraCT/CTIS	European Union Drug Regulating Authorities Clinical Trials (European Clinical Trials Database)/ Clinical Trials Information System
FDA	(US) Food and Drug Administration
GBT	Global Blood Therapeutics, Inc.
GCP	Good Clinical Practice
Hb	hemoglobin
HbF	fetal hemoglobin
HbS	sickle hemoglobin

Abbreviation	Description
HbS/β^0	sickle hemoglobin and one beta thalassemia gene
HbSS	sickle hemoglobin with 2 sickle cell genes
HC	hydroxycarbamide
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identification
IEC	Independent Ethics Committee
IID	Inactive Ingredient Database
IRB	Institutional Review Board
ITT	Intent to Treat
IXRS	Interactive Response System
LDH	lactate dehydrogenase
LFT	liver function test
MQI	Medically Qualified Individual
NCI	National Cancer Institute
O_2	oxygen
OLE	Open-label Extension
oxyHb	oxyhemoglobin
PD	pharmacodynamics
PE	physical examination
PGI-C	Patient Global Impression of Change
Ph. Eur.	European Pharmacopoeia
PRO	Patient-reported outcome
PROMIS	Patient-Reported Outcome Measurements Information System
PSSA	Pfizer's Serious Adverse Event Submission Assistant
QOL	quality of life
RBC	red blood cell

Abbreviation	Description
RSI	Reference Safety Information
SAE	serious adverse event
SAP	statistical analysis plan
SCA	sickle cell anemia
SCD	sickle cell disease
SOA	Schedule of Assessments
SOC	standard of care (wound care per protocol for SCD leg ulcers)
SRSD	Single Reference Safety Document
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
VAS	visual analog scale
WHO	World Health Organization

PROTOCOL SYNOPSIS

Study Number	GBT440-042 (C5341026)
Study Title	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
Short Title	Resolution of Sickle Cell Leg Ulcers with Voxelotor (RESOLVE)
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
Study Description	This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled trial to evaluate the efficacy of voxelotor for the treatment of leg ulcers in participants with sickle cell disease (SCD).
Number of Clinical Sites	The study will be conducted at approximately 20 global sites.
Number of Study Participants	Approximately 80 eligible participants will initiate treatment in this study.
Investigational Product	Voxelotor, 500 mg tablets, administered orally Matching placebo, administered orally
Treatment	During the Randomized Treatment Period, participants will be randomized in a 1:1 ratio to receive 1500 mg of voxelotor once daily (administered as three 500 mg tablets) or matching placebo for 12 weeks. In this study, all participants will receive the standard of care (SOC) per protocol for SCD leg ulcers during the Run-in, Randomized Treatment, and Open-label Treatment periods. During the Open-label Treatment Period, all participants will receive 1500 mg of voxelotor once daily (administered as three 500 mg tablets) for a minimum of 12 weeks. 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 not associated with this protocol (eg, through a clinical Open-label Extension [OLE] study sponsored by Pfizer, commercialization of the product, or a managed access program).
Objectives	**Primary** The primary objective of this study is to assess the effect of voxelotor and SOC compared to placebo and SOC on leg ulcer healing in participants ≥ 12 years of age with SCD, as measured by the proportion of participants achieving resolution of target ulcer(s) in each treatment group by Week 12. **Secondary** The secondary objectives of this study are to evaluate the effect of voxelotor and SOC compared to placebo and SOC on: • Time to resolution of target ulcer(s)

	• Change in total surface area of target ulcer(s) • Incidence of new ulcers **Exploratory** The exploratory objectives will assess the effect of voxelotor and SOC compared to placebo in addition to SOC (or open-label voxelotor and SOC, where applicable) on: • Correlation between change in hemoglobin (Hb) and target ulcer(s) healing • Correlation between change in hemolytic parameters (% reticulocytes, indirect bilirubin, lactate dehydrogenase [LDH]) and target ulcer(s) healing • Health-related quality of life (HRQOL) using patient-reported outcome (PRO) measures, when available (pending translation and cultural validation requirements) o Patient-Reported Outcome Measurements Information System (PROMIS) Pediatric Profile-37 v2.0/PROMIS-43 v2.1 o Visual analog scale (VAS) assessment of pain level linked to target ulcer(s) o Patient Global Impression of Change (PGI-C) • Clinician Global Impression of Change (CGI-C) **Safety** The safety objective is to assess the safety and tolerability of voxelotor compared to placebo based on adverse events (AEs), clinical laboratory tests, physical examinations, vital signs, and other clinical measures (eg, discontinuations due to AEs, dose reductions).
Study Design	The study is divided into a Screening Period, a Run-in Period, a Randomized Treatment Period, an Open-label Treatment Period, and a Follow-up Period/End of Study (EOS) Visit. **Screening Period (within 28 days prior to Run-in Period):** During this period, participants will sign the informed consent form/assent form (ICF/AF), after which they will complete the screening assessments, including target leg ulcer(s) surface area measurement(s) by digital photography, as detailed in the Schedule of Assessments (SOA) in Appendix 1 and in the Leg Ulcer Assessment and Measurement Manual. All Screening assessments must be completed within 28 days before the Run-in Period. **Run-in Period (2 weeks prior to Randomization [± 3-day window]):** Participants will enter a 2-week Run-in Period (Day -14 to Day -1 [+3 days]), during which assessments, including target leg ulcer(s) surface area measurement(s) by digital photography will be conducted and SOC initiated per protocol, following best practice guidelines (see Minniti, 2014 for guidance and the Leg Ulcer Management Manual for additional details). These assessments

	must be completed prior to randomization to ensure that the participant continues to qualify for the study. **Randomized Treatment Period (12 weeks [± 3-day window for each visit after Day 1 Visit]):** After completion of the 2-week Run-in Period, target leg ulcer(s) surface area measurement(s) will be reassessed to ensure that the participant continues to qualify for the study before randomization. Eligible participants (target CCI [redacted]) will be randomized 1:1 to receive voxelotor 1500 mg once daily and SOC or placebo once daily and SOC for 12 weeks. At the time of randomization, participants will be stratified CCI [redacted] The treatment period is considered the continuous 12 weeks of voxelotor and SOC or placebo and SOC treatment from date of randomization (first dose, Day 1). The target leg ulcer(s) will be assessed by visual inspection and surface area measurement(s) CCI [redacted] scheduled visits every 2 weeks during the 12-week Randomized Treatment Period. CCI [redacted]
Study Design (continued)	**Open-label Treatment Period (minimum 12 weeks [± 3-day window for each visit]):** At the end of the 12-week Randomized Treatment Period, all participants (with the exception of those demonstrating initial ulcer re-epithelialization at Week 12) will receive open-label voxelotor 1500 mg per day and SOC for an additional 12 weeks and target ulcer(s) that failed to heal during the initial 12 weeks will be followed for delayed healing. Assessments will continue to be performed per the SOA (Appendix 1). *Note: 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.* **Follow-up Period (4 weeks after last dose [± 7-day window for EOS visit]):** Following completion of the Open-label Treatment Period in this study, eligible participants will be given the option to continue to receive voxelotor (under this protocol, until access is provided through an alternative source). Participants

	who do not continue voxelotor will be followed for 4 weeks after the last dose of treatment and instructed to return to the site to complete the EOS visit. **Early Termination Visit:** If a participant terminates the study for any reason, this should be documented on the electronic case report form (eCRF) and the assessments for the Early Termination visit should be performed per the SOA (Appendix 1). Safety and tolerability will be monitored during the entire study using standard measures, including the assessment of AEs, clinical laboratory tests, physical examinations, and vital signs.
Duration of Study Participation	The approximate study duration for an individual participant includes the Screening Period (within 28 days), a Run-in Period of 2 weeks, a Randomized Treatment Period of 12 weeks, an Open-label Treatment Period of a minimum of 12 weeks, and a Follow-up Period/EOS visit (4 weeks [± 7 days] after the last dose of study drug). 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). From Screening through Follow-up, total participation in this study for an individual participant may last from approximately 31 weeks to up to 34 weeks (if the participant does not continue to receive voxelotor beyond 12 weeks in the Open-label Treatment Period as stated above). Participants will continue to be followed for efficacy and safety through at least the primary endpoint visit (Week 12) regardless of treatment discontinuation. The study will end when the last participant's last visit occurs.
Study Population	**Inclusion Criteria**: Participants who meet all the following criteria will be eligible for enrollment in this study: 1. Male or female participants with documented diagnosis of SCD (sickle hemoglobin with 2 sickle cell genes [HbSS], sickle hemoglobin and one beta thalassemia gene [HbS/β^0] thalassemia) 2. Age 12 years and older 3. At least one cutaneous ulcer on the lower extremity (leg, ankle, or dorsum of foot) that meets the following criteria: • Duration: ≥ 2 weeks and < 6 months at Screening, and • Size: > 2 square centimeters (cm^2) prior to randomization • Note: Participants with multiple ulcers are eligible for the study. For each participant, target ulcer(s) for evaluation in this study will be identified and tracked. To qualify as a target ulcer, the ulcer must meet the criteria above. 4. Participants, who if female and of child-bearing potential, agree to use highly effective methods of contraception from study start to 30 days after the last dose of study drug and who if male, agree to use barrier methods of contraception from study start to 30 days after the last dose of study drug.

	5. Females of child-bearing potential are required to have a negative pregnancy test before the administration of study drug. 6. Written informed consent (≥ 18 years) or parental/guardian consent and participant assent (≥ 12–17 years) per International Ethics Committee (IEC) policy and requirements, consistent with International Council for Harmonisation (ICH) guidelines. **Exclusion Criteria**: Participants meeting any of the following exclusion criteria will not be eligible for study enrollment: 1. Target ulcer(s) healed by ≥ 25% during the SOC Run-in prior to randomization *Note: For participants with multiple ulcers, the participant is not eligible for the study if all target ulcers have healed by ≥ 25% during the SOC Run-in.* 2. Active infection/purulence at ulcer site, or exposed tendon or bone at the ulcer site, based on Investigator's clinical judgment. 3. Current osteomyelitis at or near the ulcer site 4. Known vascular abnormalities that would preclude healing in the opinion of the Investigator (eg, pre-existing severe arterial insufficiency in the affected limb) 5. Serum albumin < 2.0 g/dL 6. Red blood cell (RBC) transfusion within 60 days of initiation of study drug 7. Receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) during the study. 8. Planned elective surgery within the next 6 months. 9. Anemia due to bone marrow failure (eg, myelodysplasia) 10. Absolute reticulocyte count < 100×10^9/L 11. Screening alanine aminotransferase (ALT) > 4 × upper limit of normal (ULN) 12. Severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 by Schwartz formula) or is on chronic dialysis.
Study Population (continued)	13. Clinically significant bacterial, fungal, parasitic, or viral infection that requires therapy: • Participants with acute bacterial infection requiring systemic antibiotic use should delay Screening/enrollment until the course of antibiotic therapy has been completed. • Participants with known active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive. • Participants with active SARS-CoV-2 infection (COVID-19) 14. Females who are breast-feeding or pregnant 15. History of hematopoietic stem cell transplant or gene therapy 16. Participated in another clinical trial of an investigational product (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another trial of an investigational product (or medical device)

	17. Medical, psychological, or behavioral condition that, in the opinion of the Investigator, would confound or interfere with evaluation of safety and/or efficacy of the study drug, prevent compliance with the study protocol; preclude informed consent; or render the participant unable/unlikely to comply with the study procedures. 18. This exclusion criterion (EC) was revised to EC #18A in the Global Protocol Amendment 2.0. 18A. Use of drugs with drug-drug interaction potential with voxelotor, including the following categories of drugs, within 30 days of Day 1: • herbal medications (eg, St. John's wort), or moderate or strong CYP3A4 inducers • sensitive cytochrome P450 (CYP3A4) substrates with a narrow therapeutic index
Concomitant Medications and Restrictions	The following concomitant medications are **allowed**: • Hydroxyurea (HU)/hydroxycarbamide (HC) (stable dose for at least 90 days prior to signing the ICF and with no dose modifications planned or anticipated by the Investigator and no sign of hematological toxicity) • L-glutamine, over-the-counter analgesics, and opioids • Erythropoietin-stimulating agents (stable dose for at least 4 weeks with no dose modifications planned or anticipated by the Investigator) The following concomitant medications are **prohibited**: • Sensitive CYP3A4 substrates with a narrow therapeutic range • Moderate and strong CYP3A4 inducers • Crizanlizumab (Adakveo®) • Other experimental SCD therapy

Study Endpoints	The primary efficacy 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 participants with more than one target ulcer, all target ulcers must be confirmed resolved in order for the participant to be considered a responder. Secondary endpoints in this study include a comparison of voxelotor and SOC versus placebo and SOC in: • Time (in days) to resolution of target ulcer(s) up to Week 12 • Change from baseline in total surface area of target ulcer(s) at Week 12 • Incidence of new ulcers by Week 12 Exploratory 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 Week 12 and Week 24 • Correlation between change in markers of hemolysis (% reticulocytes, indirect bilirubin, LDH) and target ulcer(s) healing at Week 12 and Week 24 • Change from baseline in HRQOL PRO measures: PROMIS-37 v2.0 Pediatric Profile/PROMIS-43 v2.1 at Week 12 and Week 24 • Change from baseline in pain level linked to target ulcer(s) assessed by VAS at Week 12 and Week 24 • PGI-C score at Week 12 and Week 24 • CGI-C score at Week 12 and Week 24 Safety endpoints: Assessments of AEs, clinical laboratory parameters, physical examinations, and vital signs.

