VOXELOTOR

GBT440-029

A Phase 2, Open-Label, Multiple Dose Escalation Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Voxelotor in Patients With Sickle Cell Disease

ABBREVIATED CLINICAL STUDY REPORT

Indication studied:	Sickle cell disease
Developmental phase of study:	Phase 2
First subject enrolled:	09 January 2020
Last subject completed:	08 June 2021
Release date of report:	14 February 2022
Company/Sponsor signatory:	Patrick Yue, MD, Executive Director, Head of Clinical Sciences
	Global Blood Therapeutics, Inc. 181 Oyster Point Blvd South San Francisco, CA 94080 USA

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the ICH Harmonized Tripartite Guideline.

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

4. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialized terms are used in this study report.

Table 1: Abbreviations and Specialized Terms

Abbreviation or Specialized Term	Explanation
ACS	acute chest syndrome
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
CGI-C	Clinical Global Assessment of Change
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CYP	cytochrome P450
FDA	Food and Drug Administration
GCP	Good Clinical Practice
Hb	hemoglobin
HbS	sickle hemoglobin
HbSS	homozygous genotype for HbS
HU	hydroxyurea
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDH	lactate dehydrogenase
LORRCA	Laser-Optical Rotational Red Cell Analyzer
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
PD	pharmacodynamic(s)
PGI-C	Patient Global Assessment of Change
PK	pharmacokinetic(s)
PT	Preferred Term
RBC	red blood cell
RDW	RBC distribution width
SAE	serious adverse event

Abbreviation or Specialized Term	Explanation
SCD	sickle cell disease
SMC	Safety Monitoring Committee
SOC	System Organ Class
TEAE	treatment-emergent adverse event
US	United States
VOC	vaso-occlusive crisis

5. ETHICS

5.1. Independent Ethics Committee or Institutional Review Board

The Investigator informed, and obtained approval from, the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for the conduct of the study at named sites, for the protocol, the subject informed consent form (ICF), and any other written information that was provided to the subjects and any advertisements that were used. Proposed amendments to the protocol and documents were discussed with the Sponsor and contract research organization (CRO), and then submitted to the IEC/IRB for approval as well as submitted to regulatory authorities for approval prior to implementation.

Additional details are provided in Section 13.4 of the protocol (Appendix 16.1.1).

5.2. Ethical Conduct of the Study

The study was conducted according to the protocol; guidelines established by International Council for Harmonisation (ICH) for Good Clinical Practice (GCP) in clinical studies; United States (US) regulations (21 CFR Parts 50, 54, 56, and 312); and country-specific requirements, as applicable.

Additional details are provided in Sections 13.1 and 13.2 of the protocol (Appendix 16.1.1).

5.3. Subject Information and Consent

Each individual was provided with oral and written information describing the nature, purpose and duration of the study, participation/termination conditions, and risks and benefits. Prior to initiation of any study-related procedures, subjects signed and dated the ICF to participate in the study.

Additional details are provided in Sections 13.3 and 13.6 of the protocol (Appendix 16.1.1).

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was sponsored by Global Blood Therapeutics, Inc. (hereafter referred to as the Sponsor). The Sponsor was responsible for the overall conduct of the study.

Subjects were screened at a total of 6 study sites in the United Kingdom. A list of investigators is provided in Appendix 16.1.4. The signature of the Coordinating Investigator is provided in Appendix 16.1.5.

7. INTRODUCTION

Sickle cell disease (SCD) is a rare and inherited disorder caused by a point mutation in the β-globin gene, leading to formation of sickle hemoglobin (HbS). It is a devastating and debilitating disease 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. A primary and obligatory event in the molecular pathogenesis of SCD is the polymerization of deoxygenated HbS, which leads to sickling of red blood cells (RBCs). The resulting hemolytic anemia is experienced to various degrees by all patients with SCD and is a defining and serious feature of the disease. Hemolytic anemia leads to reduced oxygen-carrying capacity, tissue hypoxia, and clinical manifestations of end-organ damage in patients with SCD. The disease course is also characterized by life-long pain and frequent healthcare interactions. Chronic hemolytic anemia and its sequelae have become the leading causes of mortality in adults with SCD and are recognized as critical contributors to irreversible cumulative organ damage and dysfunction (Lanzkron, 2013; Vichinsky, 2018). Half of adult patients with SCD have irreversible organ damage, and presence of dysfunction in a single organ is an independent predictor of death and subsequent multiorgan dysfunction (Powars, 2005).

Hemoglobin (Hb) concentration is an important indicator of disease severity, indicating not only the degree of anemia but also the degree of hemolysis that occurs in patients with SCD, as evidenced by the strong inverse correlation between Hb and clinical measures of RBC destruction, such as indirect bilirubin, reticulocyte count, and lactate dehydrogenase (LDH), and the association of low Hb and elevated hemolysis with increased risk of mortality (Taylor, 2008). It is well established that low Hb levels are associated with an increased risk for end-organ complications in SCD, including stroke/silent cerebral infarction, chronic kidney disease, leg ulcers, and pulmonary hypertension (Powars, 1991; Ohene-Frempong, 1998; Gladwin, 2004; Ataga, 2018).

Therapies approved for the treatment of SCD in some regions include hydroxyurea (HU) (Smith, 2011), L-glutamine (Emmaus Medical, 2018), and crizanlizumab (Novartis, 2019). Hydroxyurea is indicated to reduce the frequency of painful crisis and the need for blood transfusions in patients with recurrent moderate-to-severe sickle cell crises (E.R. Squibb, 2018). L-glutamine is an approved therapy in the US that is indicated to treat the acute complications of SCD in adult and pediatric patients 5 years of age and older (Emmaus Medical, 2018). Crizanlizumab is approved in the US and the European Union to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with SCD (Novartis, 2019). Although shown to decrease VOCs, L-glutamine and crizanlizumab have no demonstrated effect on hemolytic anemia. Despite the current standard of care, patients with SCD continue to suffer serious morbidity and premature mortality (Steinberg, 2003).

Voxelotor (formerly known as GBT440) is an orally administered small molecule that inhibits HbS polymerization by allosterically modifying Hb-O_2 affinity and was developed for the treatment of SCD. In November 2019, the US Food and Drug Administration (FDA) granted accelerated approval to voxelotor, now known by the trade name Oxbryta®, for the treatment of SCD in adults and pediatric patients 12 years of age and older.

8. STUDY OBJECTIVES

In the pivotal Phase 3 Study GBT440-031, voxelotor was shown to have a dose-dependent and clinically meaningful increase in Hb (1500 mg > 900 mg following once daily oral dosing), as well as concurrent reductions in clinical measures of hemolysis. Study GBT440-029 was designed to assess the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of voxelotor cumulative daily dose levels greater than 1500 mg (the maximum dose in the pivotal Phase 3 study) and to compare these results to the 1500 mg dose. The rationale for this study was based on an exposure-response analysis from the pivotal Study GBT440-031, which showed a linear relationship between whole blood voxelotor and % Hb occupancy and efficacy as measured by improvement in Hb and clinical measures of hemolysis. The 1500 mg once daily dose in adults with SCD led to a mean Hb occupancy of 27% and a mean Hb increase of 1.1 g/dL. At a cumulative daily dose of 3000 mg voxelotor, assuming a linear relationship and no impact of splitting the dose, the mean Hb occupancy was projected to be 49.3% with an Hb increase of 2.04 g/dL. Furthermore, no maximum tolerated dose (MTD) had previously been defined up to 1500 mg once daily. Treatment-related adverse events (AEs) in prior studies were mostly Grade 1/Grade 2 gastrointestinal events. Given the predicted improved PD of higher doses and lack of dose-limiting safety concerns, this study was designed to investigate the potential for greater benefit/risk associated with higher doses in patients with SCD.

The primary objective of this study was to evaluate the tolerability and safety of voxelotor at daily doses greater than 1500 mg (2000 to 3000 mg) in subjects with SCD. The secondary and exploratory study objectives are provided in Section 2 of the protocol (Appendix 16.1.1).

Due to enrollment issues impacted by the coronavirus disease 2019 (COVID-19) pandemic, the decision to terminate the conduct of this study was made by the Sponsor. Additional details are provided in Section 9.8.2.

9. INVESTIGATIONAL PLAN

9.1. Overall Study Design and Plan: Description

This was a Phase 2 study of the tolerability and safety of intra-subject dose escalation to cumulative daily voxelotor doses of 2000, 2500, and 3000 mg in adult subjects with SCD ≥ 18 to < 60 years of age. The study was designed as an open-label, sequential period, within-subject dose escalation study. Up to 40 subjects with SCD (HbSS or $HbSB^0$ genotype) were planned for enrollment.

