16 October 2025
EMA/354175/2025
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Procedure under Article 20 of Regulation (EC) 726/2004

Oxbryta EMEA/H/A-20/1538/C/004869/0014

INN/active substance: voxelotor

Note:

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Information on the procedure

In May 2024, dosing was paused in two clinical post-authorisation studies due to a potential safety concern. In study GBT440-032 (also known as C5341021 or HOPE Kids 2), the concern related to an imbalance of deaths between voxelotor and placebo groups, whilst in the study GBT440-042 (also known as C5341026 or RESOLVE) the total number of deaths was higher than anticipated. Dosing was also paused for participants of those two studies who enrolled in the open label extension (GBT440-038, also known as C5341023). Most of the fatal cases described incidence of infection. Given that concerns due to possible immunosuppressive effects of voxelotor were raised at time of the marketing authorisation (MA), and the study populations partially overlap with the authorised indication, the findings from these emerging safety data needed to be further reviewed. Therefore, all available data needed to be assessed to determine whether there is an impact on the benefit-risk balance of Oxbryta in its authorised indication.

On 26 July 2024 the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of the centrally authorised medicinal product Oxbryta (voxelotor) and to issue a recommendation on whether the marketing authorisation should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Sickle cell disease (SCD) is a group of autosomal recessive inherited disorders caused by mutations in haemoglobin B, encoding haemoglobin subunit β, resulting in the presence of a mutated form of haemoglobin, haemoglobin S (HbS). The most common type is known as sickle cell anaemia (SCA) that results in an abnormality in the oxygen-carrying protein haemoglobin found in red blood cells (RBCs). This leads to the RBCs adopting an abnormal sickle-like shape under certain circumstances; with this shape, they are unable to deform as they pass through capillaries, causing blockages. SCD may lead to attacks of pain (SCA with crisis, vaso-occlusive crises (VOCs)) in joints, anaemia, swelling in the hands and feet, bacterial infections, dizziness and stroke. Vaso-occlusion results in recurrent painful episodes and a variety of serious organ system complications that can lead to life-long disabilities and even death. Haemolytic anaemia and vaso-occlusion, being multifactorial pathophysiologic processes, are both a result of the primary molecular event - the formation of polymers of de-oxyhaemoglobin S and RBC sickling.

Voxelotor is a HbS polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. By increasing the affinity of haemoglobin (Hb) for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerisation. Voxelotor inhibits RBCs sickling and improves RBCs deformability.

On 14 February 2022, Oxbryta was granted a marketing authorisation in the European Union (EU) as an orphan medicinal product, for the treatment of haemolytic anaemia due to SCD in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide (HC, also called hydroxyurea (HU)). The recommended dosage was 1500 mg taken orally once daily. The efficacy was demonstrated on Hb response rate (defined as a Hb increase of > 1 g/dL (0.62 mmol/L) from baseline to Week 24). The response rate for voxelotor 1500 mg was 51.1% (46/90) compared to 6.5% (6/92) in the placebo group indicating a difference of 45.0 (33.4, 56.7; $p < 0.001$). At time of approval, no data in paediatric patients below the age of 12 years was available and the safety and efficacy of Oxbryta in this patient population could therefore not be

established. Voxelotor was shown to decrease the humoral immune response to antigens in both rats and monkeys. Further, exposure-dependent decrease in white blood cells (WBC) within the normal range was observed in clinical studies, whereas no evident increase in infection rates was observed during the pivotal study in the 1500 mg group. The effects observed in animals were reflected under warnings and precautions in the product information, together with a statement that the clinical relevance in already immunocompromised patients or in patients treated with immunosuppressive drugs could not be excluded.

In May 2024, the sponsor decided to pause dosing in two ongoing post-authorisation clinical studies due to a potential safety concern. The concern related to an imbalance of deaths observed between voxelotor and placebo in one of the studies (GBT 440-032, also known as C5341021 or HOPE Kids 2), whilst in the other (GBT440-042, also known as C5341026 or RESOLVE), the total number of deaths was higher than anticipated. Dosing was also paused for participants of those two studies who enrolled in the open label extension (GBT440-038, also known as C5341023), while an evaluation was conducted to determine the reason for the observations.