Statistical Methods	The primary study analysis will be based on complete data from the 12-week treatment period of the study, and will be performed at the earliest after all participants have completed the 12-week treatment period or discontinued early and all corresponding data have been entered into the database, reviewed, and verified. The final study analysis will be based on data from the complete study (including the Open-label Treatment Period and 4-week Follow-up Period), and will be performed after all participants have completed the study or discontinued early and all data from the study are in the database and the database is locked. **Analysis Population** Two main analysis populations are defined for this study: the intent-to-treat (ITT) population and the safety-evaluable population. Efficacy analyses will be conducted on the ITT population, defined as all randomized participants. Safety analysis will be based on safety-evaluable population, defined as randomized participants who received at least one dose of study treatment. **Sample Size** 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 12 weeks. Calculations were based on a two-sided alpha = 5% test of the difference in two binomial proportions (Normal approximation) and assumed 5% dropout by Week 12. **Primary Analysis** The proportion of participants with resolution of target leg ulcer(s) by Week 12 will be analyzed using a Cochran-Mantel-Haenszel (CMH) test to compare voxelotor + SOC with placebo + SOC groups, stratified by target ulcer size and target ulcer duration. Ulcer resolution is CCI [redacted] For participants with more than one target leg ulcer, all ulcers must be confirmed resolved in order for the participant to be considered a responder. 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 study dropout will be classified as non-responders for purposes of the primary analysis. **Secondary Analysis** Time to resolution of target ulcer(s) up to Week 12: a stratified log-rank test will be used to compare the treatment groups. A Cox regression model will be used to estimate the hazard ratio between voxelotor + SOC and placebo + SOC groups, as appropriate. Change from baseline in total surface area of target ulcer(s) at Week 12: a mixed-effect model for repeated measures will be used to estimate and compare change from baseline in sum of target ulcer(s) surface area between voxelotor + SOC and placebo + SOC groups.

Statistical Methods (continued)	Incidence of new ulcers by Week 12: the proportion of participants with new ulcer occurrence within 12 weeks of treatment will be compared between treatment groups using a CMH test, stratified by target ulcer size and target ulcer duration, as appropriate. **Safety Analysis** Adverse events will be classified according to Medical Dictionary for Regulatory Activities (MedDRA). The frequency of AEs will be tabulated by system organ class, preferred term, severity, and relationship to study treatment. Changes in laboratory parameters and vital signs will be summarized descriptively.

1. INTRODUCTION

1.1. Disease Background

1.1.1. Sickle Cell Disease

Sickle cell disease (SCD) is an inherited blood disorder caused by a point mutation in the β globin gene resulting in the formation of "sickle hemoglobin" (HbS), which polymerizes in the deoxygenated state and leads to red blood cell (RBC) sickling. The disease is marked by the pathophysiologic features of hemolytic anemia, vaso-occlusion, and progressive end-organ damage, with a clinical course characterized by life-long disability and early death (Gladwin, 2014; Nouraie, 2013). In addition to unpredictable and recurrent vaso-occlusive pain episodes, hemolytic anemia directly damages blood vessels, resulting in a systemic vasculopathy that leads to chronic and progressive tissue and organ injury (Kato, 2007). With improved survival in children, the natural history of SCD has shifted from a disease of childhood to a chronic, debilitating disease of young and middle-aged adults. Cumulative injury to multiple organ systems from repeated episodes of RBC sickling, vaso-occlusion, and chronic hemolytic anemia exact a high clinical burden in the aging adult, significantly impacting quality of life (QOL) and overall functioning (Swanson, 2011).

1.2. Voxelotor

Voxelotor (previously GBT440) is an HbS polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. Voxelotor binds covalently and reversibly to the N-terminal valine of the Hb α chain and allosterically increases HbS-oxygen (O_2) affinity (Eaton, 1999), stabilizing the oxyhemoglobin (oxyHb) state and inhibiting polymerization (Oksenberg, 2016). The voxelotor binding site (Kato, 2007) is distant from heme pockets and it can therefore increase O_2 affinity without sterically blocking the release of O_2.

A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS. Because oxyHb is a potent inhibitor of HbS polymerization, increasing the proportion of oxyHb in all RBCs with voxelotor can reduce HbS polymerization, decrease RBC membrane damage and destruction, and has the potential to subsequently achieve long-term disease modification. This principle is supported by the finding that in patients with sickle hereditary persistence of fetal hemoglobin (HbF), the dilution of HbS by 20% to 30% HbF in all RBCs is sufficient to inhibit HbS polymerization, preventing RBC damage and SCD clinical sequelae. This suggests that pharmacologically maintaining approximately 20% to 30% of Hb in the nonpolymerizing oxygenated state in all RBCs may be an effective approach for the treatment of SCD. This therapeutic effect was demonstrated in the pivotal Phase 3 study (Study GBT440-031) where 1500 mg of voxelotor, achieving Hb modification of 20% to 30%, administered daily orally for 24 weeks showed a significant and clinically meaningful increase in Hb and decrease in hemolysis.

Voxelotor was approved for use in the US under the tradename OXBRYTA® in 2019 by the Food and Drug Administration (FDA), and is indicated for the treatment of SCD in adults and pediatric patients 4 years of age and older (Oxbryta® USPI). Marketing approval in other regions has been received or is being sought. For details on other country approvals for marketing, please refer to the current Investigator's Brochure (IB). However, for this study,

the study drug voxelotor is considered an investigational drug as the study will be conducted in countries where voxelotor is not approved.

Voxelotor continues to be evaluated in ongoing clinical studies exploring the safety, tolerability, pharmacokinetics, pharmacodynamics (PD), and treatment response in pediatric and adult participants with SCD as well as in clinical pharmacology studies in healthy adult participants.

1.3. Summary of Relevant Nonclinical Data and Clinical Data

1.3.1. Leg Ulcers in Patients with SCD

Leg ulcers are a common complication of SCD, particularly among individuals with the more severe genotypes (sickle hemoglobin with 2 sickle cell genes [HbSS] or sickle hemoglobin and one beta thalassemia gene [HbS/β^0] thalassemia) of sickle cell anemia (SCA).

Global prevalence of leg ulcers in the SCD population varies geographically, with estimates of 14% to 18% in the United States (US) and Europe, 10% to 30% in sub-Saharan Africa, and 30% to 40% in Jamaica and Brazil. With increasing survival beyond childhood and a growing population of adults living with chronic manifestations of SCD, the lifetime prevalence of leg ulcers is likely to be much higher.

Leg ulcers usually occur in young adults with SCA, typically manifesting in the peri-malleolar area which is vulnerable due to thin skin and little protective subcutaneous fat. Up to 50% of patients with leg ulcers report preceding minor trauma and/or pruritus that provokes scratching and skin breakage (Singh, 2016). Once formed, these leg ulcers are slow to heal, have a high rate of recurrence, and are associated with severe unremitting pain. The sequelae of chronic leg ulcers in SCD include restricted mobility, depression, diminished work capacity, and sleep impairment, as well as increased healthcare utilization (Herber, 2007; Persoon, 2004).

The pathogenesis of leg ulcers in SCD is complex and not fully understood. Microvascular occlusion by dense sickled RBCs, reduced oxygen-carrying capacity from anemia, and vascular endothelial damage due to ischemia, hemolysis, and depletion of nitric oxide have been implicated (Bartolucci, 2012; Ballas, 1991; Kato, 2007). Individuals with SCA and leg ulcers have exhibited laboratory markers of particularly severe hemolytic anemia, including lower hemoglobin (Hb) and higher reticulocyte counts, serum lactate dehydrogenase (LDH), bilirubin, and aspartate aminotransferase (AST) than SCA patients without leg ulcers (Nolan, 2006; Taylor, 2008; Cumming, 2008). They also have a higher incidence of severe SCD complications, including stroke, renal impairment, and elevated tricuspid jet regurgitation, compared to SCA patients without leg ulcers (Minniti, 2014). These epidemiologic associations with leg ulcers support a common pathogenesis driven by HbS polymerization and are linked to anemia and hemolysis-associated vasculopathy (Kato, 2007). Histopathologic findings in SCD leg ulcers showing blood vessel occlusion, activated endothelium, thickened intima and luminal distortion as well as capillary proliferation are consistent with severe vasculopathy (Minniti, 2014).

Leg ulcers are a well-recognized debilitating complication of SCD, yet there are still no specific guidelines for management nor effective treatments. This remains a large unmet need for these patients. In a Cochrane review of five randomized trials of interventions for

treating leg ulcers in patients with SCD, none of the therapies resulted in complete ulcer healing (Marti-Carvajal, 2014). Although hydroxyurea (HU)/hydroxycarbamide (HC) and chronic transfusions are used to treat SCD, no controlled studies have demonstrated efficacy of these therapies in the treatment of leg ulcers. Current management of SCD leg ulcers thus relies primarily on the practice approach used for other cutaneous ulcers, involving debridement, wet to dry dressings, and topical agents.

1.3.2. Nonclinical Data

Primary PD studies of voxelotor consisted of in vitro and in vivo studies to characterize (a) voxelotor binding and affinity for Hb, (b) the effect of voxelotor on HbS modification using purified Hb, washed RBCs, and whole blood, and (c) the efficacy of voxelotor in vivo in a mouse model of SCD. These in vitro assays of increasing complexity included measuring Hb-O_2 via hemoximetry, quantifying stabilization of the oxyhemoglobin state conformation, delaying HbS polymerization at low O_2 tension, preventing in vitro sickling induced by a low O_2 environment, decreasing viscosity, and improving deformability of RBCs in blood from patients with SCD (Dufu, 2018). In addition, these studies show that voxelotor-modified Hb retains the Bohr Effect, which is the ability to offload O_2 from Hb in metabolically active (low pH) tissues.

Collectively, these studies demonstrate that voxelotor increases Hb-O_2 affinity with high specificity of binding to Hb, stabilizes the oxy or R-state conformation of Hb, prevents HbS polymerization and RBC sickling in vitro, and improves sickle blood viscosity and deformability in vitro. In addition, voxelotor increases HbS-O_2 affinity and RBC half-life, while decreasing ex vivo sickling and reticulocyte count in a SCD mouse model.

Additional information regarding nonclinical pharmacology (including safety pharmacology and metabolism) and toxicology is provided in the most current version of the voxelotor IB, provided separately.

1.3.3. Clinical Data

Voxelotor as a potential treatment for leg ulcers

In an exploratory post hoc analysis of 24-week data from the HOPE trial (Study GBT440-031), 13 participants had an active leg ulcer at treatment initiation (4 in the voxelotor 1500 mg group, 6 in the voxelotor 900 mg group, and 3 in the placebo group). Of these 13 participants, 3 of 4 (75%) in the 1500 mg group, 3 of 6 (50%) in the 900 mg group, and 0 of 3 in the placebo group showed complete resolution of the leg ulcer during 24 weeks of treatment per the site Investigator's assessment (Minniti, 2019). Additionally, no new leg ulcers occurred in the 1500 mg group during 24 weeks of treatment. Resolution of leg ulcers was associated with an Hb occupancy of approximately 20% or higher, within the target range for inhibition of HbS polymerization. These findings suggest that voxelotor may be an effective treatment for leg ulcers. By directly targeting the underlying mechanism of disease, inhibiting HbS polymerization and consequent hemolysis, voxelotor may have therapeutic effects beyond leg ulcers for coexisting complications caused by anemia and hemolysis.

The effect of voxelotor on leg ulcer healing and safety will be assessed in participants 12 years of age and older with SCD and active leg ulcer(s) in this study.

Details regarding the Pfizer clinical development program for SCD are available in the current version of the IB.

Information regarding the safety and tolerability, and efficacy of voxelotor is provided in Section 1.4 of this protocol.

1.4. Summary of the Known and Potential Risks and Benefits of Voxelotor

Voxelotor is well tolerated in adult and pediatric participants 4 years of age and older with SCD. Adverse events, primarily associated with underlying disease and gastrointestinal events, were generally low grade in severity, were managed by dose reduction and/or symptomatic treatment, and seldom resulted in discontinuation of therapy. Identified risks, which include the adverse drug reactions of diarrhea, abdominal pain, nausea, rash, and drug hypersensitivity, were low grade in severity and clinically manageable.

In the pivotal Phase 3 study, Study GBT440-031, voxelotor was shown to significantly increase Hb, improve anemia, and reduce clinical measures of hemolysis in adult and pediatric participants 12 years of age and older with SCD.

In conclusion, voxelotor has a favorable benefit-risk profile based on clinical data from studies enrolling participants 4 years of age and older with SCD. Overall, by inhibiting HbS polymerization voxelotor has the potential to alter the clinical course of the disease by improving anemia and hemolysis in SCD disease.

Further information regarding the potential benefits and risks of voxelotor and guidance for the investigator are provided in the current version of the IB.

1.5. Description of and Justification for the Route of Administration, Dosage, Dosage Regimen, and Treatment Period(s)

In this study, all participants will receive the standard of care (SOC) per protocol for SCD leg ulcers (see the Leg Ulcer Management Manual) during the Run-in, 12-week Randomized Treatment (voxelotor and SOC compared with placebo and SOC), and the Open-label Treatment (voxelotor and SOC) periods.

1.5.1. Dose Rationale for Voxelotor

Voxelotor is available in an oral form and is intended for once daily administration. See Section 5.1 for additional information regarding the dose to be used in this study.

The dose of voxelotor to be evaluated in this study is 1500 mg orally daily. This dose of voxelotor is the currently approved dose for the treatment of SCD and is supported by: 1) absence of concerning exposure-related safety findings from the pivotal Phase 3 Study GBT440-031 in adults and adolescents with SCD; 2) a statistically significant and clinically meaningful increase in Hb, and reductions in clinical measures of hemolysis observed with voxelotor 1500 mg, which were more robust than those observed with voxelotor 900 mg (Vichinsky, 2018); 3) the efficacy of the 1500-mg dose in adolescents is also supported by similar improvements in Hb and hemolysis measures observed in the Phase 2a Study GBT440-007 (Brown, 2018); 4) exposure-response analyses using data from both Study GBT440-031 and Study GBT440-007 demonstrating dose-dependent treatment effects of voxelotor on Hb and hemolysis measures; 5) the majority of adult and adolescent participants receiving voxelotor 1500 mg in Study GBT440-031 achieved the intended

therapeutic target of 20% to 30% mean % Hb occupancy; and 6) the majority of participants with leg ulcers receiving voxelotor 1500 mg in Study GBT440-031 had healed leg ulcers at 24 weeks.