Study subjects were to undergo up to four periods of voxelotor administration at progressively higher cumulative daily dose levels from 1500 mg until either an MTD or 3000 mg cumulative daily dose was reached, whichever occurred first (Figure 1):

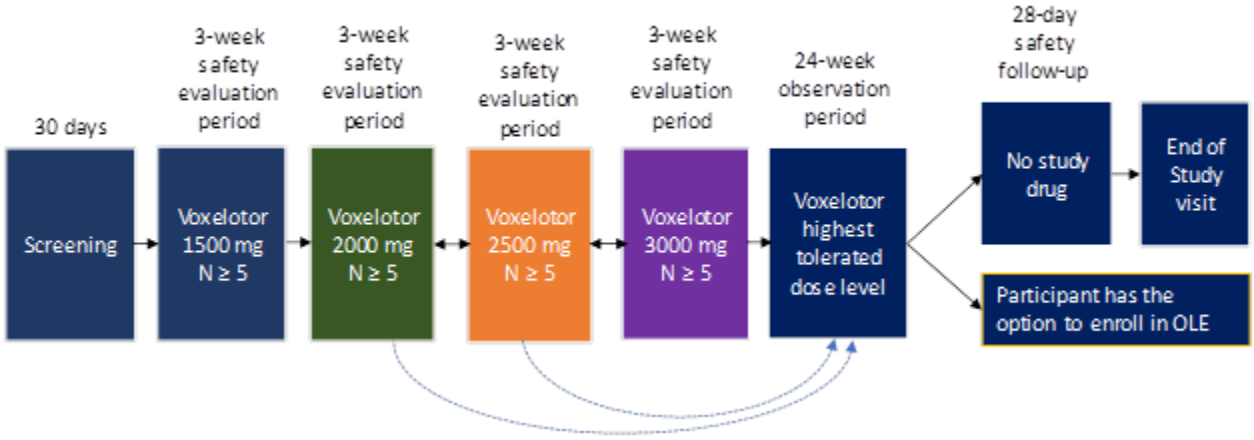
- **Period 1**: 1500 mg per day: 1500 mg once daily (3 × 500 mg tablets) for 3 weeks (± 3 days)
- **Period 2**: 2000 mg per day: 1000 mg (2 × 500 mg) twice daily for 3 weeks (± 3 days)
- **Period 3**: 2500 mg per day: 1500 mg (3 × 500 mg) in the morning and 1000 mg (2 × 500 mg) in the evening daily for 3 weeks (± 3 days)
- **Period 4**: 3000 mg per day: 1500 mg (3 × 500 mg) twice daily for 3 weeks (± 3 days)
- **Observation Period**: MTD or 3000 mg daily for 24 weeks
- **Safety Follow-up Period**: from day of last dose to 28 days postdose

If at any time a cumulative daily dose level greater than 1500 mg was not tolerated by a subject in the dose-escalation period, the dose could be reduced to a previous level for the subject, which was then administered for 24 additional consecutive weeks as an observation period. Dose modifications were allowed during the Observation Period in consultation with the Sponsor's Medical Monitor (Appendix C of the protocol; Appendix 16.1.1).

If 1500 mg daily was the MTD for a subject, then the subject entered the Observation Period and continued to receive 1500 mg once daily for up to 24 weeks. If the subject discontinued early from the study, the subject was to undergo an end of study visit approximately 28 days after the last dose.

The safety of study subjects was closely monitored by the study team. A Safety Monitoring Committee (SMC) reviewed the safety, tolerability, and available PK and PD data at regular intervals as described in Section 3.4 of the protocol, and individual stopping rules are specified in Section 3.7 of the protocol (Appendix 16.1.1).

Figure 1: Study Schema



Abbreviations: OLE, open-label extension.

Study participation was up to 44 weeks in duration, which included up to 30 days in the Screening Period; 21 days (3 weeks) each in Periods 1, 2, 3, and 4; 168 days (24 weeks) in the Observation Period; and 28 days in the Safety Follow-up Period. The study ended when the last subject's last visit occurred.

9.2. Discussion of Study Design, Including the Choice of Control Groups

An overall discussion of the study design is provided in Section 8.

9.3. Selection of Study Population

9.3.1. Inclusion Criteria

Subjects who fulfilled all the inclusion criteria were eligible for study enrollment. The inclusion criteria for this study are provided in Section 4.1 of the protocol (Appendix 16.1.1).

9.3.2. Exclusion Criteria

Subjects who met any of the exclusion criteria were not eligible for study enrollment. The exclusion criteria for this study are provided in Section 4.2 of the protocol (Appendix 16.1.1).

9.3.3. Removal of Subjects From Therapy or Assessment

The stopping rules for the study are provided in Section 3.7 of the protocol, and individual subject's reasons for discontinuation from the study are provided in Section 8.17 of the protocol (Appendix 16.1.1).

9.4. Treatments

9.4.1. Identity of Investigational Product(s)

Voxelotor was supplied as 500 mg tablets. A listing of subjects receiving study drug from specific batches is provided in Appendix 16.1.6.

9.4.2. Treatments Administered

Subjects received voxelotor tablets administered orally, once daily or twice daily, as described in Section 9.1.

9.4.3. Method of Assigning Subjects to Treatment Groups

This was an open-label, non-randomized, sequential period, within-subject dose escalation study (Figure 1).

9.4.4. Selection of Doses in the Study

As described in Section 9.1, the cumulative oral daily doses of voxelotor evaluated in this study ranged from 1500 mg up to 3000 mg. These doses of voxelotor were supported by (1) absence of concerning exposure-related safety findings with the 1500 mg daily dose from the pivotal Phase 3 Study GBT440-031 in adults and pediatric subjects aged ≥ 12 years with SCD; (2) demonstration of dose-dependent treatment effects of voxelotor on PD and efficacy measures; and (3) not yet achieving MTD in prior studies up to a single dose of 2800 mg in healthy subjects and up to 1500 mg once daily dosing in healthy subjects and subjects with SCD. A conservative escalation approach for cumulative daily dose was undertaken with increments of 500 mg at a time, representing 33% increase at the lowest dose level and 20% increase at the highest, with careful monitoring and assessments prior to escalation to the next dose level.

9.4.5. Selection and Timing of Dose for Each Subject

As described in Section 9.1, subjects were to undergo up to 4 periods of voxelotor administration at progressively higher cumulative daily dose levels from 1500 mg until either an MTD or 3000 mg cumulative daily dose was reached, whichever occurred first. Each individual period was planned to last 21 days (3 weeks) followed by the Observation Period, which was planned for 168 days (24 weeks).

9.4.6. Blinding

This was an open-label study.

9.4.7. Prior and Concomitant Therapy

Concomitant and prohibited medications and therapies are described in Section 5.8 of the protocol (Appendix 16.1.1). Medications were recorded on the subject's case report form (CRF) from signing the ICF until 28 days (4 weeks) after the subject's last dose of study drug.

9.4.8. Treatment Compliance

Drug disposition records were maintained, specifying the amount dispensed to each subject and the date of dispensation. Compliance was to be determined by returned tablet count.

9.5. Pharmacokinetic and Safety Variables

9.5.1. Pharmacokinetic and Safety Assessments and Flow Chart

The Schedule of Assessments is provided in Appendix A (Dose Escalation Phase) and Appendix B (Observation and Safety Follow-up Periods) of the protocol (Appendix 16.1.1).

9.5.2. Appropriateness of Measurements

All safety assessments used in this study were standard (ie, widely used and generally recognized as reliable, accurate, and relevant).

9.5.3. Primary Variable(s)

The primary objective of this study was to evaluate the tolerability and safety of voxelotor at daily doses greater than 1500 mg (2000 to 3000 mg) in subjects with SCD. The primary endpoints evaluated in this study were treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), as described in Section 10.1.1 of the protocol. The other secondary and exploratory endpoints are provided in Sections 10.1.2 and 10.1.3 of the protocol, respectively (Appendix 16.1.1).

9.5.4. Pharmacokinetic Assessments

Blood samples for whole-blood and plasma PK assessments were collected according to the Schedule of Assessments provided in Appendix A (Dose Escalation Phase) and Appendix B (Observation and Safety Follow-up Periods) of the protocol and protocol amendments (Appendix 16.1.1). Whole-blood and plasma concentrations of voxelotor were measured using a validated liquid chromatography-mass spectrometry assay.

9.5.5. Pharmacodynamic Assessments

Blood samples for whole-blood PD assessments (hemoximetry and RBC deformability) were collected according to the Schedule of Assessments provided in Appendix A (Dose Escalation Phase) and Appendix B (Observation and Safety Follow-up Periods) of the protocol and protocol amendments (Appendix 16.1.1). Hemoximetry was measured using a TCS Hemox Analyzer (TCS Scientific Corp), and RBC deformability was assessed via the Laser-Optical Rotational Red Cell Analyzer (LORRCA) OxygenScan and a measure of dense cells via the Siemens Advia Hematology Analyzer 2120.

9.6. Data Quality Assurance

The quality control and quality assurance procedures implemented in this study to assure the quality of the data are described in Section 12 of the protocol (Appendix 16.1.1).

9.7. Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1. Statistical and Analytical Plans

A TEAE, defined as an event that occurs on or after Day 1 of study drug or the worsening of a pre-existing condition on or after Day 1 of study drug until 28 days after discontinuation of study drug, was classified according to the Medical Dictionary for Regulatory Activities (MedDRA).