Study GBT440-032 intended to assess the effect of voxelotor on the transcranial doppler (TCD) ultrasound measurements in SCD participants in children 2 to <15 years of age with SCD and at risk for stroke. In this global study, the majority of study participants were enrolled in sub-Saharan Africa (SSA). Eight (8) deaths were reported in the treatment arm, compared to 2 in the placebo arm (all in SAA). Most of the fatal cases in the voxelotor group were describing incidence of infection, including 5 patients who developed (fatal) malaria or sepsis.

Study GBT440-042 intended to assess the effect of voxelotor and standard of care (SoC), compared to placebo and SoC on leg ulcer healing in participants ≥ 12 years of age with SCD. It was conducted in Kenya, Nigeria, and Brazil. Concomitant treatment with hydroxyurea/hydroxycarbamide (HU/HC) was allowed. The number of fatal events reported in study participants receiving voxelotor was higher than anticipated. The study had not yet been unblinded at the time, but most of these deaths (8/9 fatal cases) occurred in patients who entered the open-label part of this study. In 4 cases, malaria was identified either as the cause, or as contributing factor for the death.

At the time the pauses of the studies were notified, overall information was limited and some case narratives from both studies were still not available (the final clinical study reports (CSRs) became available during the procedure and the final figures are reflected below). However, since concerns due to possible immunosuppressive effects of voxelotor were raised at time of the marketing authorisation (with immunosuppressive effects observed in animal studies, and decrease in WBC in clinical studies), and the study population in those studies partially overlap with the target population defined by the authorised indication, these emerging safety data needed to be further reviewed, taking into account all available data, to assess any potential impact on the benefit-risk balance of Oxbryta in its authorised indication.

On 26 July 2024, the EC therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of Oxbryta and issue an opinion on whether its marketing authorisation should be maintained, varied, suspended or revoked. In addition, the EC requested the Agency/CHMP to give its opinion, as soon as possible, as to whether temporary measures would be necessary to ensure the safe and effective use of this medicinal product.

On 23 September 2024, the MAH informed the EMA of their intention to cease the marketing of Oxbryta, and to initiate a recall of all batches worldwide. The MAH also informed the Agency that it was discontinuing all ongoing active voxelotor clinical trials and expanded access programs worldwide. The MAH indicated that their decision was based on a review and analysis of the data currently available

from ongoing clinical trials and from registry studies, in particular emerging data regarding a safety signal of VOC. On 26 September 2024, considering the newly available data, the CHMP recommended the suspension of the marketing authorisation for Oxbryta (voxelotor) as temporary measure until adoption of a definitive decision in the context of this Article 20 procedure. The Committee also recommended that the marketing and the supply of Oxbryta (voxelotor) be suspended in all concerned EU Member States, as well as the recall of all batches available on the EU market up to the level of pharmacies and hospitals. These temporary measures were communicated with a direct healthcare professional communication (DHPC). The European Commission issued a Decision on the temporary measures on 04 October 2024.

On 16 October 2024, the MAH notified EMA of programming errors in the Real World Evidence (RWE) study GBT440-4R2 (also known as C5341019 or the PROSPECT study). This programming error was then found to affect the previously shared results of both registry-based studies, i.e., study GBT440-4R2 and the other RWE study, GBT440-4R1 (also known as C5341018 or the RETRO study). Corrected results and related analyses became available in March 2025.

The CHMP considered all available data, including data from the two above mentioned post-authorisation studies GBT440-032 and GBT440-042, from the pivotal study of the initial marketing authorisation GBT440-031 (also known as the registration study or HOPE), the extension studies GBT440-034 (also known as C5341022), GBT440-038 (also known as HOPE 1) and the corrected data from the two registry-based studies (PROSPECT and RETRO), as well as from the literature and cumulative review of the MAH safety database (see also table 1 for the studies). The CHMP also consulted an ad hoc expert group (AHEG) and the Pharmacovigilance Risk Assessment Committee (PRAC).

A summary of the most relevant information is included below.

