CLINICAL STUDY REPORT SYNOPSIS

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
Study Number:	GBT440-042 (C5341026)
Study Phase:	3
Regulatory Agency or Public Disclosure Identifier Number:	ClinicalTrials.gov ID: NCT05561140
Pediatric Investigational Plan Number:	Not Applicable
Study Intervention:	Voxelotor (PF-06759497, GBT440)
Trade Name	Oxbryta
Indication:	Leg ulcer
Study Sponsor:	Global Blood Therapeutics, Inc., a wholly owned subsidiary of Pfizer, Inc.
Study Initiation Date (FPFV):	30 May 2022
Primary Completion Date (PCD):	26 June 2024
Presentation of data in this CSR synopsis based on: **Study Completion (LPLV) Date:**	22 October 2024
Early Termination Status	As of 25 September 2024, this study was terminated by the sponsor because the benefit-risk balance of voxelotor was no longer favorable upon the sponsor's review of the totality of clinical data and real-world evidence data.
CSR Version and Report Date:	**Document Version** / **Report Date** Interim PCD CSR Version 1.0 / 28 February 2025 Interim PCD CSR (amendment to 28 February 2025) Version 2.0 / 24 March 2025 Final LPLV CSR Version 1.0 / 08 May 2025 Final LPLV CSR (amendment to 08 May 2025) Version 2.0 / 25 July 2025

GOOD CLINICAL PRACTICE STATEMENT

CLINICAL STUDY REPORT SYNOPSIS

This study was conducted in compliance with GCP guidelines and, where applicable, local country regulations relevant to the use of new therapeutic agents in the country/countries of conduct, including the archiving of essential documents.

CLINICAL STUDY REPORT SYNOPSIS

Number of Study Center(s) and Investigator(s):

A total of 206 participants were screened at 17 centers in 3 countries, and 88 participants were randomized at 16 centers. A list of study centers and investigators involved in this study is provided in Appendix 16.1.4.1.

Publications: None.

Brief Description of the Trial Design and Methodology:

This study was a Phase 3, multicenter, randomized, placebo-controlled study to evaluate the efficacy of voxelotor and standard of care (SOC) for the treatment of leg ulcers in participants with sickle cell disease (SCD). The study was divided into 5 study periods: Screening, Run-in, blinded Randomized Treatment, Open-Label Treatment, and Follow-up/End of Study (Figure S1).

After the Screening Period, participants entered a 2-week Run-in Period (Day -14 to Day -1 [+3 days]), during which assessments, including target leg ulcer surface area measurements by digital photography were conducted and SOC was initiated per protocol, following best practices.

After completion of Run-in period, eligible participants were stratified, at the time of randomization (Day 1), by target ulcers(s) size (<8 cm^2 versus ≥8 cm^2) and duration (<9 weeks versus ≥9 weeks) at presentation to evenly balance factors known to affect the likelihood of healing. For participants with >1 target ulcer, stratification was based on the total target ulcer surface area (ie, sum of all target ulcer surface areas) and longest duration of any individual target ulcer(s) present.

The Randomized Treatment Period was 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) was/were assessed by visual inspection and surface area measurement(s) using digital photography at scheduled visits every 2 weeks during the 12-week Randomized Treatment Period. Target ulcer resolution was defined as skin re-epithelialization confirmed at 2 consecutive study visits 2 weeks apart. To qualify as an event, ulcer re-epithelialization that was first assessed at Week 12 must be confirmed at Week 14. Participants demonstrating initial ulcer re-epithelialization at Week 12 continued treatment in their assigned treatment group for an additional 2 weeks to confirm ulcer resolution.

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) received open-label voxelotor 1500 mg once a day (QD) and SOC for a minimum 12 weeks and target ulcer(s) that had failed to heal during the initial 12 weeks was/were followed for delayed healing.