The overall planned analysis of the data is described in Section 10.4 of the protocol (Appendix 16.1.1). However, due to the early termination of the study and the limited number of subjects enrolled (N = 6), the final analysis consisted of subject listings and selected summary tables for TEAEs (Section 9.8.3).

9.7.2. Determination of Sample Size

This was an exploratory study to provide descriptive information on the safety, tolerability, PK, and PD of voxelotor at cumulative daily dose levels greater than 1500 mg. The sample size of up to 40 subjects was chosen based on previous experience in exploratory studies to support the assessment of an MTD based on descriptive summaries of safety and PK data. Additional details are provided in Section 10.2 of the protocol (Appendix 16.1.1).

9.8. Changes in the Conduct of the Study or Planned Analyses

9.8.1. Protocol Amendments

The original protocol (dated 11 July 2019) was amended twice. The original protocol and the current protocol (Amendment 2.0) and summaries of changes for all previous amendments are available in Appendix 16.1.1.

9.8.1.1. Amendment 1.0: 13 September 2019

A complete summary of changes is available in Appendix 16.1.1.4.2. Key changes are listed below.

- Excluding patients who require strong inducers of cytochrome P450 (CYP) 2B6, CYP2C9, CYP2C19, and CYP3A4/CYP3A5 and patients who use astemizole, cisapride, or terfenadine
- Excluding patients who use strong inhibitors of CYP3A4

9.8.1.2. Amendment 2.0: 05 October 2020

A complete summary of changes is available in Appendix 16.1.1.4.1. Key changes are listed below.

- Duration of Periods 1 and 4 (originally Cohort A, Periods 1 and 4) was reduced from 9 weeks to 3 weeks.
- Cohort B and associated evaluations, including magnetic resonance imaging and cardiopulmonary exercise testing, were removed from the protocol.

- The study design was changed from a single site in the United Kingdom to up to 10 sites without reference to region.
- A new secondary objective and secondary endpoint were added to evaluate the incidence rate of VOCs.
- Assessment of the Clinical Global Assessment of Change (CGI-C) and Patient Global Assessment of Change (PGI-C) was added as an exploratory objective, and CGI-C and PGI-C were added as exploratory endpoints.
- Multidose PK analysis (serial PK sampling) was changed to population PK approach (sparse sampling), and assessments of voxelotor PK and PD were changed from secondary objectives/endpoints to exploratory objectives/endpoints.

9.8.2. Other Changes in the Conduct of the Study

Due to issues with enrollment impacted by the COVID-19 pandemic, the decision to terminate the conduct of this study was made by the Sponsor. Given that (1) there are no current plans to commercialize voxelotor at cumulative daily doses greater than 1500 mg, (2) the study was not designed to be label enabling, and (3) in consideration of the enrollment issues, the Sponsor elected to terminate the study. The decision to terminate the study prior to planned completion was not based on any identified safety issues.

9.8.3. Changes to the Planned Analyses

Due to the early study termination, no formal statistical or PK/PD analysis plans were written for this study. However, the overall planned analysis of the data is described in Section 10.4 of the protocol (Appendix 16.1.1). Due to the limited number of subjects enrolled in this study (N = 6), the final analysis consisted of subject listings and selected summary tables for TEAEs. The final list of tables and listings is provided in Section 14.

Voxelotor plasma and whole-blood concentration and PD listings are provided in Appendix 16.5.1. Any analyses of PK and PD data will be reported separately.

10. STUDY SUBJECTS

10.1. Disposition of Subjects

A total of 9 subjects were screened for inclusion in the study prior to study termination; of these, 3 subjects did not meet eligibility criteria (Listing 16.2.1). Of the 6 subjects who were treated with at least one dose of voxelotor, 4 subjects discontinued treatment and 2 subjects completed treatment. According to Listing 16.2.16, only 1 subject completed treatment through Period 4 (voxelotor cumulative daily dose of 3000 mg); the other subject completed treatment up to Period 3 (voxelotor cumulative daily dose of 2500 mg) in accordance with Protocol Amendment 1.0 but did not wish to continue with Protocol Amendment 2.0. The reasons for discontinuation included discontinued due to AE, discontinued due to other reason (pregnancy), withdrew consent, and discontinued by the Investigator (Listing 16.2.7).

10.2. Protocol Deviations

Two subjects had important protocol deviations recorded during the conduct of this study; these deviations are described in Listing 16.2.13. These reported protocol deviations were not expected to have any impact on the evaluation of PK/PD or safety in this study.

11. EFFICACY EVALUATION

The primary objective of this study was to evaluate the tolerability and safety of voxelotor at daily doses greater than 1500 mg (2000 to 3000 mg) in subjects with SCD. Therefore, only data and results from the safety analyses are presented in the abbreviated clinical study report; no efficacy analyses were performed.

11.1. Data Sets Analyzed

The safety population consisted of all 6 subjects who received at least one dose of study drug. No other population was analyzed as part of the final analysis.

11.2. Demographic and Other Baseline Characteristics

11.2.1. Demographic and Baseline Characteristics

Of the 6 subjects included, all were Black or African American (3 males and 3 females). Age ranged from 27 to 36 years (Listing 16.2.2). The body mass index ranged from 17 to 28 kg/m^2 (Listing 16.2.3).

All 6 subjects entering the study had the homozygous genotype for HbS (HbSS). Two subjects reported receiving blood transfusions in the previous 12 months. Four subjects were currently taking HU; each of the 2 subjects not currently taking HU reported having taken HU in the past (Listing 16.2.4).

All but 1 subject reported at least one SCD disease complication; these included leg ulcers, priapism (male patients only), acute chest syndrome (ACS), pain crisis, and other (infection – acute tonsillitis) (Listing 16.2.5). A listing of other medical histories is provided in Listing 16.2.6.

11.2.2. Prior and Concomitant Medications

The medications recorded during this study are provided in Listing 16.2.14. In general, the medications reported encompassed a variety of medication classes commonly used as supportive care in subjects with SCD, including folic acid, ibuprofen, paracetamol, hydroxycarbamide, and medications in the Anatomical Therapeutic Chemical (ATC) class of natural opium alkaloids.

11.3. Measurements of Treatment Compliance

Study drug administration records are provided in Listing 16.2.16.

11.4. Efficacy Results and Tabulations of Individual Subject Data

Not applicable

12. SAFETY EVALUATION

12.1. Extent of Exposure

The extent of exposure to study drug is summarized by cumulative daily dose level in Table 2.

Overall, 6 subjects received at least one dose of study drug (Table 2). All 6 subjects received voxelotor 1500 mg once daily in Period 1 with a median duration of 8.7 weeks. Subjects in Period 2 (voxelotor cumulative daily dose of 2000 mg) and Period 3 (voxelotor cumulative daily dose of 2500 mg) received study drug for a median duration of 2.9 and 3.0 weeks, respectively. One subject received the highest dose (voxelotor cumulative daily dose of 3000 mg) in Period 4 for 9.0 weeks.

Table 2: Study Drug Exposure—Safety Population

Duration of Exposure (weeks)	Cumulative Daily Dose of Voxelotor			
	1500 mg (N = 6)	2000 mg (N = 4)	2500 mg (N = 3)	3000 mg (N = 1)
Mean (SD)	6.5 (3.54)	2.9 (0.07)	5.2 (4.00)	9.0
Median	8.7	2.9	3.0	9.0
Min, Max	1.9, 8.9	2.9, 3.0	2.9, 9.9	9.0, 9.0
Q1, Q3	2.0, 8.9	2.9, 2.9	2.9, 9.9	9.0, 9.0

Abbreviations: Max, maximum; Min, minimum; Q1, first quartile; Q3, third quartile; SD, standard deviation.
Source: Table 14.1.

12.2. Adverse Events

All events described in this section were TEAEs (as defined in Section 9.7.1). Non-SCD-related TEAEs and SCD-related TEAEs are presented separately to assist with assessing potential non-SCD-related safety signals with voxelotor and to minimize confounding by underlying SCD comorbidities in the determination of the safety profile of voxelotor. SCD-related TEAEs included the following preferred terms (PTs): ACS, pneumonia, sickle cell anaemia with crisis, osteonecrosis, and priapism. Non-SCD-related TEAEs are all PTs that are not defined as SCD-related. Non-SCD-related AEs are presented in Section 12.2.2. SCD-related AEs are presented in Section 12.2.3.

12.2.1. Listing of Adverse Events by Subject

Individual subject-level AE data are provided in Listing 16.2.8.1.

12.2.1.1. Displays of Adverse Events

Treatment-emergent AEs are summarized for each period by system organ class (SOC) and PT, severity, and relationship to study drug. Serious AEs and discontinuations due to TEAEs are listed by treatment group and subject number.

12.2.2. Non-SCD-related Adverse Events

12.2.2.1. Brief Summary of Non-SCD-related Adverse Events

A brief summary of non-SCD–related TEAEs is provided by cumulative daily dose level in Table 3.