Table 1. Overview of key efficacy and safety data submitted

Study ID and design / reference	Key objectives / endpoints	Population and area	Inclusion criteria	Treatment	Main results
Studies considered during the initial marketing authorisation					
Study identifiers: **GBT440-031; C5341043; HOPE** Design: Phase III, randomised, double-blind, placebo-controlled, multicentre	Primary endpoint: improvement in Hb levels (>1 g/dL) at week 24 Secondary endpoint: change from baseline in Hb at week 24	Randomised: 274 patients. Area: 105 patients in North America, 56 in Europe (includes Turkey), and 113 in other countries (Egypt, Jamaica, Lebanon, Oman and Kenya (49)).	Main criteria for inclusion: adult and paediatric patients 12 to 65 years of age with SCD	Voxelotor 900mg (n=92) Voxelotor 1500mg (n=90) Placebo (n=92) 63.0%, 68.5%, and 64.4% of patients in voxelotor 900 mg, 1500 mg, and placebo concomitantly used hydroxyurea (HU), respectively.	Dose-dependent increase in Hb, observable after 2 weeks of voxelotor administration and sustained through 72 weeks.
Study identifier: **GBT440-034; C5341022** Extension of HOPE study, open-label, multicentre, uncontrolled	To assess the long-term safety and treatment effect of voxelotor in participants who completed study GBT440-031.	178 participants (90% of subjects who completed Study -031). Area: Canada, Egypt, France, UK, Italy, Kenya, Lebanon, Netherlands, Oman, Turkey, and the US.	Main criteria for inclusion: adult and paediatric patients with SCD who completed 72 weeks of treatment in Study GBT440-031.	132 participants (74.2%) completed 48 weeks, 97 (54.5%) 96 weeks, and 74 (41.6%) 216 weeks of treatment. Of the 74 participants with ≥ 216 weeks of treatment in this study, 47 participants were previously treated with voxelotor (1500 mg or 900 mg) for approximately 72 weeks in Study GBT440-031 for a cumulative voxelotor treatment duration of ≥288 weeks (>5.5 years).	Efficacy: Improvements in Hb and clinical measures of haemolysis Safety: the only SCD-related SAE considered by the Investigator as related to treatment was priapism, reported in 1 subject. Ten fatal SAEs considered non-related to treatment by the investigator.
Post-authorisation studies					
Study identifier: **GBT440-032; C5341021; HOPE Kids 2** Phase III, randomised, double-blind, placebo-controlled	Primary endpoint: Change from baseline at 24 weeks in TAMMV arterial cerebral blood flow, as measured by TCD Secondary endpoint: change in TCD flow velocity at Week 48 and Week 96, the conversion of TCD category from conditional to abnormal, the reversion of	Randomised: 236 Area: 195 patients (82.6%) in SSA (Nigeria n=166, Kenya n=24, Ghana n=5). Remaining: Egypt (n=34), US (n=4), Oman (n=1), Saudi	Main criteria for inclusion: Paediatric patients (2-15 years) with SCD	Dosage: 1500 mg/day in patients ≥12 years old; participants <12 years of age received voxelotor at a weight-based dose (1500 mg-equivalent).	Efficacy: primary and secondary endpoints met. Safety: SCD-related TEAE and SAE: higher percentage of participants in the voxelotor group reported an SCD-related TEAE and SAE (59.2% and 36.7% respectively) than in the placebo group (42.2% and 15.5%).