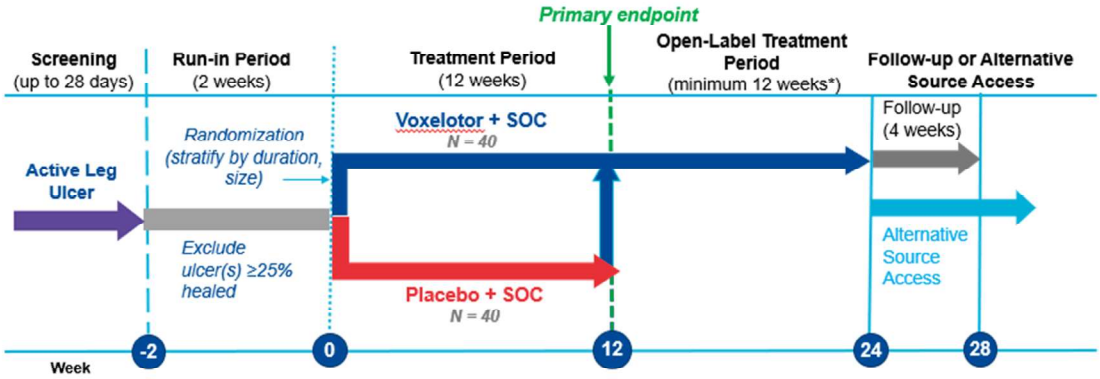
Participants who had completed 12 weeks in the Open-Label Treatment Period might continue to receive voxelotor as long as they continued to receive clinical benefit that outweighed risk as determined by the investigator or until the participant had access to voxelotor from an alternative source not associated with this protocol (eg, through a clinical Open-Label Extension [OLE] study sponsored by Pfizer, commercialization of the product,

CLINICAL STUDY REPORT SYNOPSIS

or a managed access program). Participants who planned not to continue to receive voxelotor from an alternative source continued to the follow-up period after completing 12 weeks in the Open-Label Treatment Period.

This report provides full data of efficacy and safety for all the treated participants at the end of study, ie, last participant last visit (LPLV).

Figure S1: Study Schema



* Participants who had completed 12 weeks in the Open-Label Treatment Period might continue to receive voxelotor as long as they continued to receive clinical benefit that outweighed risk as determined by the investigator or until the participant had access to voxelotor from an alternative source (eg, through a clinical OLE study sponsored by the sponsor, commercialization of the product, or a managed access program). Participants who did 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.

Number of Participants (planned and analyzed):

Approximately 80 participants were planned and a total of 88 participants were randomized and treated.

Two analysis sets were predefined for the study: intent-to-treat (ITT) population, which included all randomized participants; and safety-evaluable population, which included all randomized participants who received at least one dose of study intervention.

All of the 88 randomized participants were treated, and thus included in both the ITT and safety-evaluable populations.

Diagnosis and Main Criteria for Inclusion and Exclusion:

This study enrolled male or female participants aged ≥12 years, with documented diagnosis of SCD (sickle hemoglobin with 2 sickle cell genes [HbSS], sickle hemoglobin and one beta thalassemia gene [HbS/β^0] thalassemia) and with at least 1 cutaneous ulcer on the lower extremity (leg, ankle, or dorsum of foot) that had lasted for ≥2 weeks and <6 months as of Screening, and of >2 cm^2 size prior to randomization (Day 1).

CLINICAL STUDY REPORT SYNOPSIS

Study Intervention:

During the Randomized Treatment Period, participants were randomized in a 1:1 ratio to receive voxelotor 1500 mg QD (500 mg ×3 tablets) or matching placebo orally administered for 12 weeks. During the Open-Label Treatment Period, all participants received voxelotor 1500 mg QD (500 mg ×3 tablets) for a minimum of 12 weeks. In this study, all participants received the SOC per protocol for SCD leg ulcers during the Run-in, Randomized Treatment, and Open-Label Treatment periods.

The manufacturing lot numbers for the study intervention(s) dispensed in this study are provided in Table S1.

Table S1. Study Intervention(s) Administered

Investigational Product Description	Vendor Lot No.	Pfizer Lot No.	Strength/Potency	Dosage Form
Voxelotor	4339753	NA	500 mg	Tablet
Placebo	CGSWG	NA	0 mg	Tablet
Voxelotor (Open-label)	CFTDG	NA	500 mg	Tablet
Voxelotor (Open-label)	CNZWP	NA	500 mg	Tablet
Voxelotor	CDVSW	NA	500 mg	Tablet
Placebo	CFDWK	NA	0 mg	Tablet
Voxelotor	CFTDT	NA	500 mg	Tablet
Placebo	CFDSM	NA	0 mg	Tablet
Voxelotor (Open-label)	4339753	NA	500 mg	Tablet
Voxelotor (Open-label)	4079299	NA	500 mg	Tablet

Abbreviation: NA = not applicable

Global Substantial Modifications

Not applicable.