At each dose level, the majority of subjects in that period reported at least one non-SCD-related TEAE (Table 3). Most subjects experienced non-SCD-related TEAEs that were Grades 1 to 2 and nonserious. No subjects died during the study. Two subjects discontinued treatment due to non-SCD-related TEAE (see Section 12.3.4 for additional details). The majority of events reported were not related to voxelotor and resolved with no action taken with study drug (Listing 16.2.8.1).

Table 3: Overview of Non-SCD-related Treatment-emergent Adverse Events—Safety Population

	Cumulative Daily Dose of Voxelotor, Number (%) of Subjects			
	1500 mg (N = 6)	**2000 mg (N = 4)**	**2500 mg (N = 3)**	**3000 mg (N = 1)**
Number of subjects with at least one TEAE	6 (100)	4 (100)	2 (66.7)	1 (100)
Number of subjects with at least one TEAE ≥ Grade 3	2 (33.3)	0	0	0
Number of subjects with at least one related TEAE	5 (83.3)	2 (50.0)	1 (33.3)	0
Number of subjects having study dose reduction due to TEAE	0	0	1(33.3%)	0
Number of subjects having study drug interrupted due to TEAE	1(16.7%)	0	0	0
Number of subjects having study drug permanently discontinued due to TEAE	1 (16.7)	0	1 (33.3)	0
Number of subjects with at least one SAE	2 (33.3)	0	0	0
Number of subjects with at least one related SAE	1 (16.7)	0	0	0
Deaths	0	0	0	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included. Subjects may be counted in more than one row. Summary excludes SCD-related events.
Source: Table 14.3.1.1.1.

12.2.2.2. Analysis of Non-SCD-related Adverse Events

12.2.2.2.1. All Non-SCD-related Adverse Events

Non-SCD-related TEAEs are summarized by SOC, PT, and cumulative daily dose level for events reported in 2 or more subjects in Table 4.

The majority of events occurred in the gastrointestinal disorders SOC (Table 4). All 6 subjects reported PTs in the gastrointestinal disorders SOC in Period 1. The most commonly reported PT was diarrhoea. All TEAEs of diarrhoea were Grade 1, nonserious, resolved, and clinically manageable and/or self-limiting (Table 14.3.1.2.1 and Listing 16.2.8.1). The only reported PT in the subject treated with the highest voxelotor dose (cumulative daily dose of 3000 mg) was pain in extremity.

Table 4: Non-SCD-related Treatment-emergent Adverse Events (Reported in ≥ 2 Subjects) by System Organ Class and Preferred Term—Safety Population

System Organ Class Preferred Term	Cumulative Daily Dose of Voxelotor, Number (%) of Subjects			
	1500 mg (N = 6)	2000 mg (N = 4)	2500 mg (N = 3)	3000 mg (N = 1)
Subjects with at least one event	6 (100)	4 (100)	2 (66.7)	1 (100)
Musculoskeletal and connective tissue disorders	2 (33.3)	2 (50.0)	0	1 (100)
Pain in extremity	0	1 (25.0)	0	1 (100)
Back pain	2 (33.3)	0	0	0
Gastrointestinal disorders	6 (100)	1 (25.0)	1 (33.3)	0
Abdominal pain upper	2 (33.3)	0	0	0
Constipation	2 (33.3)	0	0	0
Diarrhoea	4 (66.7)	0	0	0
Dry mouth	1 (16.7)	0	1 (33.3)	0
Nausea	2 (33.3)	0	0	0
General disorders and administration site conditions	2 (33.3)	0	0	0
Fatigue	2 (33.3)	0	0	0
Infections and infestations	2 (33.3)	1 (25.0)	0	0
Urinary tract infection	1 (16.7)	1 (25.0)	0	0
Investigations	1 (16.7)	0	2 (66.7)	0
Alanine aminotransferase increased	1 (16.7)	0	2 (66.7)	0
Aspartate aminotransferase increased	0	0	2 (66.7)	0

System Organ Class Preferred Term	Cumulative Daily Dose of Voxelotor, Number (%) of Subjects			
	1500 mg (N = 6)	2000 mg (N = 4)	2500 mg (N = 3)	3000 mg (N = 1)
Nervous system disorders	1 (16.7)	2 (50.0)	1 (33.3)	0
Headache	1 (16.7)	2 (50.0)	1 (33.3)	0
Skin and subcutaneous tissue disorders	2 (33.3)	0	0	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included. Subjects were counted only once for each preferred term. Summary excludes SCD-related events.
Source: Table 14.3.1.2.1.

12.2.2.2.2. Non-SCD-related Adverse Events by Severity

Non-SCD-related TEAEs are summarized by severity in Table 14.3.1.2.1.

At each dose level, the majority of non-SCD TEAEs were Grade 1 or 2 in severity. No subjects reported non-SCD-related TEAEs that were higher than Grade 3.

12.2.2.2.3. Non-SCD-related Adverse Events by Relationship to Study Drug

Non-SCD-related TEAEs assessed by the Investigator to be related to study drug are summarized in Table 14.3.1.3.1.

Overall, at least 1 subject reported at least one non-SCD-related TEAE assessed as related to study drug at each dose level (5 subjects, 2 subjects, and 1 subject for voxelotor cumulative daily doses of 1500, 2000, and 2500 mg, respectively), except for the highest dose (voxelotor cumulative daily dose of 3000 mg).

12.2.3. SCD-related Adverse Events

For the purposes of this report, SCD-related TEAEs included the following PTs: ACS, pneumonia, sickle cell anaemia with crisis, osteonecrosis, and priapism. These events are common complications associated with SCD (Kato, 2018).

12.2.3.1. Brief Summary of SCD-related Adverse Events

A brief summary of non-SCD–related TEAEs is provided in Table 5.

Subjects reported at least one SCD-related TEAE at each dose level, except for the highest dose (voxelotor cumulative daily dose of 3000 mg). Three subjects experienced TEAEs that were Grade 3 or higher in Period 1 (voxelotor cumulative daily dose of 1500 mg). Three subjects reported at least one SAE in Period 1, and 1 subject reported at least one SAE in Period 3. All SCD-related TEAEs were assessed as not related to voxelotor and resolved with no action taken with study drug (Listing 16.2.8.1).

Table 5: Overview of SCD-related Treatment-emergent Adverse Events—Safety Population

	Cumulative Daily Dose of Voxelotor, Number (%) of Subjects			
	1500 mg (N = 6)	2000 mg (N = 4)	2500 mg (N = 3)	3000 mg (N = 1)
Number of subjects with at least one TEAE	5 (83.3)	1 (25.0)	1 (33.3)	0
Number of subjects with at least one TEAE ≥ Grade 3	3 (50.0)	0	0	0
Number of subjects with at least one related TEAE	0	0	0	0
Number of subjects having study dose reduction due to TEAE	0	0	0	0
Number of subjects having study drug interrupted due to TEAE	0	0	0	0
Number of subjects having study drug permanently discontinued due to TEAE	0	0	0	0
Number of subjects with at least one SAE	3 (50.0)	0	1 (33.3)	0
Number of subjects with at least one related SAE	0	0	0	0
Deaths	0	0	0	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SAE, serious adverse event; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included. Subjects may be counted in more than one row. Summary includes SCD-related events.
Source: Table 14.3.1.1.2.

12.2.3.2. Analysis of SCD-related Adverse Events

12.2.3.2.1. All SCD-related Adverse Events

SCD-related TEAEs are summarized by SOC and PT in Table 6.

Overall, 5 subjects in Period 1 (voxelotor cumulative daily dose of 1500 mg) reported at least one SCD-related TEAE, including sickle cell anaemia with crisis (5 subjects) and priapism (1 subject). One subject (each) reported sickle cell anaemia with crisis during Periods 2 and 3 (voxelotor cumulative daily doses of 2000 and 2500 mg, respectively). There were no SCD-related TEAEs reported in the subject treated with the highest voxelotor dose (cumulative daily dose of 3000 mg).

Table 6: SCD-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term—Safety Population

System Organ Class Preferred Term	Cumulative Daily Dose of Voxelotor, Number (%) of Subjects			
	1500 mg (N = 6)	2000 mg (N = 4)	2500 mg (N = 3)	3000 mg (N = 1)
Subjects with at least one event	5 (83.3)	1 (25.0)	1 (33.3)	0
Blood and lymphatic system disorders	5 (83.3)	1 (25.0)	1 (33.3)	0
Sickle cell anaemia with crisis	5 (83.3)	1 (25.0)	1 (33.3)	0
Reproductive system and breast disorders	1 (16.7)	0	0	0
Priapism	1 (16.7)	0	0	0

Abbreviations: MedDRA, Medical Dictionary for Regulatory Activities; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included. Subjects were counted only once for each preferred term. Summary includes SCD-related events.
Source: Table 14.3.1.2.2.

12.2.3.2.2. SCD-related Adverse Events by Severity

SCD-related TEAEs are summarized by SOC, PT, and severity in Table 14.3.1.2.2.

In Period 1 (voxelotor cumulative daily dose of 1500 mg), sickle cell anaemia with crisis occurred in 5 subjects; three of these events were assessed as Grades 1 to 2 and the other two were assessed as Grade 3. There was one Grade 3 PT of priapism in Period 1. Periods 2 and 3 (voxelotor cumulative daily doses of 2000 and 2500 mg, respectively) each had one Grade 2 PT of sickle cell anaemia with crisis.