1.5.2. Use of a Placebo Control

This study will use placebo as a comparator on the background of SOC treatment. Placebo was chosen as the control because it is necessary to determine the efficacy of voxelotor for the treatment of leg ulcers by allowing efficacy to be estimated while controlling for background healing rates with SOC. The use of a placebo control will also allow safety signals to be distinguished from AEs occurring due to SCD.

Randomization to placebo treatment in this study does not place study participants at increased risk, as the SOC for patients with leg ulcers will be provided during the study.

2. STUDY OBJECTIVES

See Section 3 for details regarding the investigational plans.

2.1. Primary Objective

The primary objective of this study is to assess the effect of voxelotor and SOC compared to placebo and SOC on leg ulcer healing in participants ≥ 12 years of age with SCD, as measured by the proportion of participants achieving resolution of target ulcer(s) in each treatment group by Week 12.

2.2. Secondary Objectives

The secondary objectives of this study are to evaluate the effect of voxelotor and SOC compared to placebo and SOC on:

- Time to resolution of target ulcer(s)
- Change in total surface area(s) of target ulcer(s)
- Incidence of new ulcers

2.3. Exploratory Objectives

The exploratory objectives will assess the effect of voxelotor and SOC compared to placebo and SOC (or open-label voxelotor and SOC, where applicable) on:

- Correlation between change in Hb and target ulcer(s) healing
- Correlation between change in hemolytic parameters (% reticulocytes, indirect bilirubin, LDH) and target ulcer(s) healing
- Health-related quality of life (HRQOL) using patient-reported outcome (PRO) measures, when available (pending translation and cultural validation requirements)
  - Patient-Reported Outcome Measurements Information System (PROMIS) Pediatric Profile-37 v2.0/PROMIS-43 v2.1
  - Visual analog scale (VAS) assessment of pain level linked to target ulcer(s)
  - Patient Global Impression of Change (PGI-C)

- Clinician Global Impression of Change (CGI-C)

2.4. Safety Objective

The safety objective is to assess the safety and tolerability of voxelotor compared to placebo based on AEs, clinical laboratory tests, physical examinations, vital signs, and other clinical measures (eg, discontinuations due to AEs, dose reductions).

3. INVESTIGATIONAL PLAN

3.1. 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 a 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. The overall study design is illustrated in the Study Schema provided in Figure 1.

Screening Period (within 28 days prior to the Run-in Period)

During this period, participants will sign the informed consent form/assent form (ICF/AF), after which they will complete the Screening assessments, including target leg ulcer(s) surface area measurement(s) by digital photography, as detailed in the Schedule of Assessments (SOA) in Appendix 1 and in the Leg Ulcer Assessment and Measurement Manual. All Screening assessments must be completed within 28 days before the Run-in Period.

Run-in Period (2 weeks prior to Randomization [± 3-day window])

Participants will enter a 2-week Run-in Period (Day -14 to Day -1 [+3 days]), during which assessments, including target leg ulcer(s) surface area measurement(s) by digital photography will be conducted and SOC initiated per protocol, following best practice guidelines (see Minniti, 2014 for guidance and the Leg Ulcer Management Manual for additional details). These assessments must be completed prior to randomization to ensure that the participant continues to qualify for the study.

Randomized Treatment Period (12 weeks [± 3-day window for each visit after Day 1 Visit])

After completion of the 2-week Run-in Period, target leg ulcer(s) surface area measurement(s) CCI [redacted] will be reassessed on Day 1 (+1-day window) to ensure that the participant continues to qualify for the study before randomization. Eligible participants CCI [redacted] will be randomized 1:1 to receive voxelotor 1500 mg once daily and SOC or placebo once daily and SOC for 12 weeks. At the time of randomization, participants will be stratified CCI [redacted]

The treatment period is considered the continuous 12 weeks of voxelotor and SOC or placebo and SOC from date of randomization (first dose, Day 1). The target leg ulcer(s) will be assessed by visual inspection and surface area measurement(s) CCI scheduled visits every 2 weeks during the 12-week Randomized Treatment Period. CCI

[redacted]

Open-label Treatment Period (minimum 12 weeks [± 3-day window for each visit])

At the end of the 12-week Randomized Treatment Period, all participants (with the exception of those demonstrating initial ulcer re-epithelialization at Week 12) will receive open-label voxelotor 1500 mg per day and SOC for a minimum of 12 weeks and target ulcers that failed to heal during the initial 12 weeks will be followed for delayed healing. Assessments will continue to be performed per the SOA (Appendix 1).

> *Note: 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.*

Follow-up Period (4 weeks after last dose [± 7-day window for EOS Visit])

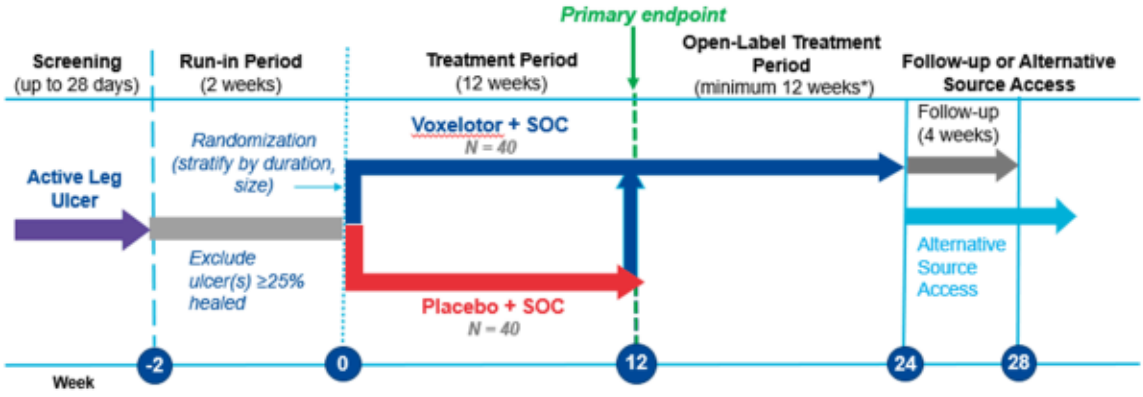
Following completion of the Open-label Treatment Period, eligible participants will be given the option to continue to receive voxelotor (under this protocol, until access is provided through an alternative source). Participants who do not continue to receive voxelotor from an alternative source will be followed for 4 weeks after the last dose of treatment and instructed to return to the site to complete the EOS visit.

Early Termination Visit

If a participant terminates the study for any reason, this should be documented on the electronic case report form (eCRF) and the assessments for the Early Termination visit should be performed per the SOA (Appendix 1).

Safety and tolerability will be monitored during the entire study using standard measures, including the assessment of AEs, clinical laboratory tests, physical examinations, and vital signs.

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.

3.1.1. Study Treatment

See Section 5 for dosage and treatment administration of voxelotor and placebo.

3.1.2. Study Assessments

Study procedures and assessments are described in Section 6. The timing for the study procedures and assessments is provided in the SOA (Appendix 1).

Participant safety and tolerability will be monitored during the study using standard measures, including physical examinations, vital signs (including temperature, blood pressure, and pulse rate), clinical laboratory tests, and AE monitoring.

3.1.3. Study Endpoints

Target leg ulcer images will be sent for central review (see Section 6.7).

3.1.3.1. Primary Endpoint

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

3.1.3.2. Secondary Endpoints

Secondary endpoints in this study include a comparison of voxelotor and SOC versus placebo and SOC in:

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

3.1.3.3. Exploratory Endpoints

Exploratory 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 Week 12 and Week 24
- Correlation between change in markers of hemolysis (% reticulocytes, indirect bilirubin, LDH) and target ulcer(s) healing at Week 12 and Week 24

- Change from baseline in PRO HRQOL measures: PROMIS-37 v2.0 Pediatric Profile/PROMIS-43 v2.1 at Week 12 and Week 24
- Change from baseline in pain level linked to target ulcer(s) assessed by VAS at Week 12 and Week 24
- PGI-C score at Week 12 and Week 24
- CGI-C score at Week 12 and Week 24

3.1.3.4. Safety Endpoints

The safety endpoints include assessments of AEs, clinical laboratory parameters, physical examinations, and vital signs.

3.1.4. Minimization of Bias

This study uses a double-blind, randomized, multicenter design to minimize bias.

3.2. Duration of Study Participation and of the Study

The approximate study duration for an individual participant includes the Screening Period (within 28 days), a Run-in Period of 2 weeks, a Randomized Treatment Period of 12 weeks, an Open-label Treatment Period of a minimum of 12 weeks, and a Follow-up Period/EOS visit (4 weeks [± 7 days] after the last dose of study drug). From Screening through Follow-up, total participation in this study for an individual participant may last from approximately 31 weeks to up to 34 weeks, except for participants who continue to receive voxelotor beyond 12 weeks in the Open-label Treatment Period (see below). Participants will continue to be followed for efficacy and safety through at least the primary endpoint visit (Week 12) regardless of treatment discontinuation.

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 choose not to continue voxelotor after 12 weeks in the Open-label Treatment Period will be followed for 4 weeks after the last dose of treatment and instructed to return to the site to complete the EOS visit (Visit 16-B, Appendix 1).

The study will end when the last participant's last visit occurs.

For participants who terminate the study prior to their last visit, refer to Section 3.3.1.

3.3. Stopping Rules

3.3.1. Early Discontinuation of the Study

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the incidence or severity of TEAEs in this or other studies with voxelotor indicating a potential health risk to participants.

In any instance of early termination of the study, the Sponsor will notify, in writing, the Investigators, regulatory authorities, and Independent Ethics Committees (IECs) and will specify the reason(s) for termination.

3.3.2. Discontinuation of Individual Participants

3.3.2.1. Withdrawal of Consent

Participants and/or their caregiver/legal representative will be informed participation is voluntary and that they may discontinue treatment or withdraw from the study at any time and for any reason. Any participant who requests to be withdrawn or whose caregiver/legal guardian requests withdrawal will be withdrawn from the study by the Investigator.

3.3.2.2. Early Discontinuation of Study Treatment

Participants may be discontinued from study treatment for any of the following reasons:

- Participant is lost to follow-up
- Adverse event(s)
- Repeated surgical debridement of target ulcer(s) needed to address wound deterioration
- Discretion of the Investigator
- Discretion of the Sponsor
- Pregnancy

The participant should return to the study site for an EOS/Early Termination visit approximately 28 days (±7 days) after the last dose of study treatment, as indicated in the SOA.

3.4. Randomization and Unblinding

3.4.1. Randomization

Randomization will be carried out through an Interactive Response System (IXRS). Permuted blocks within randomization strata will be used. Eligibility of the participant will be confirmed by the Investigator prior to randomization.

3.4.1.1. Preventing Unblinding due to Laboratory Assessments

Because knowledge of certain laboratory assessments (Hb, hematocrit, RBC count, total and unconjugated bilirubin, or absolute and % reticulocyte count) may suggest the treatment assignment in the Randomized Treatment Period, these measurements will be redacted to the Investigator.

Results of redacted laboratory tests will be communicated to the Investigator if a participant's absolute reticulocyte count declines to $< 80 \times 10^9$/L, or Hb declines to < 5.0 g/dL, or if the Hb declines ≥ 2 g/dL from Screening. This does not require breaking of the treatment assignment blind. This is to ensure participant safety by allowing the Investigator to monitor for potential bone marrow suppression, as described in HU monitoring guidelines (McGann, 2015; Yawn, 2014). De-identified laboratory results will be available to the Sponsor.

3.4.1.2. Unblinding for Medical Need

If a medical condition should arise for which appropriate treatment cannot be decided without knowledge of the study treatment assignment, the Investigator may unblind a study participant. The Investigator should promptly document and notify the Sponsor of any premature study treatment unblinding (eg, accidental unblinding, unblinding due to a serious adverse event [SAE]). Pregnancy is considered an event that requires unblinding. Unblinding procedures specified in the IXRS Manual will be followed and documented in the Investigator site file.

4. SELECTION OF STUDY PARTICIPANTS

Eligibility will be based on assessments performed during the Screening Period and Run-In Period. A participant will be enrolled after signing the ICF or AF for this study. Informed consent/assent must be properly executed prior to the performance of any protocol-required assessments or procedures.

4.1. Inclusion Criteria

Participants who meet all of the following criteria will be eligible for study enrollment:

1. Male or female participants with documented diagnosis of SCD (HbSS, HbS/β^0 thalassemia)
2. Age 12 years and older
3. At least 1 cutaneous ulcer(s) on the lower extremity (leg, ankle, or dorsum of foot) that meets the following criteria:
   - Duration: $\geq$ 2 weeks and < 6 months at Screening, and
   - Size: > 2 cm^2 prior to randomization

   Note: Participants with multiple ulcers are eligible for the study. For each participant, target ulcer(s) for evaluation in this study will be identified and tracked. To qualify as a target ulcer, the ulcer must meet the criteria above.
4. Participants, who if female and of child-bearing potential, agree to use highly effective methods of contraception from study start to 30 days after the last dose of study drug and who if male, agree to use barrier methods of contraception from study start to 30 days after the last dose of study drug
5. Females of child-bearing potential are required to have a negative pregnancy test before the administration of study drug
6. Written informed consent ($\geq$ 18 years) or parental/guardian consent and participant assent ($\geq$ 12–17 years) per IEC policy and requirements, consistent with International Council for Harmonisation (ICH) guidelines

4.2. Exclusion Criteria

Participants meeting any of the following exclusion criteria will not be eligible for study enrollment:

1. Target ulcer(s) healed by $\geq$ 25% during the SOC Run-in prior to randomization

Note: For participants with multiple ulcers, the participant is not eligible for the study if all target ulcers have healed by ≥ 25% during the SOC Run-in.