Global Interruptions and Re-starts

On 10 May 2024, the administration of the study intervention, voxelotor, was voluntarily paused by Pfizer (the sponsor) due to the overall number of fatal events observed in the study which required further assessment of accrued data.

On 25 September 2024, voxelotor was voluntarily withdrawn by Pfizer from all markets in which it was approved, and all ongoing voxelotor clinical studies and early access and compassionate use programs have been discontinued.

CLINICAL STUDY REPORT SYNOPSIS

Endpoints and Statistical Methods:

Table S2. Statistical Analyses and Methods

Objective	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
Primary					
Characterize the effect of voxelotor and SOC compared to placebo and SOC on leg ulcer healing in participants ≥12 years of age with SCD by Week 12	The status of participants achieving resolution of the target ulcer(s) by Week 12.	Primary efficacy analysis	ITT	Participants who had lost to follow-up or otherwise had dropped out of the study without confirmation of resolution of all target study ulcer(s) prior to Week 12, were classified as non-responders.	Exact Cochran-Mantel-Haenszel (CMH) test with stratification factors of target ulcer size and duration.
Secondary					
Characterize the effect of voxelotor and SOC compared to placebo and SOC on secondary endpoints	Time (in days) to resolution of target ulcer(s) up to Week 12.	Secondary efficacy analysis	ITT	For participants who had not had the last target ulcer confirmed resolved by Week 12 or who had discontinued from study, the time to resolution was censored.	• Kaplan-Meier method (product-limit estimates) and estimated survival curves were displayed graphically when appropriate. Graphs described the number of participants at risk over time. • A stratified log-rank test with stratification factors was performed to test for differences between the voxelotor and placebo treatment groups.

CLINICAL STUDY REPORT SYNOPSIS

Table S2. Statistical Analyses and Methods

Objective	Endpoints	Analysis Type	Analysis Population	Data Inclusion and Rules for Handling Intercurrent Events and Missing Data	Analysis Model
	Change from baseline in total surface area of target ulcer(s) at Week 12			NA	• Mixed model repeated measures (MMRM) analysis with the stratification factors including target ulcer size (categorical) and target ulcer duration (categorical) as covariates. • The p-value for least squared (LS) means difference (voxelotor versus placebo) at Week 12 was provided.
	Incidence of new ulcers by Week 12				Exact CMH test with stratification factors of target ulcer size and duration.
Safety					
Assess the safety and tolerability of voxelotor compared to placebo	• Adverse events (AEs) • Clinical laboratory tests • Physical examinations • Vital signs • Other clinical measures (eg, discontinuation due to AEs, dose reductions)	Safety analysis	Safety-evaluable	NA	Descriptive statistics.

CLINICAL STUDY REPORT SYNOPSIS

SUMMARY OF RESULTS:

Participant Disposition

Of the 206 participants screened, 88 were randomized and treated, including 43 in the placebo group and 45 in the voxelotor group. Of these participants, 79 (89.8%) were in Africa (62 [70.5%] in Kenya and 17 [19.3%] in Nigeria), and 9 (10.2%) were in Latin America (all in Brazil).

Out of 88 participants, 2 discontinued the study intervention during the Randomized Treatment Period, both in the voxelotor group, 1 due to AE, and the other due to withdrawal by participant.

After the Randomized Treatment Period, 86 out of 88 participants entered the Open-Label Treatment Period. Of the 86 participants, 43 originally randomized to the placebo group received voxelotor (referred to "delayed voxelotor" hereafter), and 43 originally randomized to the voxelotor group continued voxelotor treatment.

During the Open-Label Treatment Extension Period (including the Open-Label Treatment Period and the Follow-up Period), 75 (87.2%) participants discontinued study intervention (37 in the delayed voxelotor group and 38 in the voxelotor group), among whom the majority [59 (68.6%) participants] were discontinued due to study termination, and a total of 10 (11.6%) participants discontinued due to AEs (4 in the delayed voxelotor group and 6 in the voxelotor group).