12.2.3.2.3. SCD-related Adverse Events by Relationship to Study Drug

There were no SCD-related TEAEs assessed by the Investigator to be related to study drug (Table 14.3.1.3.2).

12.3. Deaths, Serious Adverse Events, and Other Significant Adverse Events

Deaths are presented in Section 12.3.2, and other SAEs are presented in Section 12.3.3. Other significant TEAEs (including treatment discontinuations and dose modifications) are presented in Section 12.3.4.

12.3.1. Listing of Deaths, Serious Adverse Events, and Other Significant Adverse Events

Individual subject-level AE data are provided in Listing 16.2.8.1. Individual subject-level SAE data are provided in Listing 16.2.8.2.

12.3.2. Deaths

There were no deaths reported in this study (Listing 16.2.8.2).

12.3.3. Other Serious Adverse Events

Serious adverse events are listed by subject in Listing 16.2.8.2. Individual subject narratives for these SAEs are provided in Appendix 16.6.

A total of 5 subjects reported SAEs during the study. Two subjects reported non-SCD-related SAEs in Period 1 (abortion spontaneous and rash maculo-papular), and 4 subjects reported SCD-related SAEs during the study, including sickle cell anaemia with crisis and priapism.

The maculo-papular rash was assessed as related to study drug, and treatment was discontinued due to this SAE. All other SAEs were assessed as not related to study drug. The spontaneous abortion SAE is discussed in Section 12.3.5. All SAEs had resolved (with or without sequelae) by the end of the study.

Complete narratives for all reported SAEs are provided in Appendix 16.6.2.

12.3.4. Other Significant Adverse Events

Treatment discontinuations due to TEAEs and dose modifications due to TEAEs are listed by subject in Listing 16.2.8.1. Individual subject narratives for treatment discontinuations due to TEAEs are provided in Appendix 16.6.

Two subjects discontinued treatment due to non-SCD-related TEAEs (rash maculo-papular in Period 1 and alanine aminotransferase [ALT] and aspartate aminotransferase [AST] increased in Period 3). The events of ALT and AST increased were assessed as not related to study drug and remained ongoing at the end of study. The rash maculo-papular was previously listed in Section 12.3.3.

Two subjects experienced dose modifications (including dose reductions and dose interruptions) due to non-SCD-related TEAEs. One subject had a dose interruption due to oral pain reported in Period 1, which was not related to study drug. This subject received transfusions of packed RBCs as part of a planned tooth extraction (Listing 16.2.15). The other subject experienced a dose reduction due to ALT and AST increased and lethargy reported in Period 3. These events were all assessed as related to study drug. All four PTs had resolved by the end of study.

12.3.5. Pregnancies

One subject experienced a miscarriage (PT: abortion spontaneous) in Period 1. This event was reported as an SAE and listed in Section 12.3.3.

12.3.6. Narratives of Deaths, Serious Adverse Events, and Other Significant Adverse Events

Individual subject narratives of deaths, SAEs, and TEAEs that led to discontinuation of study drug are provided in Appendix 16.6.

12.4. Clinical Laboratory Evaluation

12.4.1. Listing of Individual Laboratory Measurements by Subject and Each Abnormal Laboratory Value

Individual subject-level data for laboratory values are provided in Listing 16.2.9.1 (hematology), Listing 16.2.9.2 (serum chemistry), Listing 16.2.9.3 (serum erythropoietin), Listing 16.2.9.4 (coagulation), and Listing 16.2.9.5 (urinalysis). A listing of serum and urinalysis pregnancy test results is provided in Listing 16.2.10.

12.4.2. Evaluation of Each Laboratory Parameter

12.4.2.1. Laboratory Values Over Time

Not applicable

12.4.2.2. Individual Subject Changes

Not applicable

12.4.2.3. Individual Clinically Significant Abnormalities

There were 2 subjects who had clinically significant abnormalities in ALT or AST (Listing 16.2.9.2). The first subject had ALT and AST values of 130 U/L and 116 U/L, respectively, during Period 3; the corresponding values at baseline were 121 U/L and 117 U/L, respectively. The second subject had ALT of 157 U/L during Period 1; the corresponding baseline value was 14 U/L. Each of these clinically significant abnormalities was reported as TEAEs (Table 4), and 1 additional subject had TEAEs of ALT and AST increased in Period 3.

No subject had any clinically significant abnormalities in serum erythropoietin (Listing 16.2.9.3), coagulation (Listing 16.2.9.4), or urinalysis results (Listing 16.2.9.5). There was 1 subject who had a clinically significant abnormality in RBC distribution width (RDW); however, this finding occurred during the Screening Period prior to the first dose of study drug (Listing 16.2.9.1).

12.5. Vital Signs and Electrocardiograms

12.5.1. Vital Signs

Individual subject-level data for vital sign results are provided in Listing 16.2.11. No clinically meaningful trends were observed.

12.5.2. Electrocardiogram

Individual subject-level data for electrocardiogram results are provided in Listing 16.2.12. No clinically significant abnormalities were observed.

12.6. Safety Conclusions

- A total of 6 subjects with SCD were treated with at least one dose of study drug across the four planned study periods, consisting of voxelotor cumulative daily dose levels of 1500, 2000, 2500, and 3000 mg. All 6 subjects received voxelotor 1500 mg once daily in Period 1 with a median duration of 8.7 weeks. Subjects in Period 2 (voxelotor cumulative daily dose of 2000 mg) and Period 3 (voxelotor cumulative daily dose of 2500 mg) received study drug for a median duration of 2.9 weeks and 3.0 weeks, respectively. One subject received the highest dose (voxelotor cumulative daily dose of 3000 mg) in Period 4 for 9.0 weeks.
- There were no deaths reported in this study. A total of 5 subjects reported SAEs during the study. Two subjects reported non-SCD-related SAEs (abortion spontaneous and rash maculo-papular), and 4 subjects reported SCD-related SAEs, including sickle cell anaemia with crisis and priapism.
- Two subjects discontinued treatment due to non-SCD-related TEAEs (rash maculo-papular and ALT and AST increased). There were no treatment discontinuations due to SCD-related TEAEs.
- Two subjects experienced dose modifications due to non-SCD-related TEAEs. One subject had a dose interruption due to oral pain. The other subject experienced a dose reduction due to ALT and AST increased and lethargy. There were no dose modifications due to SCD-related TEAEs.
- Most subjects experienced non-SCD-related TEAEs that were Grades 1 to 2 and nonserious. No subjects reported non-SCD-related TEAEs that were higher than Grade 3.
- The most commonly reported non-SCD–related TEAE was diarrhoea. All events of diarrhoea were Grade 1. The most commonly reported SCD–related TEAE was sickle cell anaemia with crisis. Three of these events were Grades 1 to 2, and the other two were Grade 3.
- Voxelotor cumulative daily doses up to 3000 mg were well tolerated by the subjects in this study, and there were no new safety signals. Based on the limited data from this study, the safety profile of voxelotor at cumulative daily doses up to 3000 mg was consistent with the safety profile of the voxelotor 1500 mg once daily dose (Vichinsky, 2018).

13. DISCUSSION AND OVERALL CONCLUSIONS

13.1. Discussion

This study was designed to assess the safety, tolerability, PK, and PD of voxelotor dose levels greater than 1500 mg daily and to compare these results to the 1500 mg dose. Due to issues with enrollment impacted by the COVID-19 pandemic, the decision to terminate the conduct of this study was made by the Sponsor. A total of 6 subjects were enrolled and treated in this study. Voxelotor at daily doses ranging from 1500 to 3000 mg was well tolerated by all 6 subjects.

13.2. Conclusions

Based on the limited data from this study, the safety profile of voxelotor at cumulative daily doses up to 3000 mg was consistent with the safety profile of the voxelotor 1500 mg once daily dose (Vichinsky, 2018).

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1. Demographic Data Summary Figures and Tables

Not applicable

14.2. Efficacy Data Summary Figures and Tables

Not applicable

14.3. Safety Data Summary Figures and Tables

Table 14.1	Study Drug Exposure (Safety Population)
Table 14.3.1.1.1	Overview of Non-SCD-related Treatment-emergent Adverse Events and Serious Adverse Events (Safety Population)
Table 14.3.1.1.2	Overview of SCD-related Treatment-emergent Adverse Events and Serious Adverse Events (Safety Population)
Table 14.3.1.2.1	Non-SCD-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (Safety Population)
Table 14.3.1.2.2	SCD-related Treatment-emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (Safety Population)
Table 14.3.1.3.1	Non-SCD-related Treatment-emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term, and Maximum Severity (Safety Population)
Table 14.3.1.3.2	SCD-related Treatment-emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity (Safety Population)

14.3.1. Displays of Adverse Events

See Section 12.2.1.1.

14.3.2. Listings of Deaths, Other Serious, and Significant Adverse Events

See Section 12.3.1.