2. Active infection/purulence at ulcer site, or exposed tendon or bone at the ulcer site, based on Investigator's clinical judgment
3. Current osteomyelitis at or near the ulcer site
4. Known vascular abnormalities that would preclude healing in the opinion of the Investigator (eg, pre-existing severe arterial insufficiency in the affected limb)
5. Serum albumin < 2.0 g/dL
6. RBC transfusion within 60 days of initiation of study drug
7. Receiving regularly scheduled RBC transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) during the study
8. Planned elective surgery within the next 6 months
9. Anemia due to bone marrow failure (eg, myelodysplasia)
10. Absolute reticulocyte count < 100×10^9/L
11. Screening alanine aminotransferase (ALT) > 4 × upper limit of normal (ULN)
12. Severe renal dysfunction (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2 by Schwartz formula) or is on chronic dialysis
13. Clinically significant bacterial, fungal, parasitic, or viral infection that requires therapy:
    - Participants with acute bacterial infection requiring systemic antibiotic use should delay screening/enrollment until the course of antibiotic therapy has been completed.
    - Participants with known active hepatitis A, B, or C or who are known to be human immunodeficiency virus (HIV) positive
    - Participants with active SARS-CoV-2 infection (COVID-19)
14. Females who are breast-feeding or pregnant
15. History of hematopoietic stem cell transplant or gene therapy
16. Participated in another clinical trial of an investigational product (or medical device) within 30 days or 5 half-lives of date of informed consent, whichever is longer, or is currently participating in another trial of an investigational product (or medical device)
17. Medical, psychological, or behavioral condition that, in the opinion of the Investigator, would confound or interfere with evaluation of safety and/or efficacy of the study drug, prevent compliance with the study protocol; preclude informed consent; or render the participant unable/unlikely to comply with the study procedures

18. This exclusion criterion (EC) was revised to EC #18A in the Global Protocol Amendment 2.0.

18A. Use of drugs with drug-drug interaction potential with voxelotor, including the following categories of drugs, within 30 days of Day 1:

- herbal medications (eg, St. John's wort), or moderate or strong CYP3A4 inducers
- sensitive cytochrome P450 (CYP3A4) substrates with a narrow therapeutic index

5. TREATMENTS ADMINISTERED

5.1. Treatment Regimen

During the Randomized Treatment Period, participants will be randomized in a 1:1 ratio to receive 1500 mg of voxelotor once daily (administered as three 500 mg tablets) or matching placebo for 12 weeks. In this study, all participants will receive the SOC per protocol for SCD leg ulcers (see the Leg Ulcer Management Manual) during the Run-in, Randomized Treatment, and Open-label Treatment periods. During the Open-label Treatment Period, all participants will receive 1500 mg of voxelotor once daily (administered as three 500 mg tablets) for a minimum of 12 weeks.

In addition, 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 not associated with this protocol (eg, through a clinical OLE study sponsored by Pfizer, commercialization of the product, or a managed access program).

5.1.1. Dose Frequency

Participants will receive a voxelotor dosage form or matching placebo administered orally, once daily. If a participant misses a dose, the participant should resume normal dosing the next day (ie, the dose, on the day after the day of a missed dose, should not be increased or decreased).

5.1.2. Dose Modification

Participants should adhere to their assigned dose level. However, reducing or holding the dose for a short period of time during the study may be used for AEs that impact the participant's safety and tolerability. All instances of study drug dose modification (dose reduction, interruption, or discontinuation) should be documented in the participants' medical record and recorded in the eCRF. If the conditions/event leading to the dose modification have resolved, the original dose level should be resumed unless, in the judgment of the Investigator, this cannot be done safely. Dose modifications may be determined by the Investigator in consultation with the Sponsor's Medical Monitor [redacted].

Table 1: Dose Modification Guidelines for Study Drug-related Adverse Events

Dose Reduction	
Event	**Recommended Action**
Grade ≥2 (NCI grading scale) AE deemed considered related to study drug by the Investigator AND Precludes continued dosing at the current dose level due to safety concern or lack of tolerability (in the Investigator's judgment)	**Study drug**: May be reduced by one (1) tablet If, in the opinion of the Investigator, a Grade 2 AE has resolved to ≤ Grade 1, participant may resume study drug at the original dose. If, in the opinion of the Investigator, the AE poses a significant safety concern such that a dose hold is considered, the Investigator should contact the Medical Monitor.
Dose Interruption (Hold)	
Event	**Recommended Action**
Grade ≥3 (NCI grading scale) AE deemed considered related to study drug by the Investigator AND Precludes continued dosing at the current or at a reduced dose level due to safety concern or lack of tolerability in the Investigator's judgment	**Study drug**: Hold dose until ≤ Grade 2, then resume study drug at original dose. If, in the opinion of the Investigator, dosing should be resumed at a lower dose, contact the Medical Monitor for further discussion. If the AE recurs or worsens, reduce dose by one tablet. Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion.
NOTE: Study drug-related rash Grade 2 study drug-related rash that persists after a dose reduction	Management: Consider antihistamines, topical steroids as clinically indicated. **Study Drug**: If rash does not resolve or improve to Grade 1 after a dose reduction, consider a dose hold. Once the rash has resolved or improved, dosing may be resumed at the reduced level or if, in the opinion of the Investigator, participant may resume study drug at the original dose. The Medical Monitor may be contacted for further discussion. Maximum dose hold is 5 continuous days. If, in the opinion of the Investigator, a longer dose hold is clinically needed, the Medical Monitor should be contacted for discussion.
Drug Discontinuation	
Grade ≥3 study drug-related AE that, at the discretion of the Investigator, warrants discontinuation of study drug (eg, has not improved or resolved after dose hold).	**Study drug:** Discontinue study drug. If the Investigator considers that the participant would benefit from continuing treatment, the Medical Monitor should be contacted.

Abbreviations: AE, adverse event; NCI, National Cancer Institute.

5.2. Physical Description of Voxelotor

Voxelotor is a synthetic small molecule bearing the chemical name 2-hydroxy-6-((2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde. The chemical formula is $C_{19}H_{19}N_3O_3$ and the molecular weight is 337.4 g/mol.

5.3. Formulation

5.3.1. Voxelotor

Voxelotor (500 mg) tablets contain voxelotor drug substance along with several formulation excipients. All of the excipients used in the formulations are listed in the FDA Inactive Ingredient Database (IID) or are pharmaceutical excipient mixtures entirely composed of FDA IID components).

All of the excipients used in the formulations are either compendial per European Pharmacopoeia (Ph. Eur.) or are composed of mixtures which are compendial per Ph. Eur. or accepted by E number or European Commission regulation.

Additional details are provided in the Pharmacy Manual.

5.3.2. Placebo

The placebo matching tablets contain several formulation excipients. All of the excipients used in the formulations are listed in the FDA IID or are pharmaceutical excipient mixtures entirely composed of FDA IID components.

All of the excipients used in the formulations are either compendial per Ph. Eur. or are composed of mixtures which are compendial per Ph. Eur. or accepted by E number or European Commission regulation. The matching placebos do not contain any voxelotor drug substance.

5.4. Packaging and Labeling

Voxelotor tablet drug product and placebos will be supplied to clinical sites in high-density polyethylene bottles with induction sealed polypropylene child resistant caps. Additional details are provided in the Pharmacy Manual.

5.5. Investigational Product Supply

Pfizer or their representative will supply the packaged and labeled drug product to the investigational sites. Participants will receive a 3-month (90-day) supply of investigational product at the Day 1 and Week 12 visits. Participants who continue to receive voxelotor beyond 12 weeks in the Open-label Treatment period will receive a 3-month supply of voxelotor every 12 weeks. Additional details are provided in the Pharmacy Manual.

5.6. Storage and Handling Procedure

All study drug will be stored at controlled room temperature between 15°C to 25°C (59°F to 77°F), in the storage area of the investigational site pharmacy, which is a secure, temperature controlled, locked environment with restricted access.

The Sponsor or its representatives will be permitted upon request to audit the supplies, storage, dispensing procedures, and records, provided that the blind of the study is not compromised.

5.7. Concomitant and Prohibited Medications

5.7.1. Concomitant Medications

A concomitant medication is defined as any prescription or over-the-counter preparation, including vitamins and supplements.

In the interests of participant safety and acceptable standards of medical care, the Investigator will be permitted to prescribe treatment(s) at his/her discretion. For all study participants who initiate treatment, all administered concomitant medications from signing the consent/assent until 28 days (4 weeks) after the participant's last dose of study drug, must be recorded on the participant's eCRF.

All reported prior and concomitant medications will be coded using the current version of the World Health Organization (WHO) Drug Dictionary.

5.7.2. Restrictions Regarding Usage of Concomitant Medications

Concomitant treatment with HU/HC is allowed, provided that the dose has been stable for at least 90 days prior to signing the ICF/AF. Participants who are on HU/HC may have their dose adjusted (based on change in their weight) if the mg/kg dose is stable, in the opinion of the Investigator. If HU/HC treatment is initiated after a participant has been screened or after being randomized, the eligibility of the participant to continue in the study must be discussed with the Sponsor's Medical Monitor.

5.7.3. Transfusion

Participants who require initiation of chronic transfusion will be discontinued from study treatment and 28 days later will undergo the EOS/Early Termination visit. Episodic transfusions for acute SCD indications, pre-operative procedures, surgery, or trauma are permitted.

> *Note: Participants who continue to receive voxelotor beyond 12 weeks in the Open-label Treatment Period (see Section 5.1) may initiate chronic transfusions without being discontinued from study treatment.*

5.7.4. Other Therapies

Penicillin prophylaxis and vaccinations are allowed as per SOC.

Other concomitant medications are allowed, unless the restrictions in Section 5.7.5 apply. Permitted concomitant medications include folic acid, L-glutamine, and over-the-counter analgesics, and opioids, which are among the chronic medications commonly taken by participants with SCD. Erythropoietin-stimulating agents (stable dose for at least 4 weeks with no dose modifications planned or anticipated by the Investigator) are allowed.

Participants who are already on malaria prophylaxis therapy may be allowed to participate in the study at the discretion of the Investigator. Participants may also be initiated on malaria prophylaxis therapy during study, at the discretion of the Investigator and as per SOC.

Participants who test positive for acute malaria during the study should be provided SOC treatment and may continue in the study, at the discretion of the Investigator and the Sponsor.

Participants who test positive for acute hepatitis or HIV during the study will be discontinued from study drug and will return for the EOS/Early Termination visit (28 days after the last dose of study drug).

5.7.5. Prohibited Concomitant Medications

Use of an investigational product other than that under study in this trial, regardless of its intended use, is prohibited throughout the trial and for 28 days after the last dose.

Additionally, concomitant medications (eg, crizanlizumab) that confound the ability to interpret data from the study are prohibited.

Voxelotor is a moderate CYP3A4 inhibitor and should not be coadministered with sensitive CYP3A4 substrates with a narrow therapeutic index (refer to Table 2 for examples).

Table 2: Sensitive CYP3A4 Substrates with Narrow Therapeutic Range

Sensitive CYP3A4 Substrates with Narrow Therapeutic Range
Alfentanil, sirolimus, and tacrolimus

Abbreviations: CYP, cytochrome P450.
Note: **This is not an exhaustive list.** Country-specific lists may be used if available.
For an updated list, refer to the following link:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table 3-2.

Concomitant use of voxelotor and moderate or strong inducers of CYP3A4 is not allowed within 30 days of Day 1 or during the study (refer to Table 3 for examples). In the event that concomitant use of voxelotor with a moderate or strong CYP3A4 inducer is unavoidable, the Investigator should contact the Medical Monitor.

Table 3: Examples of Moderate and Strong CYP Inducers

CYP3A4	Examples
Moderate CYP3A4 inducers	Cenobamate, dabrafenic, efavirenz, bosentan, etravirine, lorlatinib, pexidartinib, phenobarbital, primidone, and sotorasib
Strong CYP3A4 inducers	Rifampin, apalutamide, phenytoin, carbamazepine, enzalutamide, ivosidenib, lumacaftor, St John's wort, and mitotane

Abbreviations: CYP, cytochrome P450.
Note: **This is not an exhaustive list.** Country-specific lists may be used if available.
For an updated list, refer to the following link:
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#table3-3 (last accessed 30 March 2023).

Additional prohibited medications are shown in Table 4.

Table 4: Additional Prohibited Medications

Prohibited Medications
Crizanlizumab

5.8. Fertility/Contraceptive Requirements

All female participants of child-bearing potential (post menarche) should avoid pregnancy, and all sexually active male participants should avoid fathering a child. Pregnancy is considered a medical condition that requires unblinding (refer to Section 1.1).

5.8.1. Instructions for Female Participants of Child-Bearing Potential

For female participants of child-bearing potential (post menarche) and sexually active, pregnancy should be avoided by either abstinence from sex/sexual intercourse or the use of highly effective means of contraception for the duration of the study, and for a total period of 30 days after the participant has taken her last dose of voxelotor. Highly effective means of contraception are listed below in Section 5.9. Pregnancy reporting requirements are outlined in Section 1.1.

Female participants who become pregnant during the study will be withdrawn from the study.

5.8.2. Female Participants of Non-Child-Bearing Potential

A female participant of non-child-bearing potential is defined as one who: 1) has reached natural menopause (defined as 12 months of spontaneous amenorrhea without an alternative medical cause); 2) is 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or 3) has undergone bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (ie, anorexia nervosa).

5.8.3. Instructions for Male Participants Capable of Fathering a Child

There is no information about effects that voxelotor could have on the development of the fetus in humans. Therefore, it is important that the partners of male participants do not become pregnant during the study and for a total period of 30 days after the male participant has taken the last dose of voxelotor.