Demographic and Other Baseline Characteristics:

Of the 88 participants randomized, the majority were Black or African American (87 participants), having a diagnosis of HbSS SCD genotype (87 participants). Demographic and baseline characteristics were generally balanced between the 2 treatment groups, with notable findings as follows: the percentage of participants at ≥18 to <25 years old was higher (48.9% versus 27.9%), the rate of hydroxyurea use was higher (51.1% versus 32.6%), the mean total ulcer (target and non-target ulcers) surface area was slightly smaller (21.19 cm^2 versus 25.86 cm^2) with the mean total surface area of target ulcers of 20.8 cm^2 versus 25.8 cm^2, and the median of the maximum duration of target leg ulcer(s) was slightly longer (19.57 weeks versus 17.36 weeks) in the voxelotor group than in the placebo group.

Exposure:

The duration of study intervention exposure was similar between the treatment groups in both periods:

- During the Randomized Treatment Period, the mean duration of study intervention exposure was 12.09 weeks for voxelotor group and 12.32 weeks for placebo group.

CLINICAL STUDY REPORT SYNOPSIS

- During the Open-Label Treatment Extension Period, the mean duration of study intervention exposure was 28.86 weeks for voxelotor group and 31.87 weeks for delayed voxelotor group.

Summary of Efficacy/Safety Results

Efficacy Results

- By Week 12, the proportion of participants achieving resolution of the target ulcer(s) was similar across the groups: 6.7% (3/45) in the voxelotor group and 7.0% (3/43) in the placebo group; the difference in the exact CMH proportion between the voxelotor and placebo groups was -0.3% (95% confidence interval [CI]: -10.9% to 10.2%) and not statistically significant (2-sided p=1.0000).

- For time to resolution of target ulcer(s) up to Week 12, the hazard ratio for voxelotor versus placebo was 0.85 (95% CI: 0.17 to 4.22), numerically favoring the placebo group.

- At Week 12, the LS mean change from baseline (CFB) in total surface area of target ulcer(s) was -4.8 cm^2 for the voxelotor group and 3.4 cm^2 for the placebo group; the difference in the LS means between the voxelotor and placebo groups was -8.2 (95% CI: -15.6 to -0.8) cm^2, numerically favoring the voxelotor group. The median (first quartile, third quartile [Q1, Q3]) CFB at Week 12 was -4.6 (-8.8, 0.3) cm^2 for the voxelotor group and -3.2 (-8.4, 0.9) cm^2 for the placebo group.

- The incidence of a new ulcer by Week 12 was similar between the 2 treatment groups: 24.4% (11/45) in the voxelotor group and 32.6% (14/43) in the placebo group. The difference in the exact CMH incidence of a new ulcer by Week 12 for voxelotor versus placebo was -8.1% (95% CI: -26.9% to 10.7%), numerically favoring the voxelotor group.

Safety Results

Overview of TEAEs

AEs described under this section are all treatment-emergent unless otherwise specified. For AEs, SCD-related events are summarized separately and include sickle cell anaemia with crisis, acute chest syndrome, pneumonia, pneumonia viral, priapism, dactylitis, splenic sequestration, hepatic sequestrations, and osteonecrosis. All other events are considered as non-SCD-related AEs.

During the Randomized Treatment Period, in the voxelotor group a total of 42 (93.3%) participants experienced 144 TEAEs, 18 (40.0%) experienced serious TEAEs, 15 (33.3%) experienced Grade 3 or 4 TEAEs, and 1 (2.2%) experienced fatal TEAE, discontinued the study intervention due to TEAE, and discontinued from the study due to TEAE; in the placebo group a total of 29 (67.4%) participants experienced 86 TEAEs, 14 (32.6%) each

CLINICAL STUDY REPORT SYNOPSIS

experienced serious TEAEs and Grade 3 or 4 TEAEs, none experienced fatal TEAEs or discontinued the study intervention or discontinued from the study due to TEAEs.

- The percentage of participants with non-SCD-related TEAEs, none considered treatment-related by the investigator, was higher in the voxelotor group (84.4%) than in placebo group (65.1%).

- The percentage of participants with Grade ≥3 non-SCD-related TEAEs was comparable between the voxelotor (24.4%) and placebo (30.2%) groups.