14.3.3. Narratives of Deaths, Other Serious, and Certain Other Significant Adverse Events

Individual subject narratives of deaths, SAEs, and TEAEs that led to discontinuation of study drug are provided in Appendix 16.6.

14.3.4. Abnormal Laboratory Value Listing

See Section 12.4.1.

Table 14.1
Study Drug Exposure
Safety Population

	1500 mg (N=6)	2000 mg (N=4)	2500 mg (N=3)	3000 mg (N=1)
Duration of Exposure (weeks)				
N	6	4	3	1
Mean (SD)	6.5 (3.54)	2.9 (0.07)	5.2 (4.00)	9.0
Median	8.7	2.9	3.0	9.0
Min, Max	1.9, 8.9	2.9, 3.0	2.9, 9.9	9.0, 9.0
Q1, Q3	2.0, 8.9	2.9, 2.9	2.9, 9.9	9.0, 9.0

Table 14.3.1.1.1
Overview of Non-SCD-Related Treatment-Emergent Adverse Events and Serious Adverse Events
Safety Population

	1500 mg (N=6)	2000 mg (N=4)	2500 mg (N=3)	3000 mg (N=1)
Number of TEAEs	37	7	7	1
Number of subjects with at least 1 TEAE	6(100.0%)	4(100.0%)	2(66.7%)	1(100.0%)
Number of TEAEs ≥ Grade 3	2	0	0	0
Number of subjects with at least 1 TEAE ≥ Grade 3	2(33.3%)	0	0	0
Number of related TEAEs	12	2	4	0
Number of subjects with at least 1 related TEAE	5(83.3%)	2(50.0%)	1(33.3%)	0
Number of TEAEs leading to study dose reduction	0	0	3	0
Number of subjects having study dose reduction due to TEAE	0	0	1(33.3%)	0
Number of TEAEs leading to study drug interruption	1	0	0	0
Number of subjects having study drug interrupted due to TEAE	1(16.7%)	0	0	0
Number of TEAEs leading to study drug discontinuation	1	0	2	0
Number of subjects having study drug permanently discontinued due to TEAE	1(16.7%)	0	1(33.3%)	0
Number of SAEs	2	0	0	0
Number of subjects with at least 1 SAE	2(33.3%)	0	0	0
Number of related SAEs	1	0	0	0
Number of subjects with at least 1 related SAE	1(16.7%)	0	0	0
Deaths	0	0	0	0

SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects may be counted in more than one row. Summary excludes SCD related events.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_oae_nscd.sas Date/time of run: 29SEP2021:05:09:46
Final Data Transfer: 14JUL2021

Table 14.3.1.1.2
Overview of SCD-Related Treatment-Emergent Adverse Events and Serious Adverse Events
Safety Population

	1500 mg (N=6)	2000 mg (N=4)	2500 mg (N=3)	3000 mg (N=1)
Number of TEAEs	11	1	2	0
Number of subjects with at least 1 TEAE	5(83.3%)	1(25.0%)	1(33.3%)	0
Number of TEAEs ≥ Grade 3	4	0	0	0
Number of subjects with at least 1 TEAE ≥ Grade 3	3(50.0%)	0	0	0
Number of related TEAEs	0	0	0	0
Number of subjects with at least 1 related TEAE	0	0	0	0
Number of TEAEs leading to study dose reduction	0	0	0	0
Number of subjects having study dose reduction due to TEAE	0	0	0	0
Number of TEAEs leading to study drug interruption	0	0	0	0
Number of subjects having study drug interrupted due to TEAE	0	0	0	0
Number of TEAEs leading to study drug discontinuation	0	0	0	0
Number of subjects having study drug permanently discontinued due to TEAE	0	0	0	0
Number of SAEs	4	0	2	0
Number of subjects with at least 1 SAE	3(50.0%)	0	1(33.3%)	0
Number of related SAEs	0	0	0	0
Number of subjects with at least 1 related SAE	0	0	0	0
Deaths	0	0	0	0

SAE = serious adverse event; TEAE = treatment-emergent adverse event.
Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects may be counted in more than one row. Summary includes SCD related events.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_oae_scd.sas Date/time of run: 29SEP2021:05:09:46
Final Data Transfer: 14JUL2021

Table 14.3.1.2.1
Non-SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	1500 mg (N=6) All Grades	Grade 1	Grade 2	Grade 3 [a]
Number of subjects with at least one event	6 (100.0%)	1 (16.7%)	3 (50.0%)	2 (33.3%)
Musculoskeletal and connective tissue disorders	2 (33.3%)	2 (33.3%)	0	0
Pain in extremity	0	0	0	0
Arthralgia	0	0	0	0
Back pain	2 (33.3%)	2 (33.3%)	0	0
Coccydynia	0	0	0	0
Gastrointestinal disorders	6 (100.0%)	4 (66.7%)	2 (33.3%)	0
Abdominal discomfort	0	0	0	0
Abdominal distension	1 (16.7%)	1 (16.7%)	0	0
Abdominal pain upper	2 (33.3%)	2 (33.3%)	0	0
Constipation	2 (33.3%)	1 (16.7%)	1 (16.7%)	0
Dental caries	1 (16.7%)	0	1 (16.7%)	0
Diarrhoea	4 (66.7%)	4 (66.7%)	0	0
Dry mouth	1 (16.7%)	1 (16.7%)	0	0
Nausea	2 (33.3%)	1 (16.7%)	1 (16.7%)	0
Oral pain	1 (16.7%)	0	1 (16.7%)	0
Rectal haemorrhage	1 (16.7%)	1 (16.7%)	0	0
Vomiting	1 (16.7%)	1 (16.7%)	0	0
General disorders and administration site conditions	2 (33.3%)	1 (16.7%)	1 (16.7%)	0
Fatigue	2 (33.3%)	1 (16.7%)	1 (16.7%)	0
Influenza like illness	1 (16.7%)	0	1 (16.7%)	0
Malaise	1 (16.7%)	1 (16.7%)	0	0
Non-cardiac chest pain	1 (16.7%)	1 (16.7%)	0	0
Infections and infestations	2 (33.3%)	1 (16.7%)	1 (16.7%)	0
Conjunctivitis	1 (16.7%)	1 (16.7%)	0	0
Tonsillitis	1 (16.7%)	0	1 (16.7%)	0
Upper respiratory tract infection	1 (16.7%)	1 (16.7%)	0	0
Urinary tract infection	1 (16.7%)	0	1 (16.7%)	0
Investigations	1 (16.7%)	1 (16.7%)	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_nscd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.1
Non-SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

	1500 mg (N=6)			
System Organ Class Preferred Term	All Grades	Grade 1	Grade 2	Grade 3 [a]
Alanine aminotransferase increased	1 (16.7%)	1 (16.7%)	0	0
Aspartate aminotransferase increased	0	0	0	0
Nervous system disorders	1 (16.7%)	1 (16.7%)	0	0
Headache	1 (16.7%)	1 (16.7%)	0	0
Lethargy	0	0	0	0
Pregnancy, puerperium and perinatal conditions	1 (16.7%)	0	0	1 (16.7%)
Abortion spontaneous	1 (16.7%)	0	0	1 (16.7%)
Skin and subcutaneous tissue disorders	2 (33.3%)	0	1 (16.7%)	1 (16.7%)
Dry skin	1 (16.7%)	0	0	1 (16.7%)
Pruritus allergic	1 (16.7%)	0	1 (16.7%)	0
Rash maculo-papular	1 (16.7%)	0	1 (16.7%)	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_nscd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.1
Non-SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	2000 mg (N=4) All Grades	Grade 1	Grade 2	Grade 3 [a]
Number of subjects with at least one event	4 (100.0%)	2 (50.0%)	2 (50.0%)	0
Musculoskeletal and connective tissue disorders	2 (50.0%)	0	2 (50.0%)	0
Pain in extremity	1 (25.0%)	0	1 (25.0%)	0
Arthralgia	1 (25.0%)	0	1 (25.0%)	0
Back pain	0	0	0	0
Coccydynia	1 (25.0%)	0	1 (25.0%)	0
Gastrointestinal disorders	1 (25.0%)	1 (25.0%)	0	0
Abdominal discomfort	1 (25.0%)	1 (25.0%)	0	0
Abdominal distension	0	0	0	0
Abdominal pain upper	0	0	0	0
Constipation	0	0	0	0
Dental caries	0	0	0	0
Diarrhoea	0	0	0	0
Dry mouth	0	0	0	0
Nausea	0	0	0	0
Oral pain	0	0	0	0
Rectal haemorrhage	0	0	0	0
Vomiting	0	0	0	0
General disorders and administration site conditions	0	0	0	0
Fatigue	0	0	0	0
Influenza like illness	0	0	0	0
Malaise	0	0	0	0
Non-cardiac chest pain	0	0	0	0
Infections and infestations	1 (25.0%)	1 (25.0%)	0	0
Conjunctivitis	0	0	0	0
Tonsillitis	0	0	0	0
Upper respiratory tract infection	0	0	0	0
Urinary tract infection	1 (25.0%)	1 (25.0%)	0	0
Investigations	0	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_nscd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.1
Non-SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