As a precaution, all male participants who are sexually active should avoid fathering a child by either true abstinence or the use of barrier methods of contraception (Section 5.9).

5.9. Acceptable Forms of Contraception for Sexually Active Participants

For female participants:

Highly effective methods of birth control are defined as those which result in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Highly effective methods of birth control are as follows:

1. Hormonal contraceptives (must be supplemented with a barrier method, preferably male condom).
    a. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
        - Oral
        - Intravaginal
        - Transdermal

b. Progestogen-only hormonal contraception associated with inhibition of ovulation:
   - Oral
   - Injectable
   - Implantable

2. Intrauterine device
3. Intrauterine hormone-releasing system
4. Bilateral tubal occlusion
5. Sexual abstinence:
   a. Sexual abstinence is considered a highly effective method only if the participant is refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

For male participants with female partners capable of reproduction:

Barrier methods of contraception:

- Condom with occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository for female partner. The use of barrier contraceptives should always be supplemented with the use of a spermicide.

  Note: As the effects of voxelotor on pregnancy are not completely known, the female partner of male study participants should consider using an effective contraceptive method (see above) while the participant is taking study treatment and for 30 days after the last dose of study treatment.

5.10. Assessment of Treatment Compliance

Drug disposition records will be maintained, specifying the amount dispensed to each participant and the date of dispensation. This record will be available for Sponsor review at any time.

Compliance will be determined by returned tablets. A dosing diary will be dispensed for participants to complete.

6. STUDY PROCEDURES AND ASSESSMENTS

The timing for the required study procedures and assessments are outlined in the SOA (Appendix 1).

The Screening Period for a participant commences at the point at which the participant undergoes the first study-specific screening assessment. All screening assessments must be completed within 28 days before the Run-in Period.

6.1. Informed Consent/Assent

A signed and dated consent and/or assent form will be obtained before any protocol-specified screening procedures are performed.

For pediatric participants, consent should be obtained from at least one parent (or both if it is required per Investigational Site policy) or the participant's legal representative. Guidelines for the informed consent/assent process are outlined in Section 11.2.

6.2. Participant Identification Number

Upon execution of consent/assent, all participants will be given a unique participant identification number. This number will be used to identify the participant throughout the clinical study and must be used on all study documentation related to that participant.

The IXRS user manual contains the information needed for registering participant status (eg, assigning participant numbers, indicating screen failure, temporary suspension of treatment, and end of treatment).

6.3. Eligibility Assessment, Inclusion/Exclusion Review

Eligibility assessment will be conducted during Screening and following the Run-in Period, prior to receiving study drug on treatment Day 1. Both at Screening and prior to randomization, the Investigator should determine that the participant is in stable clinical condition at their steady state.

Randomization must occur on the same day as treatment, Day 1 (the first dose of study drug). If a participant is randomized and withdrawn from the study prior to the first dose of study drug, they may not be re-screened.

Pfizer will review eligibility criteria verified by the investigator or qualified designee to confirm that participants meet study eligibility criteria before they are randomized into the study. The randomization approval process will be initiated for a participant after an informed consent document has been signed and the investigator or qualified designee has assessed the participant as eligible. The randomization approval will be based on review of CRF/system data.

6.4. Medical History/Demographics

Clinically significant medical history (as determined by the Investigator), including history of previous ulcers, characteristics, and duration will be recorded at the time of the Screening.

Demographics and baseline characteristics (including gender, race, ethnicity, and age) will also be recorded at the time of the Screening.

6.5. Physical Examination

The physical examination (PE) will be a complete PE according to the standard at the site and a detailed lower extremity examination at the Screening visit. Physical examinations after the Screening visit may be abbreviated PEs. An abbreviated PE will be conducted at the scheduled study visits: Week -2 (Run-in), Day 1 (Baseline), Week 12, Week 24, and EOS/Early Termination. For participants who continue to receive voxelotor beyond 12 weeks in the Open-label Treatment Period (See Section 5.1), the PE will be conducted every 48 weeks (Appendix 1).

- A complete PE will include at a minimum: Height, weight, general appearance, examination of head, eyes, ears, nose, and throat, skin, cardiovascular and respiratory systems, abdominal examination, neurologic, musculoskeletal, and a

detailed lower extremity examination including: vascular—pedal pulses, color of skin, temperature, edema; dermatological—clinical description of the ulcer, skin integrity (calluses, dryness); musculoskeletal—foot deformities such as bunion, hammertoe, bony prominence, fat pad atrophy, altered gait; neurological—absence or presence of sensation, reflexes.

- An abbreviated PE will include at a minimum: Examination of eyes, skin, cardiovascular and respiratory systems, abdominal examination, neurologic, and target ulcer(s) examination.

6.6. Vital Signs

Vital signs (blood pressure, heart rate, and temperature) will be measured at every visit during the study, as outlined in the SOA (Appendix 1), after a participant has rested comfortably for at least 5 minutes in the supine or sitting position, as age appropriate and feasible. A repeated measurement of any of the vital signs parameters will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.

6.7. Ulcer Assessments

Target ulcer(s) assessments will be performed by visual inspection and measurement of the surface area by digital photography and will be completed at every visit during the study as detailed in the SOA (Appendix 1). The site will measure target ulcers using digital photographs. The digital photographs taken by the site will be sent to a central external reviewer for review and to determine measurements. The measurements provided by the central external reviewer (not the site) will be used to inform eligibility of participants, and assessment of initial re-epithelialization at the Week 12 visit. In addition, the measurements provided by central external reviewer will be used for assessing study efficacy endpoints.

Further details on these measurements will be provided in the Leg Ulcer Assessment and Measurement Manual.

6.8. Adverse Events and Concomitant Medications

Adverse events and concomitant medications will be recorded at every visit during the study, as detailed in the SOA (Appendix 1). See Section 7.2 for details regarding AE reporting period for this study.

6.9. Height and Weight

Height will be collected at the Screening visit only and weight will be collected at Screening and Week 12 (Appendix 1).

6.10. Laboratory Assessments

All laboratory assessments will be performed through a central laboratory. Hematology and serum chemistry will be collected at the Screening visit, Baseline (Day 1), Week 12, Week 24, and EOS/Early Termination. Serum pregnancy test will be performed at the Screening visit, and a urine pregnancy test will be performed at Baseline (Day 1), Week 6, Week 12, Week 18, and Week 24 in female participants who have experienced menarche (see Section 6.10.3 for more information on pregnancy testing). For participants who continue to receive voxelotor beyond 12 weeks in the Open-label Treatment Period (see Section 5.1), hematology and serum chemistry assessments will be conducted every 12 weeks, and urine pregnancy testing will be conducted every 24 weeks. Refer to the SOA (Appendix 1) for the additional details of laboratory tests.

It is the responsibility of the Investigator or designee to assess the clinical significance of all abnormal clinical laboratory values, as defined by the applicable list of normal values on file (ie, local or central laboratory).

For the purpose of this study, a clinically significant laboratory value will be any abnormal result that, in the judgment of the Investigator, is an unexpected or unexplained laboratory value or if medical intervention or corrective action (transfusion, hydration, initiation of antibiotics, or other concomitant medication) is required. Any abnormal values that persist should be followed at the discretion of the Investigator. All clinically significant laboratory value abnormalities are to be recorded as AEs.

Additional and repeat laboratory safety testing for the evaluation of abnormal results and/or AEs during the study may be performed at the discretion of the Investigator or upon request of the Sponsor; it is preferred for the analyses to be conducted by the central laboratory unless medical need necessitates urgent results reporting. Repeat laboratory testing of abnormal potentially clinically significant or clinically significant results for the screening evaluation of the participant may be repeated at the discretion of the Investigator.

Blood specimens collected at the Day 1 visit and Week 12 visit and found to be inadequate for laboratory testing should be redrawn and submitted for laboratory testing within 7 days of the study visit.

Total Blood Volume

On study blood volume collections for participants < 18 years old will not exceed 1% total blood volume (0.8 mL/kg based on 80 mL/kg blood volume in any given 24-h period and 3% total blood volume (2.4 mL/kg based on 80 mL/kg blood volume) in any given 4-week period. Specific blood specimens may be omitted at the discretion of the Investigator if warranted such as in the context of blood loss associated with standard clinical care, bleeding events, or if otherwise deemed appropriate. See Table 5 for blood specimen assessment priority list.

Due to volume restrictions in pediatric research, assessments will be prioritized in the following order:

Table 5: Blood Specimen Assessment Priority List

Priority	Test
1	Hematology
2	Chemistry
3	HbSS, HbS/β0 thalassemia test

6.10.1. Hematology

Hematology assessments include the following:

- RBCs
- Hematocrit
- Hb
- Platelets
- 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/β^0 thalassemia test (at Screening only for medical diagnosis of SCD, if diagnosis is not documented in medical chart)

6.10.2. Serum Chemistry

Chemistry assessments include the following:

- ALT
- Albumin
- Alkaline phosphatase (ALP)
- AST
- Bicarbonate
- Blood urea nitrogen
- Chloride
- Calcium
- Creatinine
- Glucose
- LDH
- Sodium

- Potassium
- Bilirubin (total, direct, and indirect)

6.10.3. Pregnancy Testing

Female study participants who have not experienced menarche will not undergo pregnancy testing. Should a female participant experience menarche during the study, the participant will be considered a female of child-bearing potential and will undergo urine pregnancy testing as per the SOA (Appendix 1).

If a urine pregnancy test is positive, the result must be confirmed per local standards at each site (eg, ultrasound, serum pregnancy test). See Section 1.1 for reporting a pregnancy.

6.11. Patient-Reported Outcomes

PROs (either electronic or paper) will be evaluated by the following measures which will be provided by the Sponsor, when available (pending translation and cultural validation requirements):

- National Institute of Health PROMIS-37 v2.0 Pediatric Profile/PROMIS-43 v2.1: Profile Instrument at Week 0, Week 12, and Week 24
- VAS (pain level linked to target ulcer[s]) at Week 0, Week 12, and Week 24
- The PGI-C assessment will be performed using a 7-point scale to measure the participant's overall improvement at Week 12 and Week 24.

These assessments will be self-administered by study participants at visits specified in the SOA (Appendix 1).

6.12. Clinical Global Impression of Change

Investigator's assessment of change in the overall health condition of the participant. The CGI-C assessment will be administered by the Investigator using a 7-point scale to measure the participant's overall improvement at Week 12 and Week 24, as specified in the SOA (Appendix 1).

6.13. Missed Assessments

Missed assessments should be rescheduled and performed as close to the originally scheduled date as possible. An exception is made when rescheduling becomes, in the Investigator's opinion, medically unnecessary or unsafe because it is too close in time to the next scheduled evaluation. In that case, the missed evaluation should be abandoned.

7. ADVERSE AND SERIOUS ADVERSE EVENTS

Safety assessments will consist of recording all AEs and SAEs, protocol-specified hematology and clinical chemistry variables, clinical examination findings, measurement of protocol-specified vital signs, and the results from other protocol-specified tests that are deemed critical to the safety evaluation of voxelotor.

The determination, evaluation, reporting, and follow-up of AEs will be performed, as outlined in Section 7.1. At each visit, the study participant or participant caregiver will be asked about any new or ongoing AE since the previous visit. Assessments of AEs will occur

at each study visit. See Section 7.2 for details regarding the required time periods for AE reporting.

Clinically significant changes from study baseline in PE findings, weight, vital signs, and clinical laboratory parameters will be recorded as AEs or SAEs, as appropriate.

7.1. Adverse Events

7.1.1. Definition of Adverse Events

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not thought to be related to the investigational product. An AE may also constitute complications occurring as a result of protocol-mandated interventions (eg, invasive procedures such as biopsies) or SOC procedures (eg, surgical debridement of ulcer), including the period prior to receiving the first dose of the study drug (eg, medication wash out). In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the participant signs the ICF is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

A suspected adverse reaction is any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of expedited safety reporting, "Reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the AE. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug.

Life-threatening AE or life-threatening suspected adverse reaction is an AE or suspected adverse reaction that, in the view of either the Investigator or Pfizer, places the study participant at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Reference Safety Information (RSI) section of the current IB or is not listed at the specificity or severity that has been observed.

An SAE or serious suspected adverse reaction is an AE or suspected adverse reaction that at any dose, in the view of the either the Investigator or Pfizer, results in any of the following outcomes:

- Death
- A life-threatening AE
- Inpatient hospitalization or prolongation of existing hospitalization

- Persistent or significant incapacity or disability (substantial disruption of the ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Important medical events that may not result in death, be immediately life threatening, or require hospitalization may be considered serious when based upon medical judgment, they may jeopardize the study participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

NOTE: Hospitalization planned prior to study enrollment (eg, for elective surgeries) are not considered SAEs. Hospitalizations that occur for pre-existing conditions that are scheduled after study enrollment are considered SAEs.

The Investigator will assess each AE for seriousness, severity, and relationship to investigational product.

7.1.2. Severity of Adverse Events

Whenever possible, the severity of all AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 5.0.

For AEs not adequately addressed in the NCI CTCAE Version 5.0, the following criteria should be used (Table 6).

Table 6: Grading for Adverse Events Not Covered in the NCI CTCAE

Severity	Description
Grade 1—Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2—Moderate	Minimal, local or non-invasive intervention indicated; limited age-appropriate instrumental ADL
Grade 3—Severe	Medically significant but not immediately life threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4—Life threatening	Life threatening consequences; urgent intervention indicated
Grade 5—Fatal	Death

Abbreviations: ADL, activities of daily living; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events.