- The most frequently reported (≥5% in either treatment group) non-SCD-related serious TEAEs were anaemia (8.9% versus 16.3%) and malaria (4.4% versus 9.3%) in the voxelotor and placebo groups, respectively.

- The most frequently reported non-SCD-related TEAEs (experienced in ≥10% participants in either treatment group) included anaemia (11.1% versus 18.6%), malaria (15.6% versus 18.6%), arthralgia (17.8% versus 2.3%), pain in extremity (17.8% versus 2.3%), headache (11.1% versus 7.0%), skin ulcer (20.0% versus 23.3%), and venous ulcer pain (11.1% versus 7.0%) in the voxelotor and placebo groups, respectively, among which key differences (>15%) were noted for the arthralgia (17.8% versus 2.3%) and pain in extremity (17.8% versus 2.3%).

- The percentage of participants with SCD-related TEAEs, none considered to be treatment-related by the investigator, was higher in the voxelotor group (51.1%) than in the placebo group (25.6%).

- The percentage of participants with Grade ≥3 SCD-related TEAEs with was higher in the voxelotor group (28.9%) than in the placebo group (18.6%).

- The most frequently reported SCD-related TEAE (experienced in ≥10% participants in either treatment group) was sickle cell anaemia with crisis, with a higher incidence in the voxelotor group (44.4%) than in the placebo group (25.6%).

- The most frequently reported (≥5% in either treatment group) SCD-related serious TEAEs were sickle cell anaemia with crisis (28.9% versus 20.9%) and acute chest syndrome (6.7% versus 2.3%) in the voxelotor and placebo groups, respectively.

- One discontinuation, from both the study intervention and study, due to a fatal, non-treatment-related serious adverse event (SAE) of sickle cell anaemia with crisis occurred in the voxelotor group.

During the Open-Label Treatment Extension Period, in the voxelotor group a total of 39 (90.7%) participants experienced 179 TEAEs, 30 (69.8%) experienced serious TEAEs, 23 (53.5%) experienced Grade 3 or 4 TEAEs, 6 (14.0%) experienced fatal TEAEs, and 4 (9.3%) discontinued from the study due to TEAEs; in the delayed voxelotor group a total of

CLINICAL STUDY REPORT SYNOPSIS

39 (90.7%) participants experienced 186 TEAEs, 25 (58.1%) experienced serious TEAEs, 23 (53.5%) experienced Grade 3 or 4 TEAEs, 2 (4.7%) experienced fatal TEAEs, and 1 (2.3%) discontinued from the study due to TEAEs.

- The percentage of participants with non-SCD-related TEAEs, none considered to be treatment-related by the investigator, was comparable between the voxelotor group (76.7%) and the delayed voxelotor group (81.4%).

- The percentage of participants with Grade ≥3 non-SCD-related TEAEs was comparable between the voxelotor (48.8%) and delayed voxelotor (46.5%) groups.

- The most frequently reported (≥5% in either treatment group) non-SCD-related serious TEAEs were anaemia (11.6% versus 16.3%), bacteraemia (9.3% versus 4.7%), bacterial infection (7.0% versus 4.7%), malaria (23.3% versus 20.9%), sepsis (7.0% versus 4.7%), and skin ulcer (0% versus 7.0%) in the voxelotor and delayed voxelotor groups, respectively.

- The most frequently reported non-SCD-related TEAEs (experienced in ≥10% participants in either treatment group) included anaemia (11.6% versus 16.3%), bacteraemia (14.0% versus 4.7%), malaria (37.2% versus 30.2%), upper respiratory tract infection (11.6% versus 2.3%), arthralgia (16.3% versus 14.0%), back pain (4.7% versus 11.6%), pain in extremity (14.0% versus 14.0%), headache (7.0% versus 11.6%), and skin ulcer (9.3% versus 27.9%) in the voxelotor group and delayed voxelotor group, respectively, mostly comparable between the 2 treatment groups.

- The percentage of participants with SCD-related TEAEs, none considered to be treatment-related by the investigator, was comparable between the voxelotor (60.5%) and delayed voxelotor (55.8%) groups.

- The percentage of participants with Grade ≥3 SCD-related TEAEs was comparable between the voxelotor group (53.5%) and the delayed voxelotor group (44.2%).