	2000 mg (N=4)			
System Organ Class Preferred Term	All Grades	Grade 1	Grade 2	Grade 3 [a]
Alanine aminotransferase increased	0	0	0	0
Aspartate aminotransferase increased	0	0	0	0
Nervous system disorders	2 (50.0%)	2 (50.0%)	0	0
Headache	2 (50.0%)	2 (50.0%)	0	0
Lethargy	0	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	0	0
Abortion spontaneous	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0
Dry skin	0	0	0	0
Pruritus allergic	0	0	0	0
Rash maculo-papular	0	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_nscd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.1
Non-SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	2500 mg (N=3) All Grades	Grade 1	Grade 2	Grade 3 [a]
Number of subjects with at least one event	2 (66.7%)	0	2 (66.7%)	0
Musculoskeletal and connective tissue disorders	0	0	0	0
Pain in extremity	0	0	0	0
Arthralgia	0	0	0	0
Back pain	0	0	0	0
Coccydynia	0	0	0	0
Gastrointestinal disorders	1 (33.3%)	1 (33.3%)	0	0
Abdominal discomfort	0	0	0	0
Abdominal distension	0	0	0	0
Abdominal pain upper	0	0	0	0
Constipation	0	0	0	0
Dental caries	0	0	0	0
Diarrhoea	0	0	0	0
Dry mouth	1 (33.3%)	1 (33.3%)	0	0
Nausea	0	0	0	0
Oral pain	0	0	0	0
Rectal haemorrhage	0	0	0	0
Vomiting	0	0	0	0
General disorders and administration site conditions	0	0	0	0
Fatigue	0	0	0	0
Influenza like illness	0	0	0	0
Malaise	0	0	0	0
Non-cardiac chest pain	0	0	0	0
Infections and infestations	0	0	0	0
Conjunctivitis	0	0	0	0
Tonsillitis	0	0	0	0
Upper respiratory tract infection	0	0	0	0
Urinary tract infection	0	0	0	0
Investigations	2 (66.7%)	0	2 (66.7%)	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_nscd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.1
Non-SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	2500 mg (N=3) All Grades	Grade 1	Grade 2	Grade 3 [a]
Alanine aminotransferase increased	2 (66.7%)	0	2 (66.7%)	0
Aspartate aminotransferase increased	2 (66.7%)	0	2 (66.7%)	0
Nervous system disorders	1 (33.3%)	0	1 (33.3%)	0
Headache	1 (33.3%)	0	1 (33.3%)	0
Lethargy	1 (33.3%)	0	1 (33.3%)	0
Pregnancy, puerperium and perinatal conditions	0	0	0	0
Abortion spontaneous	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0
Dry skin	0	0	0	0
Pruritus allergic	0	0	0	0
Rash maculo-papular	0	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_nscd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.1
Non-SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	3000 mg (N=1) All Grades	Grade 1	Grade 2	Grade 3 [a]
Number of subjects with at least one event	1 (100.0%)	0	1 (100.0%)	0
Musculoskeletal and connective tissue disorders	1 (100.0%)	0	1 (100.0%)	0
Pain in extremity	1 (100.0%)	0	1 (100.0%)	0
Arthralgia	0	0	0	0
Back pain	0	0	0	0
Coccydynia	0	0	0	0
Gastrointestinal disorders	0	0	0	0
Abdominal discomfort	0	0	0	0
Abdominal distension	0	0	0	0
Abdominal pain upper	0	0	0	0
Constipation	0	0	0	0
Dental caries	0	0	0	0
Diarrhoea	0	0	0	0
Dry mouth	0	0	0	0
Nausea	0	0	0	0
Oral pain	0	0	0	0
Rectal haemorrhage	0	0	0	0
Vomiting	0	0	0	0
General disorders and administration site conditions	0	0	0	0
Fatigue	0	0	0	0
Influenza like illness	0	0	0	0
Malaise	0	0	0	0
Non-cardiac chest pain	0	0	0	0
Infections and infestations	0	0	0	0
Conjunctivitis	0	0	0	0
Tonsillitis	0	0	0	0
Upper respiratory tract infection	0	0	0	0
Urinary tract infection	0	0	0	0
Investigations	0	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_nscd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.1
Non-SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

	3000 mg (N=1)			
System Organ Class Preferred Term	All Grades	Grade 1	Grade 2	Grade 3 [a]
Alanine aminotransferase increased	0	0	0	0
Aspartate aminotransferase increased	0	0	0	0
Nervous system disorders	0	0	0	0
Headache	0	0	0	0
Lethargy	0	0	0	0
Pregnancy, puerperium and perinatal conditions	0	0	0	0
Abortion spontaneous	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	0	0
Dry skin	0	0	0	0
Pruritus allergic	0	0	0	0
Rash maculo-papular	0	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_nscd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.2
SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	1500 mg (N=6) All Grades	Grade 1	Grade 2	Grade 3 [a]
Number of subjects with at least one event	5 (83.3%)	1 (16.7%)	1 (16.7%)	3 (50.0%)
Blood and lymphatic system disorders	5 (83.3%)	1 (16.7%)	2 (33.3%)	2 (33.3%)
Sickle cell anaemia with crisis	5 (83.3%)	1 (16.7%)	2 (33.3%)	2 (33.3%)
Reproductive system and breast disorders	1 (16.7%)	0	0	1 (16.7%)
Priapism	1 (16.7%)	0	0	1 (16.7%)

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary includes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_scd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.2
SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

	2000 mg (N=4)			
System Organ Class Preferred Term	All Grades	Grade 1	Grade 2	Grade 3 [a]
Number of subjects with at least one event	1 (25.0%)	0	1 (25.0%)	0
Blood and lymphatic system disorders	1 (25.0%)	0	1 (25.0%)	0
Sickle cell anaemia with crisis	1 (25.0%)	0	1 (25.0%)	0
Reproductive system and breast disorders	0	0	0	0
Priapism	0	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary includes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_scd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.2
SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	2500 mg (N=3) All Grades	Grade 1	Grade 2	Grade 3 [a]
Number of subjects with at least one event	1 (33.3%)	0	1 (33.3%)	0
Blood and lymphatic system disorders	1 (33.3%)	0	1 (33.3%)	0
Sickle cell anaemia with crisis	1 (33.3%)	0	1 (33.3%)	0
Reproductive system and breast disorders	0	0	0	0
Priapism	0	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary includes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_scd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.2.2
SCD-Related Treatment-Emergent Adverse Events by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	3000 mg (N=1) All Grades	 Grade 1	 Grade 2	 Grade 3 [a]
Number of subjects with at least one event	0	0	0	0
Blood and lymphatic system disorders	0	0	0	0
Sickle cell anaemia with crisis	0	0	0	0
Reproductive system and breast disorders	0	0	0	0
Priapism	0	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary includes SCD related events.
[a] No adverse events reported were greater than Grade 3.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teae_scd.sas Date/time of run: 29SEP2021:05:09:47
Final Data Transfer: 14JUL2021

Table 14.3.1.3.1
Non-SCD-Related Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	1500 mg (N=6) All Grades	 Grade 1	 Grade 2 [a]
Number of subjects with at least one event	5 (83.3%)	3 (50.0%)	2 (33.3%)
Gastrointestinal disorders	4 (66.7%)	4 (66.7%)	0
Abdominal discomfort	0	0	0
Abdominal distension	1 (16.7%)	1 (16.7%)	0
Abdominal pain upper	1 (16.7%)	1 (16.7%)	0
Diarrhoea	3 (50.0%)	3 (50.0%)	0
Dry mouth	1 (16.7%)	1 (16.7%)	0
Nausea	1 (16.7%)	1 (16.7%)	0
Infections and infestations	2 (33.3%)	1 (16.7%)	1 (16.7%)
Conjunctivitis	1 (16.7%)	1 (16.7%)	0
Tonsillitis	1 (16.7%)	0	1 (16.7%)
Investigations	0	0	0
Alanine aminotransferase increased	0	0	0
Aspartate aminotransferase increased	0	0	0
Nervous system disorders	1 (16.7%)	1 (16.7%)	0
Headache	1 (16.7%)	1 (16.7%)	0
Lethargy	0	0	0
Skin and subcutaneous tissue disorders	1 (16.7%)	0	1 (16.7%)
Rash maculo-papular	1 (16.7%)	0	1 (16.7%)

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 2.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teaer_nscd.sas Date/time of run: 29SEP2021:05:09:48
Final Data Transfer: 14JUL2021

Table 14.3.1.3.1
Non-SCD-Related Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	2000 mg (N=4) All Grades	 Grade 1	 Grade 2 [a]
Number of subjects with at least one event	2 (50.0%)	2 (50.0%)	0
Gastrointestinal disorders	1 (25.0%)	1 (25.0%)	0
Abdominal discomfort	1 (25.0%)	1 (25.0%)	0
Abdominal distension	0	0	0
Abdominal pain upper	0	0	0
Diarrhoea	0	0	0
Dry mouth	0	0	0
Nausea	0	0	0
Infections and infestations	0	0	0
Conjunctivitis	0	0	0
Tonsillitis	0	0	0
Investigations	0	0	0
Alanine aminotransferase increased	0	0	0
Aspartate aminotransferase increased	0	0	0
Nervous system disorders	1 (25.0%)	1 (25.0%)	0
Headache	1 (25.0%)	1 (25.0%)	0
Lethargy	0	0	0
Skin and subcutaneous tissue disorders	0	0	0
Rash maculo-papular	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 2.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teaer_nscd.sas Date/time of run: 29SEP2021:05:09:48
Final Data Transfer: 14JUL2021