	TCD category from conditional to normal, the proportion of participants with TCD response, the change in Hb over time, the change in clinical measures of haemolysis, and the annualised incidence rate of VOCs	Arabia (n=1), the UK (n=1)			Deaths: 10 fatal cases reported (8 in the voxelotor arm and 2 in the placebo arm). (2 additional deaths in the voxelotor group at 3 and at 5 months after discontinuation, respectively.) Annualised IR VOCs (95% CI):: Voxelotor vs Placebo: 1.09 (0.8, 1.4) vs 0.48 (0.35, 0.6)
Study identifier: **GBT440-042; C5341026; RESOLVE** Phase III, multicentre, randomised, double-blind, 12 weeks placebo-controlled (+ SoC)	Primary endpoint: resolution of target ulcer(s) by week 12	Randomised: 88 patients (45 voxelotor, 43 placebo) Area: 79 SSA (Nigeria n=17, Kenya n=62), and Brazil (n=9).	Main criteria for inclusion: Patients ≥12 years of age with SCD and active leg ulcers, with at least 1 cutaneous ulcer(s) in the lower extremity (leg, ankle, or dorsum of foot) that had a duration ≥2 weeks and <6 months at screening and was >2 cm^2 in size prior to randomisation	Voxelotor 1500 mg Placebo 51.1% voxelotor participants vs 32.6% placebo used HU at baseline	Primary endpoint not met. 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. Deaths: 11 fatal cases reported (none in the placebo group. 1 death due to sickle cell anaemia with crisis occurred during the randomised treatment period. 8 deaths occurred in the open label follow-up and 2 deaths occurred after the pause of study intervention due to complicated malaria.
Study identifier: **GBT440-038; OLE, HOPE 1** Extension study of previous voxelotor trials, open-label	To assess the safety and SCD-related complications of long-term treatment with voxelotor	162 participants (97 from GBT440-032, 11 from GBT440-042 and 54 from GBT440-007) Area: UK, US, Egypt, Lebanon and Nigeria	Main criteria for inclusion: ≥2 years old patients with SCD who had participated in voxelotor clinical trials, including but not limited to participants who completed studies GBT440-032 and GBT440-042	Voxelotor	57 participants (35.2%) had at least 1 TEAE; SCD Anaemia with Crisis was the most common event (32.7%). The percentage of participants experiencing a serious SCD-related TEAE was 24.7% (40/162). There was one death in the study; the Grade 5 event was Acute haemolytic transfusion reaction.
Study identifier: **GBT440-007 Part C-D (HOPE 1)** Phase IIa, multicentre, open-label study	Part C: To assess the safety, tolerability, PK, and efficacy, as well as the haematological effects and the effect on TCD flow velocity of multiple doses of voxelotor administered for up to 48 weeks.	Part C: 56 participants (45 aged 4 to 11 years and 11 aged 12 to 17 years) Part D: 32 participants	Main criteria for inclusion: paediatric subjects 4 to 17 years (part C) or 6 months to <	Voxelotor	Overall, improve anaemia and reduce clinical measures of haemolysis. Part C: >50% did not report any VOC events during the study. Most of the remaining subjects reported 1-2 VOC events. Most participants had pyrexia

	Part D: To assess the safety, tolerability, and PK of multiple doses of voxelotor administered up to 48 weeks.	Area: US, UK, and Lebanon	4years (part D) with SCD		considered unrelated to voxelotor treatment. No deaths reported. Part D: The most commonly reported (≥20%) SCD related TEAE was sickle cell anaemia with crisis. Overall, the number of study drug-related AEs was low. No deaths reported.
Registry studies					
Study identifier: **GBT440-4R2; C5341019; PROSPECT** Post-authorisation multicentre, open-label, prospective Real-World Data collection and analysis study	To characterise health outcomes in treated with voxelotor as part of their usual care	256 participants Area: US.	Patients with SCD aged ≥5 years	Voxelotor	The annualised IR of VOCs was 4.78 events/patient-year prior to voxelotor initiation and 3.15 events/patient-year after voxelotor treatment 6 deaths, none related to voxelotor.
Study identifier: **GBT440-4R1; C5341018; RETRO** Post-authorisation multicentre, retrospective Real-World Data collection and analysis study	To characterise health outcomes in participants treated with voxelotor as part of their usual care	216 participants Area: US.	Patients with SCD aged ≥12 years	Voxelotor	The annualised IR of VOCs was 1.33 events/patient-year prior to voxelotor initiation and 1.54 events/patient-year after voxelotor. 5 deaths, none considered voxelotor related.

2.2. Data on safety

2.2.1. Study GBT440-032 (HOPE KIDS 2, C5341021)

Study design and baseline characteristics

This post-marketing Phase III, randomised, double-blind, placebo-controlled study was initiated on 11 November 2020 and terminated on 25 September 2024 per sponsor decision. An interim and then final CSR became available during the procedure.