To make sure there is no confusion or misunderstanding between the terms "serious" and "severe," which are not synonymous, the following note of clarification is provided. The term "severe" is often used to describe the intensity (severity) of a specific event (ie, mild, moderate, or severe); the event itself, however, may be of relatively minor medical significance (eg, severe headache). This is not the same as "serious" which is based on the study participant/event outcome or action criteria associated with events that post a threat to a

participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

7.1.3. Relationship to Investigational Product

The relationship of an AE to the investigational product should be determined by the Investigator according to the following definitions:

- NOT RELATED: Evidence exists that the AE has an etiology other than the study drug and/or the temporal relationship of the AE/SAE to the investigational product administration makes the relationship unlikely. If an SAE is not considered related to study drug, then an alternative explanation should be provided.
- RELATED: A temporal relationship exists between the event onset and the administration of the study drug makes a causal relationship possible or probable. It cannot be readily explained by the participant's clinical state or concomitant therapies and may appear, with some degree of certainty, to be related based on the known therapeutic and pharmacologic actions of the drug. Good clinical judgment should be used for determining causal assessment.

7.1.4. Unexpected Adverse Reactions

An AE is "unexpected" if its nature and severity are not consistent with the information about the study drug provided in the RSI in the voxelotor IB.

7.2. Adverse Event Reporting

7.2.1. General

All AEs/SAEs will be recorded from the time the study participant signs the ICF/assent until 28 days after last dose of study drug (EOS/Early Termination). All AEs/SAEs must be recorded on the AE eCRF via the electronic data capture (EDC) system. The Investigator is responsible for evaluating all AEs/SAEs, obtaining supporting documents, and ensuring documentation of the event is complete. Details of each reported AE must include, at minimum, severity, relationship to study treatment, duration, and outcome. All AEs (both serious and nonserious) must be followed until they are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

Any participant who experiences an AE/SAE may be discontinued from study treatment at any time, at the discretion of the Investigator. The Sponsor and the contract research organization (CRO)'s Medical Monitor must be notified of the study participant discontinuation.

When a clinically important AE remains ongoing at the end of the active collection period, follow-up by the investigator continues until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant permanently discontinues or temporarily discontinues study drug because of an AE or SAE, the AE or SAE must be recorded on the eCRF and the SAE reported to Pfizer Safety via Pfizer's Serious Adverse Event Submission Assistant (PSSA).

Investigators are not obligated to actively seek information on AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and they consider the event to be reasonably related to study drug, the investigator must promptly report the SAE to the Sponsor via PSSA.

7.2.2. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded in the eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded separately in the eCRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

7.2.3. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities will be recorded on the AE eCRF (eg, abnormalities that have clinical sequelae, require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation). If the clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, ALP and bilirubin 5 × the ULN associated with cholecystitis), only the diagnosis (eg, cholecystitis) needs to be recorded in the eCRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded in the eCRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the AE eCRF, unless their severity, seriousness, or etiology changes.

Note: Potential drug-induced liver injury (DILI; Hy's law) cases are to be reported as SAEs (Section 7.3). For suggested actions and follow-up assessments in the event of potential DILI, refer to Appendix 2.

7.2.4. Pre-existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should be recorded on the Medical History and Baseline Conditions eCRF.

If a pre-existing medical condition increases in frequency or severity, or if the character of the condition worsens during the study, the condition should be recorded as an AE or SAE. When recording such events on the AE eCRF, it is important to convey the concept that the pre-existing condition has changed by including applicable descriptors (eg, "more frequent headaches").

7.2.5. Worsening of Sickle Cell Disease

SCD-related AEs that are common complications associated with the study participant's SCD may not be considered related to voxelotor unless judged by the Investigator to have worsened in severity and/or frequency or changed in nature during the study. SCD-related AEs include: SCD with vaso-occlusive pain crisis, acute chest syndrome, pneumonia, priapism, splenic or hepatic sequestrations, stroke, and osteonecrosis (Kato, 2018).

7.3. Serious Adverse Events, Serious Adverse Drug Reactions, and Requirements for Immediate Reporting

All SAEs, regardless of causal attribution, must be reported by the Investigator/designee or site personnel within 24 hours of SAE awareness on the AE eCRF and reported to Safety via PSSA. In the event PSSA is not available, paper CT SAE Report Forms will be used to report the SAE and faxed or emailed to Pfizer Safety. The information reported on the paper SAE report form should be entered into PSSA once available.

The Sponsor may request additional information pertaining to the SAE from the investigational site. Follow-up reports must be submitted within 24 hours of awareness as additional information becomes available.

All SAEs regardless of causal attribution must be followed to resolution, stabilization, or until reasonable attempts to determine resolution of the SAE are performed.

7.3.1. Reporting Suspected Unexpected Serious Adverse Reactions and Urgent Safety Issues

The Sponsor is responsible for reporting suspected unexpected serious adverse reactions (SUSARs) to regulatory agencies, competent authorities, IECs, and Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days of the Sponsor's first knowledge of the event and follow-up information submitted within an additional 8 calendar days, or as otherwise required per local laws and regulations. All other SUSARs will be submitted within 15 calendar days of the Sponsor's first knowledge of the event. The Investigator is responsible for notifying the local IECs of all SAEs that occur at his/her site as required by local regulations or IEC policies, if this responsibility resides with the site.

Investigators are required to report any urgent safety matters to the Sponsor within 24 hours of awareness. The Sponsor will inform regulatory authorities, IECs, and Investigators, as applicable, of any events (eg, change to the safety profile of voxelotor, major safety findings that may place study participants at risk) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may adversely affect the safety of study participants.

7.4. Reporting Overdose

If a participant takes more than the protocol-defined dose in a day and experiences a drug-related AE, this will be reported as an overdose and a protocol deviation. However, if the participant did not experience any AEs, this will only be reported as a protocol deviation.

The Investigator will discuss the risks and concerns of study drug exposure with the participant. Parents, guardians, or participants are to be instructed to contact their study site

immediately if an overdose of study drug is suspected. An overdose with AEs must be followed until the adverse effects are resolved or stabilized, or until reasonable attempts to determine resolution of the event are exhausted.

In the event of an overdose, the Investigator or treating physician should:

- Contact the study Medical Monitor within 24 hours.
- Closely monitor the participant for any AEs/SAEs and laboratory abnormalities as medically appropriate and follow up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.
- Overdose is reportable to Pfizer Safety **only when associated with an SAE.**

7.5. Environmental Exposure, Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Environmental exposure occurs when a person not enrolled in the study as a participant receives unplanned direct contact with or exposure to voxelotor. Such exposure may or may not lead to the occurrence of an AE or SAE. Persons at risk for environmental exposure include healthcare providers, family members, and others who may be exposed. An environmental exposure may include exposure during pregnancy (EDP), exposure during breastfeeding (EDB), and occupational exposure.

Any such exposures to voxelotor under study are reportable to the Sponsor or designee within 24 hours of Investigator awareness.

7.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing voxelotor.
- A male participant who is receiving or has discontinued voxelotor inseminates a female partner.
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to voxelotor because of environmental exposure. Below is an example of environmental EDP:
  - A female family member of healthcare provider reports that she is pregnant after having been exposed to voxelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact.
  - A male family member or healthcare provider who has been exposed to voxelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact, then inseminates his female partner prior to or around the time of conception.

The Investigator must report EDP to the Sponsor or designee within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The initial

information submitted should include the anticipated date of delivery (see below of information related to termination of pregnancy).

- If EDP occurs in a participant/participant's partner, the Investigator must report this information to Pfizer Safety using PSSA regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of voxelotor and until at least 140 days after the last dose.
- If EDP occurs in the setting of environmental exposure, the Investigator must report information to Pfizer Safety using PSSA. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the Investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The Investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. The child born to a female participant or partner of a male participant exposed to study drug will be followed for 3 months after delivery. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death), the Investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to the Sponsor or designee as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion should be reported as an SAE;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the Investigator assesses the infant death as related or possibly related to exposure to voxelotor.

Additional information regarding the EDP may be requested by the Sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the Investigator will provide the participant with the Parental Partner: Information Sheet and Informed Consent Form to deliver to his partner. The Investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

7.5.2. Exposure During Breastfeeding

An EDB occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing voxelotor.
- A female nonparticipant is found to be breastfeeding while exposed or having been exposed to voxelotor (ie, environmental exposure). An example of environmental EDB is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to voxelotor by all possible routes of exposure, eg, ingestion, inhalation, or skin contact.

The Investigator must report EDB to Pfizer Safety within 24 hours of the Investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the PSSA. When EDB occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed report is maintained in the Investigator site file.

7.5.3. Occupational Exposure

The Investigator must report any instance of occupational exposure to Pfizer Safety within 24 hours of the Investigator's awareness via PSSA regardless of whether there is an associated SAE. Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed report is maintained in the Investigator site file.

7.6. Lack Of Efficacy

The investigator must report signs, symptoms, and/or clinical sequelae resulting from lack of efficacy. Lack of efficacy or failure of expected pharmacological action is reportable to Pfizer Safety **only if associated with an SAE.**

7.7. Medication Errors

Medication errors may result from the administration or consumption of voxelotor by the wrong participant, or at the wrong time, or at the wrong dosage strength.

Medication errors are recorded and reported as follows:

Table 7: Reporting of Medication Errors

Recorded on the Medication Page of the CRF	Recorded on the Adverse Event Page of the CRF	Reported via PSSA to Pfizer Safety Within 24 Hours of Awareness
All (regardless of whether associated with an AE)	Any AE or SAE associated with the medication error	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study drug

- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
    - The administration of an incorrect dosage;
    - The administration of expired study drug;
    - The administration of an incorrect study drug;
    - The administration of study drug that has undergone temperature excursion from the specified storage range unless it is determined by the Sponsor that the study drug under question is acceptable to use.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, such medication errors occurring to a study participant are recorded on the medication error page of the CRF, which is a specific version of the AE page and, if applicable, any associated serious and nonserious AE(s) are recorded on the AE page of the CRF.

In the event of a medication dosing error, the Sponsor or designee should be notified within 24 hours.

Medication errors should be reported to Pfizer Safety within 24 hours using PSSA **only when associated with an SAE.**

8. DATA ANALYSIS AND STATISTICAL PLANS

The primary study analysis will be based on complete data from the 12-week treatment period of the study, and will be performed at the earliest after all participants have completed the 12-week treatment period or discontinued early, and all corresponding data have been entered into the database, reviewed, and verified.

The final study analysis will be based on data from the complete study (including the Open-label Treatment Period and 4-week Follow-up Period), and will be performed after all participants have completed the study or discontinued early and all data from the study are in the database and the database is locked.

8.1. Analysis Populations

Two main analysis populations are defined for this study: the intent-to-treat (ITT) population and the safety-evaluable population.

The ITT population includes all randomized participants. For analyses based on this population, participants will be grouped according to the treatment assigned at randomization. This is the primary analysis population for efficacy, demographics, and baseline characteristics data.

The safety-evaluable population includes all participants who receive at least 1 dose of study drug. For analyses based on this population, participants will be grouped according to the actual study treatment received. This is the primary analysis population for safety and exposure data.

8.2. Summary of Study Conduct

The number of participants randomized will be tabulated by country, study site, and treatment group. Participant disposition (the number of participants randomized, receiving at least 1 dose of study treatment, completing the study through the 12-week blinded Randomized Treatment Period, completing the study through the Open-label Treatment Period and Follow-up Visit) will be summarized by treatment group. Reasons for early discontinuation from study treatment and early discontinuation from the study will be summarized. Important protocol deviations will be listed and evaluated for potential impact on the interpretation of study results.

8.3. Summary of Demographics, Baseline Characteristics, and Concomitant Medications

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) will be summarized for the ITT population by treatment group. Baseline will be defined as the Day 1 assessment of the target leg ulcer(s) (post 2-week Run-in Period). Concomitant medications will be coded using the WHO Drug Dictionary and summarized.

8.4. Efficacy Analysis

The site will measure target ulcers using digital photographs. The digital photographs taken by the site will be sent to a central external reviewer for review and to determine measurements. The measurements provided by the central external reviewer (not the site) will be used to inform eligibility of participants, and assessment of initial re-epithelialization at the Week 12 visit. In addition, the measurements provided by central external reviewer will be used for assessing study efficacy endpoints.

8.4.1. Primary Endpoint

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.

The proportion of participants with resolution of target leg ulcer(s) by Week 12 will be analyzed using a Cochran-Mantel-Haenszel (CMH) test to compare voxelotor + SOC with placebo + SOC groups, stratified by target ulcer size and target ulcer duration. CCI [redacted]. For participants with more than one target leg ulcer, all ulcers must be confirmed resolved in order for the participant to be considered a responder.

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 study dropout will be classified as non-responders for purposes of the primary analysis.

8.4.2. Secondary Endpoints

Time to resolution of target ulcer(s) up to Week 12: a stratified log-rank test will be used to compare the treatment groups. A Cox regression model will be used to estimate the hazard ratio between voxelotor +SOC and placebo + SOC groups, as appropriate. Time to resolution will be measured (in days) from Day 1 to date of initial closure of the target ulcer. For participants with more than one target ulcer, time to resolution will be based on the time to closure of all target ulcers (ie, initial closure of the last target ulcer to resolve).

Change from baseline in sum of surface area of target ulcer(s) at Week 12: a mixed-effect model for repeated measures will be used to estimate and compare change from baseline in sum of target ulcer(s) surface area between voxelotor + SOC and placebo + SOC groups. The model will include terms for treatment group, study visit, treatment-by-study visit interaction, as well as the stratification factors. Within-participant variability will be modeled using an unstructured covariance matrix.

Incidence of new ulcers by Week 12: the proportion of participants with new ulcer occurrence within 12 weeks of treatment will be compared between treatment groups using a CMH test, stratified by target ulcer size, and target ulcer duration, as appropriate.

8.4.3. Exploratory Endpoints

Exploratory endpoints will be summarized by descriptive statistics. Details will be provided in the statistical analysis plan (SAP).

8.5. Safety Analysis

Safety analysis will be performed on all participants receiving at least 1 dose of study drug.

Adverse events will be classified according to Medical Dictionary for Regulatory Activities (MedDRA). The frequency of AEs will be tabulated by system organ class, preferred term, severity, and relationship to study treatment.