Table 14.3.1.3.1
Non-SCD-Related Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term	2500 mg (N=3) All Grades	 Grade 1	 Grade 2 [a]
Number of subjects with at least one event	1 (33.3%)	0	1 (33.3%)
Gastrointestinal disorders	0	0	0
Abdominal discomfort	0	0	0
Abdominal distension	0	0	0
Abdominal pain upper	0	0	0
Diarrhoea	0	0	0
Dry mouth	0	0	0
Nausea	0	0	0
Infections and infestations	0	0	0
Conjunctivitis	0	0	0
Tonsillitis	0	0	0
Investigations	1 (33.3%)	0	1 (33.3%)
Alanine aminotransferase increased	1 (33.3%)	0	1 (33.3%)
Aspartate aminotransferase increased	1 (33.3%)	0	1 (33.3%)
Nervous system disorders	1 (33.3%)	0	1 (33.3%)
Headache	1 (33.3%)	0	1 (33.3%)
Lethargy	1 (33.3%)	0	1 (33.3%)
Skin and subcutaneous tissue disorders	0	0	0
Rash maculo-papular	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 2.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teaer_nscd.sas Date/time of run: 29SEP2021:05:09:48
Final Data Transfer: 14JUL2021

Table 14.3.1.3.1
Non-SCD-Related Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity
Safety Population

	3000 mg (N=1)		
System Organ Class Preferred Term	All Grades	Grade 1	Grade 2 [a]
Number of subjects with at least one event	0	0	0
Gastrointestinal disorders	0	0	0
Abdominal discomfort	0	0	0
Abdominal distension	0	0	0
Abdominal pain upper	0	0	0
Diarrhoea	0	0	0
Dry mouth	0	0	0
Nausea	0	0	0
Infections and infestations	0	0	0
Conjunctivitis	0	0	0
Tonsillitis	0	0	0
Investigations	0	0	0
Alanine aminotransferase increased	0	0	0
Aspartate aminotransferase increased	0	0	0
Nervous system disorders	0	0	0
Headache	0	0	0
Lethargy	0	0	0
Skin and subcutaneous tissue disorders	0	0	0
Rash maculo-papular	0	0	0

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary excludes SCD related events.
[a] No adverse events reported were greater than Grade 2.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teaer_nscd.sas Date/time of run: 29SEP2021:05:09:48
Final Data Transfer: 14JUL2021

Table 14.3.1.3.2
SCD-Related Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class, Preferred Term and Maximum Severity
Safety Population

System Organ Class Preferred Term

No data available

Note: Adverse events were coded using MedDRA version 24.0. NCI-CTCAE version 4.03 was used to determine grade. Only TEAEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of study drug are included.
Subjects were counted only once for each Preferred Term. Summary includes SCD related events.
Source: Repository/gbt440/scd/gbt440_029/csr/qc/programs/t_teaer_scd.sas Date/time of run: 29SEP2021:05:09:49
Final Data Transfer: 14JUL2021

15. REFERENCE LIST

Ataga KI. New and experimental agents for sickle cell disease. Clin Adv Hematol Oncol. 2018;16(7):476-9.

E.R. Squibb & Sons, L.L.C. (2018). Droxia® (hydroxyurea) Prescribing Information. Plainsboro, NJ.

Emmaus Medical Inc (2018). ENDARITM (L-glutamine oral powder) Prescribing Information. Torrance, CA.

Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med. 2004;350(9):886-95.

Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primers. 2018;15(4):18010.

Lanzkron S, Carroll CP, Haywood C Jr. Mortality rates and age at death from sickle cell disease: U.S., 1979-2005. Public Health Rep. 2013;128(2):110-6.

Novartis (2019). Advakeo® (crizanlizumab) Prescribing Information. East Hanover, NJ.

Ohene-Frempong K, Weiner SJ, Sleeper LA, Miller ST, Embury S, Moohr JW, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. Blood. 1998;91:288-94.

Powars DR, Chan LS, Hiti A, Ramicone E, Johnson C. Outcome of sickle cell anemia: a 4-decade observational study of 1056 patients. Medicine (Baltimore). 2005;84(6):363-76.

Powars DR, Elliott-Mills DD, Chan L, Niland J, Hiti AL, Opas LM, et al. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. Ann Intern Med. 1991;115(8):614-20.

Smith WR, Jordan LB, Hassell KL. Frequently asked questions by hospitalists managing pain in adults with sickle cell disease. J Hosp Med. 2011;6(5):297-303.

Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, Kutlar A, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA. 2003;289(13):1645-51.

Taylor JG, Nolan VG, Mendelsohn L, Kato GJ, Gladwin MT, Steinberg MH. Chronic hyper-hemolysis in sickle cell anemia: association of vascular complications and mortality with less frequent vasoocclusive pain. PLoS One. 2008;3(5):e2095.

Vichinsky E, Hoppe C, Howard J, Ataga KI, Nduba V, El-Beshlawy A, et al. Results from Part A of the Hemoglobin Oxygen Affinity Modulation to Inhibit HbS Polymerization (HOPE) Trial (GBT440-031), a placebo-controlled randomized study evaluating voxelotor (GBT440) in adults and adolescents with sickle cell disease. Blood. 2018;132(Suppl 1):505.

16. APPENDICES

16.1. Study Information

16.1.1. Protocol and Protocol Amendments

16.1.1.1. Protocol Amendment 2.0 – 05 October 2020

16.1.1.2. Protocol Amendment 1.0 – 13 September 2019

16.1.1.3. Original Protocol – 11 July 2019

16.1.1.4. Summary of Changes for All Amendments

16.1.1.4.1. Summary of Changes for Amendment 2.0 – 05 October 2020

16.1.1.4.2. Summary of Changes for Amendment 1.0 – 13 September 2019

16.1.2. Sample Case Report Form

16.1.3. List of Independent Ethics Committees or Institutional Review Boards and Representative Written Information for Subject and Sample Consent Forms

Not applicable

16.1.4. List and Description of Investigators and Other Important Participants in the Study

16.1.5. Signatures of Principal or Coordinating Investigator(s) or Sponsor's Responsible Medical Officer

16.1.6. Listing of Subjects Receiving Test Drug(s)/Investigational Product(s) From Specific Batches

Available upon request

16.1.7. Randomization Scheme and Codes

Not applicable

16.1.8. Audit Certificates

Not applicable

16.1.9. Documentation of Statistical Methods

Not applicable

16.1.10. Documentation of Inter-laboratory Standardization Methods and Quality Assurance Procedures if Used

Not applicable

16.1.11. Publications Based on the Study

Not applicable

16.1.12. Important Publications Referenced in the Report

Not applicable

16.2. Subject Data Listings

Listing 16.2.1 Eligibility and Enrollment (Screen Failures)

Listing 16.2.2 Demographics (Safety Population)

Listing 16.2.3 Baseline Characteristics (Safety Population)

Listing 16.2.4 Sickle Cell Disease History (Safety Population)

Listing 16.2.5 Sickle Cell Disease Complications (Safety Population)

Listing 16.2.6 Other Medical History (Safety Population)

Listing 16.2.7 End of Treatment, Subject Follow-up, and Termination from Study (Safety Population)

Listing 16.2.8.1 Adverse Events (Safety Population)

Listing 16.2.8.2 Serious Adverse Events (Safety Population)

Listing 16.2.9.1 Hematology – Laboratory Result (Safety Population)

Listing 16.2.9.2 Serum Chemistry – Laboratory Result (Safety Population)

Listing 16.2.9.3 Serum Erythropoietin – Laboratory Result (Safety Population)

Listing 16.2.9.4 Coagulation Results – Laboratory Result (Safety Population)

Listing 16.2.9.5 Urinalysis Results – Laboratory Result (Safety Population)

Listing 16.2.10 Pregnancy Test Results (Safety Population)

Listing 16.2.11 Vital Signs (Safety Population)

Listing 16.2.12 12-Lead Electrocardiogram (Safety Population)

Listing 16.2.13 Important Protocol Deviations (Safety Population)

Listing 16.2.14 Concomitant Medications (Safety Population)

Listing 16.2.15 Transfusions (Safety Population)

Listing 16.2.16 Study Drug Administration (Safety Population)

16.3. Case Report Forms

16.4. Individual Subject Data Listings (US Archival Listings)

Available upon request

16.5. Other Documents Pertaining to the Study

16.5.1. Bioanalytical Reports

16.6. Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

16.6.1. Narratives of Deaths

Not applicable

16.6.2. Narratives of Serious Adverse Events

16.6.3. Narratives of Adverse Events Leading to Discontinuation of Study Drug