The primary objective of this trial was to evaluate the effect of voxelotor compared to placebo on the time-averaged mean of the maximum velocity (TAMMV) arterial cerebral blood flow as measured by TCD at 24 weeks in paediatric SCD participants.

The secondary objectives of this trial were to evaluate the effects of voxelotor compared to placebo on the change in TCD flow velocity at Week 48 and Week 96, the conversion of TCD category from conditional to abnormal, the reversion of TCD category from conditional to normal, the proportion of participants with TCD response, the change in Hb over time, the change in clinical measures of haemolysis, and the annualised incidence rate of VOCs. In this study, VOC was defined as a composite of acute painful crisis and/or ACS for which there was no explanation other than VOC, with moderate to severe pain lasting at least 2 hours and requiring analgesics in a medical setting.

The study enrolled paediatric participants (aged 2 to <15 years) with SCD and at higher risk of stroke, defined by a baseline conditional (170 to <200 cm/sec) TCD flow velocity.

A total of 236 participants were randomised (120 in voxelotor group and 116 in placebo group). The majority of participants were enrolled in SSA countries (195/236; 82.6%), (Nigeria n=166, Kenya n=24, and Ghana n=5). The remaining participants were from Egypt (n=34), US (n=4), Oman, (n=1), Saudi Arabia (n=1), and the UK (n=1). Participants ≥12 years old were administered a fixed dose of voxelotor 1500 mg/day; participants younger than 12 years of age received voxelotor at a weight-based (1500 mg-equivalent) dose.

Demographic characteristics were comparable between the voxelotor and placebo groups. The overall mean age was 7.2 years (Standard Deviation (SD) 3.16), with the majority of participants (77.5%, 183/236) aged between 4 and <12 years. A smaller proportion (29/236) were aged 12–15 years. The gender distribution was balanced, with 48.3% male and 51.7% female participants.

Baseline characteristics were generally similar between groups. Mean (SD) Hb at baseline was 7.7 (1.04) g/dL in the voxelotor group and 7.6 (1.03) g/dL in the placebo group. The mean (SD) TCD flow velocity was 182.6 (7.24) cm/sec and 182.8 (7.85) cm/sec, respectively. The majority of participants in both treatment groups were in the 170 cm/sec to <185 cm/sec category, 72 (60.0%) in the voxelotor group and 73 (62.9%) in the placebo group. Additionally, the majority of participants were not using HU at baseline, 79 (65.8%) in the voxelotor group and 81 (69.8%) in the placebo group. 112 (93.3%) patients in voxelotor and 112 (96.6%) in placebo arm had HbSS genotype, and 8 (6.7%) patients in the voxelotor and 4 (3.4%) of patients in the placebo arm had HbSß^0 genotype.

The percentage of participants with no VOCs in the 12 months prior to screening was lower in the voxelotor group (47.5% [57/120]) than in the placebo group (58.6% [68/116]). Of the participants who had 1 or more prior VOCs, the majority reported 1 or 2 VOCs in the prior 12 months; 53/63 (84.1%) in the voxelotor group and 42/48 (87.5%) in the placebo group. The majority of participants in both treatment groups had no VOCs in the prior 12 months that required hospitalisation, 71.7% and

79.3%, respectively. The number of prior VOCs was not a stratification factor for randomisation or endpoint analysis.

Exposure to study drug was similar in both the voxelotor and placebo groups. As of the dosing pause on 01 May 2024, the actual mean (SD) exposure to study drug was 71.9 (25.68) weeks in the voxelotor group and 70.0 (29.75) weeks in the placebo group. Few participants in either group experienced a dose reduction, 5.0% (6/120) in the voxelotor group and 3.4% (4/116) in the placebo group. The majority of participants in both treatment groups missed at least 1 dose of study drug, 78.3% (94/120) in the voxelotor group and 72.4% (84/116) in the placebo group. Of these participants, the majority of participants missed doses due to 'other' (non-compliance). All patients had minimum follow-up of 48 weeks.