Changes in laboratory parameters and vital signs will be summarized descriptively.

8.6. Determination of Sample Size

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) and assumed 5% dropout by Week 12 (PASS version 11).

8.7. Missing Data Handling

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 study dropout, will be classified as non-responders for purposes of the primary analysis.

Detailed considerations of missing data handling will be described in the SAP.

8.8. Adjustment for Multiple Comparisons

CCI [redacted]

9. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

9.1. Source Data

Original documents, data, records (eg, clinic records, laboratory notes, memoranda, participant diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, participant files, transfusion records, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study), and all relevant sections of the participant's medical records and all other data collection made specific to this study constitute source documents.

The completed eCRF is not a source document. The Investigator/institution will permit study-related monitoring, audits, IEC review, and regulatory inspection by providing direct access to source documents.

9.2. Data Collection

The Investigator will be responsible for maintaining accurate and adequate case records (source documents) from which data will be transcribed to eCRFs designed to record data pertinent to this study. All relevant observations and data related to the study will be recorded. This will include medical and medication history, PEs, a checklist of inclusion and exclusion criteria, investigational treatment administration, a record of sample collection, clinical assessments, AEs, and final evaluation(s). The monitor (clinical research associate [CRA]) will review all eCRFs and compare data to that contained in clinic notes and participants' source documents/medical records.

Data for each participant will be recorded in the eCRF. An eCRF must be completed for every participant enrolled in the study. When data are complete, the Investigator or medically qualified sub-Investigator listed on Form FDA 1572 (or Investigator's Agreement if applicable) will apply his/her signature in the eCRF indicating he/she has reviewed and approves of the data collected in the eCRF.

9.3. Essential Documentation Requirements

The Sponsor or Sponsor's representative will collect from the investigational site the required essential regulatory documents per ICH guidance prior to voxelotor shipment to the site.

10. QUALITY CONTROL AND QUALITY ASSURANCE

10.1. Monitoring

Site personnel will be provided with training on how to collect quality data for the study, and a Sponsor monitor (CRA) will be contacting the site periodically to review study conduct and data recorded at the site. At the Sponsor's discretion, on-site monitoring visits may be conducted pre-study, during the study, and following study completion. These visits are to provide the Sponsor with the opportunity to evaluate study progress; verify the accuracy and completeness of source data and eCRFs; and ensure that all protocol and Good Clinical Practice (GCP) requirements, applicable US FDA or country-specific regulations, and Investigator obligations are being fulfilled. The Sponsor may terminate study participation by a clinical study site if study-site personnel do not follow the protocol or GCPs. Additionally, individual participants may be excluded if a medical records review indicates protocol deviations or if other factors appear to jeopardize the validity of the study.

The Investigator agrees to cooperate with the monitor (CRA) to ensure that any problems detected during the course of these monitoring visits are resolved.

10.2. Quality Control and Quality Assurance

Pfizer may conduct a quality assurance audit(s) of this study. If such an audit occurs, the Investigator agrees to allow the auditor direct access to all relevant documents (eg, all participant records, medical records and eCRFs) and access to all corresponding portions of the office, clinic, laboratory, or pharmacy which may have been involved with the study. The Investigator will allocate his/her time and that of the study-site personnel to the auditor to discuss findings and any relevant issues. In addition, regulatory agencies may conduct a regulatory inspection of this study. If such an inspection occurs, the Investigator agrees to notify Pfizer upon notification by the regulatory agency. The Investigator agrees to allow the inspector direct access to all relevant documents and to allocate his/her time and that of the study-site personnel to the inspector to discuss findings and any relevant issues. The Investigator will allow Pfizer personnel to be present as an observer during a regulatory inspection, if requested.

10.3. Laboratory Accreditation

The laboratory facility used for analysis of clinical laboratory samples must provide evidence of adequate licensure or accreditation. Copies of laboratory certification, licensure, and reference ranges (as appropriate) will be supplied to the Sponsor prior to study initiation. The Sponsor or designee should be notified of any changes in reference range values or certification/license renewal during the course of the study.

10.4. Sponsor's Medically Qualified Individual

The contact information for the sponsor's Medically Qualified Individual (MQI; ie, Medical Monitor) for the study is documented in the study contact list located in the Study Binder.

To facilitate access to their Investigator and the Sponsor's MQI for study-related medical questions or problems from nonstudy healthcare professionals, participants are provided with an emergency contact card (ECC) at the time of informed consent. The ECC contains, at a minimum (a) protocol and study drug identifiers, (b) participant's study identification number, and (c) site emergency phone number active 24 hours/day, 7 days per week.

The ECC is intended to augment, not replace, the established communication pathways between the participant and their Investigator and site staff, and between the Investigator and Sponsor study team. The ECC is only to be used by healthcare professionals not involved in the research study, as a means of reaching the Investigator or site staff related to the care of a participant.

11. REGULATORY, ETHICAL, LEGAL, AND OVERSIGHT OBLIGATIONS

The study will comply with the General Data Protection Regulation 2018, and applicable local data protection regulations. Data collected will be pseudonymized.

The processing of the personal data of participants will be minimized by making use of a unique participant study number only on study documents and electronic database(s)

All study documents will be stored securely and only accessible by study staff and authorized personnel. The study staff will safeguard the privacy of participants' personal data. The patient information sheet/informed consent for the study will inform the participant of their rights and provide appropriate contact details of the Data Protection Officer.

11.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICF, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor, submitted to an IRB/EC by the investigator, and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH GCP guidelines, the IRB/EC, European regulation 536/2014 for clinical studies, European Medical Device Regulation 2017/745 for clinical device research, and all other applicable local regulations.

11.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study drug, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of the ICH GCP guidelines that the investigator becomes aware of.

11.2. Informed Consent and Assent

The Investigator or the Investigator's representative will explain the nature of the study, including the risks and benefits, to the participant (or their legally authorized representative) and answer all questions regarding the study. The participant (or their legally authorized representative) should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants (or their legally authorized representative [if allowed by local regulation]) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/EC or study center.

The Investigator must ensure that each participant (or their legally authorized representative) is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant (or their legally authorized representative) must be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant (or their legally authorized representative).

The participant (or their legally authorized representative) must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized

personnel appointed by the Sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The Investigator further must ensure that each study participant (or their legally authorized representative) is fully informed about their right to access and correct their personal data and to withdraw consent for the processing of their personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date on which the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participant (or their legally authorized representative) must be reconsented to the most current version of the IRB/EC-approved ICF(s) during their participation in the study as required per local regulations.

A copy of the ICF(s) must be provided to the participant (or their legally authorized representative).

11.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participant's personal data will be stored at any time with no prejudice to further treatment. It is the parent or legal guardian's responsibility to communicate the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the Sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the Sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to their actual identity and medical record ID. In case of data transfer, the Sponsor will protect the confidentiality of participant' personal data consistent with the clinical study agreement and applicable privacy laws.

Information technology systems used to collect, process, and store study-related data are secured by technical and organizational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorized disclosure or access.

The Sponsor maintains standard operating procedures on how to respond in the event of unauthorized access, use, or disclosure of Sponsor information or systems.

11.4. Independent Ethics Committee and Regulatory Approval

The Investigator must inform, and obtain approval from, the IEC for the conduct of the study at named sites, for the protocol, the Participant ICF, and any other written information that

will be provided to the participants and any advertisements that will be used. Written approval must be obtained prior to recruitment of participants into the study and shipment of study drug.

Proposed amendments to the protocol and documents must be discussed with the Sponsor and CRO, and then submitted to the IEC for approval as well as submitted to regulatory authorities for approval prior to implementation. Amendments may be implemented only after a copy of the IEC approval letter has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or IEC approval. However, in this case, approval must be obtained as soon as possible after implementation.

The Investigator will be responsible for ensuring that an annual update is sent to the IEC to facilitate their continuing review of the study (if needed) and that the IEC is informed about the end of the study. Copies of the update, subsequent approvals and final letter must be sent to the Sponsor. The Investigator will inform the IEC of any reportable AEs.

11.5. Essential Documentation Requirements

The Sponsor or Sponsor's representative will collect from the investigational site the required essential regulatory documents per ICH guidance prior to voxelotor shipment to the site.

11.6. Dissemination of Clinical Study Data

The Sponsor fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT/CTIS, and/or www.pfizer.com, and other public registries and websites in accordance with applicable local laws/regulation. In addition, the Sponsor reports study results outside of the requirement of local laws/regulations pursuant to its standard operating procedures.

In all cases, study results are reported by the Sponsor in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

The Sponsor posts clinical trial results on www.clinicaltrials.gov for GBT/Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

EudraCT/CTIS

The Sponsor posts clinical trial results on EudraCT/CTIS for GBT/Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

The Sponsor posts clinical study report (CSR) synopses and plain-language study results summaries on www.pfizer.com for GBT/Pfizer-sponsored interventional studies at the same

time the corresponding study results are posted to www.clinicaltrials.gov. CSR synopses will have personally identifiable information anonymized.

Documents within marketing applications

The Sponsor complies with applicable local laws/regulations to publish clinical documents included in marketing applications. Clinical documents include summary documents and CSRs including the protocol and protocol amendments, sample CRFs, and SAPs. Clinical documents will have personally identifiable information anonymized.

Data sharing

The Sponsor provides researchers secure access to participant-level data or full CSRs for the purposes of "bona-fide scientific research" that contributes to the scientific understanding of the disease, target, or compound class. The Sponsor will make data from these trials available 18 months after study completion. Participant-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information anonymized.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

11.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

Guidance on completion of CRFs will be provided in the CRF Completion Requirement document.

The Investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password-protected or secured in a locked room to prevent access by unauthorized third parties.

The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source records and documents. This verification may also occur after study completion. It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time in devoted to the process.

Monitoring details describing strategy, including definition of study-critical data items and processes (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, virtual, or on-site monitoring), are provided in the data management plan maintained and utilized by the Sponsor or designee.

The Sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the Sponsor. The Investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the Investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The Investigator(s) will notify the Sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the Investigator will cooperate with the Sponsor or its agents to prepare the Investigator site for the inspection and will allow the Sponsor or its agent, whenever feasible, to be present during the inspection. The Investigator site and Investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The Investigator will promptly provide copies of the inspection findings to the Sponsor or its agent. Before response submission to the regulatory authorities, the Investigator will provide the Sponsor or its agents with an opportunity to review and comment on responses to any such findings.

11.8. Study and Site Start and Closure

The study start date is the date of the first participant's first visit.

The Sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor, including (but not limited to) regulatory authority decision, change in opinion of the IRB/EC, or change in benefit-risk assessment. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time upon notification to the Sponsor or designee/CRO if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the Sponsor may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the Sponsor's procedures, or the ICH GCP guidelines;
- Inadequate recruitment of participants by the Investigator;
- Discontinuation of further study drug development.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

11.9. Confidentiality

The Investigator must ensure that the participant's privacy is maintained. In the eCRF and other documents submitted to the Sponsor, participants will be identified by a participant study number only. Documents that are not submitted to the Sponsor (eg, signed ICF) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory agencies, and IECs to review the portion of the participant's medical record that is directly related to the study. As part of the required content of informed consent, the participant must be informed that his/her records will be reviewed in this manner.

11.10. Study Documentation and Data Storage

The Investigator must retain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator must retain essential documents as detailed in Section 12.2. Participant files and other source data (including copies of protocols, original reports of test results, study drug dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the study) must be kept for the maximum period of time permitted by the institution. Documents should be stored in such a way that they can be accessed/data retrieved at a later date. Consideration should be given to security and environmental risks.

No study document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, written agreement must be obtained from the Sponsor.

12. DATA HANDLING AND RECORDKEEPING

12.1. Inspection of Records

Pfizer will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor (CRA) to inspect the drug storage area, study drug stocks, drug accountability records, participant charts, study source documents, and other records relative to study conduct.

The Investigator agrees to maintain a regulatory binder in a current, organized fashion; this binder will contain documentation supportive of the protocol- and GCP-compliance of the study. The contents of the binder will be organized according to the standards of ICH E6, Section 8 (Essential Documents). The Investigator agrees to make this binder accessible to the monitor (CRA), auditor, and representatives of regulatory agencies and the IEC.

12.2. Retention of Records

The Investigator will maintain adequate records, including participants' medical records, laboratory reports, signed consent forms, drug accountability records, safety reports, information regarding participants who discontinued the protocol, and any other pertinent

data. All study records must be retained for at least 2 years after the last approval of a marketing application in the US or an ICH region and until (1) there are no pending or contemplated marketing applications in the US or an ICH region or (2) at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product under study. The Investigator/institution should retain participant identifiers for at least 15 years after the completion or discontinuation of study. Study participant files and other resource data must be kept for the maximum period of time permitted by the hospital/institution but not less than 15 years. These documents should be retained for a longer period, if required by the applicable regulatory requirements or by the Sponsor. Pfizer must be notified with retention if the Investigator/institution is unable to continue with the maintenance of study participant files for the full 15 years. All study records must be stored in a secure and safe facility.

The Investigators must retain protocols, amendments, IEC approvals, copies of the Form FDA 1572 (or Investigator's Agreement if applicable), signed and dated consent forms, medical records, eCRFs, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

If the Investigator moves, withdraws from an investigation, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor. The Investigator must notify the Sponsor immediately in the event of accidental loss or destruction of any protocol records.