- Sickle cell anaemia with crisis was the most frequently reported (experienced in ≥10% participants in either treatment group) SCD-related TEAE, reported in 60.5% and 53.5% of participants in the voxelotor group and delayed voxelotor group, respectively.

- The most frequently reported (≥5% in either treatment group) SCD-related serious TEAEs were sickle cell anaemia with crisis (53.5% versus 41.9%) and acute chest syndrome (4.7% versus 7.0%) in the voxelotor and delayed voxelotor groups, respectively.

- Four discontinuations due to TEAEs, all considered to be not treatment-related by the investigator, occurred in the voxelotor group: 3 discontinued from both the study

CLINICAL STUDY REPORT SYNOPSIS

intervention and study, including 1 due to fatal SAEs of malaria and bacteraemia, 1 due to a fatal SAE of malaria, and 1 due to a fatal SAE of pulmonary embolism, and 1 discontinued from the study only, due to a fatal SAE of complicated malaria; and 1 discontinuation, from both the study intervention and study, considered to be not treatment-related by the investigator, occurred in the delayed voxelotor group, due to fatal SAEs of sickle cell anaemia with crisis, malaria, and hyperkalaemia.

Deaths

A total of 11 deaths, none assessed as treatment-related by the investigator, were reported during the study, among which 9 deaths occurred when the participants were on voxelotor and 2 occurred after the voluntary pause of study intervention administration by the sponsor:

- One death due to sickle cell anaemia with crisis occurred in the voxelotor group during the Randomized Treatment Period.
- Ten deaths occurred beyond the Randomized Treatment Period with 8 deaths prior to and 2 deaths after the pause of study intervention:
  - 6 deaths in the voxelotor group: 1 due to bacteraemia and malaria, 2 due to malaria, 1 due to cholelithiasis, hypovolaemic shock, sepsis, and sickle cell anaemia with crisis, 1 due to pulmonary embolism, and 1 due to complicated malaria happening 11 days after the pause of study intervention administration by the sponsor on 10 May 2024.
  - 4 deaths in the delayed voxelotor group: 1 due to hyperkalaemia, 1 due to dengue haemorrhagic fever, 1 due to acute pulmonary oedema, and the other due to bacterial sepsis, limb injury, and sickle cell anaemia with crisis happening 119 days after the pause of study intervention administration by the sponsor on 10 May 2024.

CONCLUSIONS:

Efficacy

- The study did not meet its primary endpoint of achieving resolution of the target ulcer(s) by Week 12: the difference in the exact CMH proportion between the voxelotor and placebo groups was -0.3% (95% CI: -10.9% to 10.2%).
- For time to resolution of target ulcer(s) up to Week 12, the hazard ratio for voxelotor versus placebo was 0.85 (95% CI: 0.17 to 4.22), numerically favoring the placebo group.
- At Week 12, the LS mean CFB in total surface area of target ulcer(s) was -4.8 cm^2 for the voxelotor group and 3.4 cm^2 for the placebo group; the difference in the LS means

CLINICAL STUDY REPORT SYNOPSIS

between the voxelotor and placebo groups was -8.2 (95% CI: -15.6 to -0.8) cm^2, numerically favoring the voxelotor group.

- The incidence of a new ulcer by Week 12 was similar across the 2 treatment groups: 24.4% (11/45) in the voxelotor group and 32.6% (14/43) in the placebo group. The difference in the exact CMH incidence of a new ulcer by Week 12 for voxelotor versus placebo was -8.1% (95% CI: -26.9% to 10.7%), numerically favoring the voxelotor group.

Safety

- Out of 88 participants treated, 11 deaths, none assessed as treatment-related, occurred during the study: 9 occurred when the participants were on voxelotor and 2 occurred after the voluntary pause of the study intervention dosing by the sponsor as of 10 May 2024.

- An imbalance in non-SCD-related and SCD-related AEs was observed during the Randomized Treatment Period, with higher rates in the voxelotor group than in the placebo group, and the percentage of participants with TEAE of sickle cell anaemia with crisis was higher in the voxelotor group than in the placebo group. During the Open-Label Treatment Extension Period, the overall incidences of TEAEs were comparable between the voxelotor and delayed voxelotor groups, though the incidence of discontinuation due to TEAEs and number of deaths were higher in the voxelotor group than in the delayed voxelotor group.