Disclosure of Information

Participants' medical information obtained as a result of this study is considered confidential, and disclosure to third parties, other than those noted in this protocol, is prohibited. Subject to any applicable authorization(s), all reports and communications relating to participants in this study will identify participants only by initials and number. Medical information resulting from a participant's participation in this study may be given to the participant's personal physician, other authorized parties, or to the appropriate medical personnel responsible for the participant's participation in this clinical study. Data generated in this study will be available for inspection on request by the FDA or other government regulatory agency auditors, the Sponsor, the Sponsor's Medical Monitor (or designee), and their designated representatives, the IEC, and other authorized parties. All information concerning the study drug and the Sponsor's operations (such as patent applications, formulas, manufacturing processes, basic scientific data, or other information supplied by the Sponsor and not previously published) are considered confidential and shall remain the sole property of the Sponsor. The Investigator agrees to use this information only in conducting this study and to not use it for other purposes without the Sponsor's prior written consent. The information developed in this clinical study will be used by the Sponsor in the clinical development of voxelotor and therefore, may be disclosed by the Sponsor as required, to authorized parties (including its corporate partners for the study drug, if any, and their designated representatives), other clinical Investigators, pharmaceutical companies, the FDA, and other government agencies. Any information, inventions, discoveries (whether patentable or not), innovations, suggestions, ideas, and reports made or developed by the Investigator(s) as a result of conducting this study shall be promptly disclosed to the Sponsor and shall be

the sole property of the Sponsor. The Investigator agrees, upon the Sponsor's request and at the Sponsor's expense, to execute such documents and to take such other actions as the Sponsor deems necessary or appropriate to obtain patents in the Sponsor's name covering any of the foregoing.

13. INSURANCE AND FINANCIAL DISCLOSURE

The Sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

Financial Disclosure statements will be handled in a separate agreement apart from the protocol, kept on file and submitted, as applicable, with any subsequent license application.

14. PUBLICATION POLICY

For multicenter trials, the primary publication will be a joint publication developed by the Investigator and the Sponsor reporting the primary endpoint(s) of the study covering all study sites. The Investigator agrees to refer to the primary publication in any subsequent publications. The Sponsor will not provide any financial compensation for the Investigator's participation in the preparation of the primary congress abstract, poster, presentation, or primary manuscript for the study.

Investigators are free to publish individual center results that they deem to be clinically meaningful after publication of the overall results of the study or 12 months after primary completion date or study completion at all sites, whichever occurs first, subject to the other requirements described in this section.

The Investigator will provide the Sponsor an opportunity to review any proposed publication or any other type of disclosure of the study results (collectively, "publication") before it is submitted or otherwise disclosed and will submit all publications to the Sponsor 30 days before submission. If any patent action is required to protect intellectual property rights, the Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days upon request from the Sponsor. This allows the Sponsor to protect proprietary information and to provide comments, and the Investigator will, on request, remove any previously undisclosed confidential information before disclosure, except for any study intervention or Sponsor related information necessary for the appropriate scientific presentation or understanding of the study results. For joint publications, should there be disagreement regarding interpretation and/or presentation of specific analysis results, resolution of, and responsibility for, such disagreements will be the collective responsibility of all authors of the publication.

For all publications relating to the study, the investigator and the Sponsor will comply with recognized ethical standards concerning publications and authorship, including those established by the International Committee of Medical Journal Editors. The Investigator will disclose any relationship with the Sponsor and any relevant potential conflicts of interest, including any financial or personal relationship with the Sponsor, in any publications. All authors will have access to the relevant statistical tables, figures, and reports (in their original format) required to develop the publication.

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Appendix 1. Schedule of Assessments

Period	**Screening**	**Run-in**	**12-Week Randomized Treatment**			**Open-label Treatment (minimum 12 weeks)**			**Follow-up/ EOS Visit[a, v]**	**Early Termination Visit**
Visit Number (Week)	***Visit 1 (Week -6 to -2)***	***Visit 2 (Week -2)***	***Visit 3 (Week 0)***	***Visits 4-8[b] (Week 2-10)***	***Visit 9 (Week 12)***	***Visits 10-14[c] (Week 14-22)***	***Visit 15 (Week 24)***	***Visit 16-A & onward[d] (Week 28)***	***Visit 16-B (Week 28)***	
Visit Day	***-42 to -14***	***-14***	***Day 1***	***Day 14-70***	***Day 84***	***Day 96-154***	***Day 168***	***Day 196 & onward***	***Day 196***	
Visit Window	—	**+3 days**	**+ 1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±5 days**	**±7 days**	—
Informed consent/assent	X									
HbSS, HbS/β[0] thalassemia test[e]	X									
Inclusion/exclusion[f]	X	X	X[g]							
Medical history	X									
Height and weight	X				X[h]					
Physical examination[i]	X	X	X		X		X	X[j]	X	X
Vital signs[k]	X	X	X	X	X	X	X	X[l]	X	X
Serum pregnancy test[m]	X									
Urine pregnancy test[n]			X	X	X	X	X	X[o]		
Hematology[p]	X		X		X		X	X[l]	X	X
Serum chemistry[q]	X		X		X		X	X[l]	X	X
PROMIS-43 v2.1 PROMIS-37 v2.0 Pediatric Profile[r]			X		X		X			
VAS[r]			X[g]		X		X			
PGI-C[r]					X		X			
CGI-C					X		X			

Period	**Screening**	**Run-in**	**12-Week Randomized Treatment**			**Open-label Treatment (minimum 12 weeks)**			**Follow-up/ EOS Visit[a,v]**	**Early Termination Visit**
Visit Number (Week)	***Visit 1 (Week -6 to -2)***	***Visit 2 (Week -2)***	***Visit 3 (Week 0)***	***Visits 4-8[b] (Week 2-10)***	***Visit 9 (Week 12)***	***Visit 10-14[c] (Week 14-22)***	***Visit 15 (Week 24)***	***Visit 16-A & onward[d] (Week 28)***	***Visit 16-B (Week 28)***	
Visit Day	***-42 to -14***	***-14***	***Day 1***	***Day 14-70***	***Day 84***	***Day 96-154***	***Day 168***	***Day 196 & onward***	***Day 196***	
Visit Window	—	**+3 days**	**+1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±5 days**	**±7 days**	—
Target ulcer(s) assessment[s]	X	X	X[g]	X	X	X	X		X	X
SOC	X	X	X	X	X	X	X	X[l]	X	X
Randomization			X							
Dispense study drug[t]			X	X	X[u]	X		X[l]		
Collect study drug				X	X	X	X	X[l]	X[w]	X
Dispense dosing diary			X		X					
Collect dosing diary				X	X	X	X		X[w]	X
Concomitant medications	X	X	X	X	X	X	X	X[l]	X	X
Adverse events	X	X	X	X	X	X	X	X[l]	X	X

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CGI-C, Clinician Global Impression of Change; EOS, End of study; Hb, hemoglobin; HbS/β0, sickle hemoglobin and one beta thalassemia gene; HbSS, sickle hemoglobin with 2 sickle cell genes; LDH, lactate dehydrogenase; MCH, mean cell hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PGI-C, Patient Global Impression of Change; PROMIS, Patient-Reported Outcome Measurements Information System; RBC, red blood cell; RDW, red blood cell distribution width; SOC, standard of care; VAS, visual analog scale; WBC, white blood cell.

a. Week 28 (Visit 16-B) will be for participants who choose not to enroll or are ineligible for the provision of voxelotor through an alternative source study. At this visit, safety and efficacy assessments will be collected.
b. Visits at Weeks 2, 4, 6, 8, and 10.
c. Visits at Weeks 14, 16, 18, 20, and 22.
d. For participants who have completed 12 weeks in the Open-label Treatment Period and continue to receive voxelotor until they have 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; See Section 5.1). The final study visit for these participants will occur on the day of access to voxelotor from an alternative source.

Period	Screening	Run-in	12-Week Randomized Treatment			Open-label Treatment (minimum 12 weeks)			Follow-up/ EOS Visit[a,v]	Early Termination Visit
Visit Number (Week)	*Visit 1 (Week -6 to -2)*	*Visit 2 (Week -2)*	*Visit 3 (Week 0)*	*Visits 4-8[b] (Week 2-10)*	*Visit 9 (Week 12)*	*Visit 10-14[c] (Week 14-22)*	*Visit 15 (Week 24)*	*Visit 16-A & onward[d] (Week 28)*	*Visit 16-B (Week 28)*	
Visit Day	*-42 to -14*	*-14*	*Day 1*	*Day 14-70*	*Day 84*	*Day 96-154*	*Day 168*	*Day 196 & onward*	*Day 196*	
Visit Window	—	**+3 days**	**+1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±5 days**	**±7 days**	—

e. This test will be performed at Screening only for the medical diagnosis of SCD, if this diagnosis is not documented in the participant's medical chart.
f. All Screening evaluations must be completed and reviewed before the Run-in Visit to confirm all eligibility criteria are met. Inclusion and exclusion criteria should be reviewed at Screening, Run-in, and just prior to randomizing each participant to ensure study eligibility is met.
g. These assessments must be completed before participants are randomized to study treatment.
h. Only weight will be measured.
i. Physical examinations after the Screening Period may be abbreviated, focused on abnormalities identified on the Screening examination, the target leg ulcer(s), and as related to adverse events.
j. Every 48 weeks
k. Vital signs (heart rate, blood pressure, and body temperature) will be measured after a participant has rested for at least 5 minutes in the supine or sitting position. A repeated measurement of any of the vital signs parameters will be taken within 5 minutes if the first reading is outside the normal range and deemed clinically significant.
l. Every 12 weeks
m. Females of child-bearing potential and postmenopausal females will have a serum pregnancy test at Screening.
n. Urine pregnancy tests will be performed at scheduled visits for women of child-bearing potential and postmenopausal females. If a urine pregnancy test is positive, the result must be confirmed with a serum pregnancy test. Urine pregnancy test will be performed at Baseline (Day 1), Week 6, Week 12, Week 18, and Week 24 in female participants who have experienced menarche.
o. Every 24 weeks for women of child-bearing potential.
p. Hematology assessments will include WBC (with differential), RBC count, Hb, hematocrit, RDW, MCH, MCHC, MCV, platelet count, reticulocyte percentage, and absolute reticulocyte count. Blood specimens collected at the Day 1 visit and Week 12 visit and found to be inadequate for laboratory testing should be redrawn and submitted for laboratory testing within 7 days of the study visit.
q. Serum chemistry will include sodium, potassium, bicarbonate, chloride, calcium, phosphorus, BUN, creatinine, glucose, bilirubin (total, direct, and indirect), total protein, albumin, ALT, alkaline phosphatase, AST, and LDH.
r. The PRO assessments will be evaluated when available (pending translation and cultural validation requirements).
s. Target ulcer(s) assessments will be performed by visual inspection (including the lower extremity examination and detailed description of the target ulcer[s]' characteristics) and measurement of the surface area by digital photography. See the Leg Ulcer Assessment and Measurement Manual for additional details.

Period	Screening	Run-in	12-Week Randomized Treatment			Open-label Treatment (minimum 12 weeks)			Follow-up/ EOS Visit[a,v]	Early Termination Visit
Visit Number (Week)	*Visit 1 (Week -6 to -2)*	*Visit 2 (Week -2)*	*Visit 3 (Week 0)*	*Visits 4-8[b] (Week 2-10)*	*Visit 9 (Week 12)*	*Visit 10-14[c] (Week 14-22)*	*Visit 15 (Week 24)*	*Visit 16-A & onward[d] (Week 28)*	*Visit 16-B (Week 28)*	
Visit Day	*-42 to -14*	*-14*	*Day 1*	*Day 14-70*	*Day 84*	*Day 96-154*	*Day 168*	*Day 196 & onward*	*Day 196*	
Visit Window	—	**+3 days**	**+1 day**	**±3 days**	**±3 days**	**±3 days**	**±3 days**	**±5 days**	**±7 days**	—

t. Study drug will be dispensed at the Day 1, Week 6, Week 12, and Week 18 visits. For participants who continue to receive voxelotor beyond 12 weeks in the Open-label Treatment Period (See Section 5.1), study drug will be dispensed every 12 weeks.
u. Participants demonstrating initial ulcer-re-epithelization at Week 12 will continue treatment in their assigned treatment group for an additional 2 weeks to confirm ulcer resolution.
v. Participants transitioning to a program providing voxelotor through an alternative source will complete assessments on the day they transition to that program. Study drug for this study should not be taken on the day of that visit (dose will be taken on that day as part of the alternative source program).
w. Only required for participants transitioning to a program providing voxelotor through an alternative source

Appendix 2. Liver Safety: Suggested actions and follow-up assessments and study drug rechallenge guidelines

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed "tolerators," while those who show transient liver injury but adapt are termed "adaptors." In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are "susceptible" to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above 3 × the upper limit of normal (ULN) should be monitored more frequently to determine if they are "adaptors" or are "susceptible."

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST (aspartate aminotransaminase) and/or ALT (alanine aminotransaminase) precede total bilirubin elevations (> 2 × ULN) by several days or weeks. The increase in total bilirubin typically occurs while AST/ALT is/are still elevated above 3 × ULN (ie, AST/ALT and total bilirubin values will be elevated within the same laboratory sample). In rare instances, by the time total bilirubin elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST or ALT in addition to total bilirubin that meet the criteria outlined below are considered potential DILI (assessed per Hy's law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant's individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy's law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and total bilirubin values within the normal range who subsequently present with AST/ALT values ≥ 3 × ULN AND a total bilirubin value ≥ 2 × ULN with no evidence of hemolysis and an alkaline phosphatase value < 2 × ULN or not available.
- For participants with baseline AST **OR** ALT **OR** total bilirubin values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
  - Preexisting AST/ALT baseline values above the normal range: AST/ALT values ≥ 2 times the baseline values AND ≥ 3 × ULN; or ≥ 8 × ULN (whichever is smaller).

- Preexisting values of total bilirubin above the normal range: total bilirubin level increased from baseline value by an amount of ≥ 1 × ULN **or** if the value reaches ≥ 3 × ULN (whichever is smaller).

Rises in AST/ALT and total bilirubin separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and total bilirubin for suspected Hy's law cases, additional laboratory tests should include albumin, creatine kinase, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio, eosinophils (%), and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, or supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection, total bile acids, liver imaging (eg, biliary tract), and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and total bilirubin elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

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