Results

Non-SCD–related Treatment-Emergent Adverse Events (TEAEs)

A similar percentage of participants reported at least 1 non-SCD-related TEAE in the voxelotor (70.8%) group and in the placebo (70.7%) group. The most frequently reported non-SCD-related events (≥10% of participants in either treatment group) included malaria (27.5% and 24.1%), upper respiratory tract infection (12.5%, 6.0%), pyrexia (30.8%, 12.9%), anaemia (16.4%, 13.3%), abdominal pain (10.0%, 6.9%), and cough (10.0%, 2.6%).

Non-SCD-related TEAEs reported in 5% or more voxelotor participants compared to placebo participants included pyrexia (30.8%, 12.9%), cough (10.0%, 2.6%), and sepsis (9.2%, 3.4%).

General infection rates (SOC infections and infestations) were 59.2% in the voxelotor group compared to 50.0% in the placebo group, while serious infection rates were 23.3% and 17.2%, respectively, mainly due to malaria (27.5% voxelotor vs. 24.1% placebo), upper respiratory tract infection (12.5% voxelotor vs. 6.0% placebo) and sepsis (7.5% voxelotor vs. 3.4% placebo). Median time to onset was 23.4 weeks in the voxelotor group versus 42.6 weeks for placebo group.

In line with previously published hydroxyurea (HU) data (Namazzi et al. 2024, Olupot-Olupot et al. 2023), the rate of malaria was lower in participants on HU compared to those not on HU up to Week 96 in the voxelotor arm ((no: 38.0% (30/79) vs. yes: 7.3% (3/41)) and in the placebo arm (no: 29.6% (24/81) vs. yes: 11.4% (4/35)).

Few participants in either treatment group had TEAEs that were considered related to the study drug by the investigator (7 [5.8%] in the voxelotor group and 4 [3.4%] in the placebo group).

A higher percentage of participants in the voxelotor group had non-SCD-related SAEs (35.8%) than in the placebo group (25.9%).

Few participants in either the voxelotor (6 [5.0%]) or placebo (3 [2.6%]) groups experienced non-SCD-related TEAEs that led to study intervention discontinuation.

SCD–related TEAEs

SCD-related TEAES are defined as dactylitis, splenic sequestration, hepatic sequestration, acute painful crisis, priapism, acute chest syndrome (ACS), transient ischemic attack, stroke and sepsis.

A higher percentage of participants in the voxelotor group (59.2%) reported a SCD-related TEAE than in the placebo group (42.2%), primarily due to the difference in SCA with crisis events, which was the most frequent SCD-related TEAE.

Based on a total person-years of 171.3 versus 160.2, the adjusted annualised incidence rate of VOCs was low in both treatment groups, but in the voxelotor group, a higher percentage of patients

experienced at least 1 VOC compared to the placebo group and the adjusted annualised incidence rate was also higher in the voxelotor group. Adjusted annualised VOC rate: 1.098 (95% CI: 0.869, 1.387) voxelotor; 0.580 (95% CI: 0.439, 0.765) placebo, with an incidence rate ratio (IRR) of 1.894 (95% CI: 1.318, 2.722) and 2-sided p=0.0006.

With regards to malaria status, for voxelotor the rate of SCA with crisis was 78.8% (26/33) if there were any malaria adverse events (AEs) vs 51.7% (45/87) if there were none and for placebo 57.1% (16/28) vs 31.8% (28/88), respectively.

The incidence of ACS was comparable with 9 (7.5%) in the voxelotor arm versus 8 (6.9%) in the placebo arm.

A higher percentage of participants in the voxelotor group had a SCD-related serious adverse event (36.7%%) than in the placebo group (15.5%%).

No participants in the voxelotor group experienced a stroke; 3 participants in the placebo group experienced 1 stroke each; 2 were considered cerebrovascular accidents and 1 was a haemorrhagic stroke.

Deaths

A higher number of fatal events was reported in the voxelotor arm (8) vs 2 in the placebo arm. The age at enrolment of participants with fatal events ranged from 3 to 14 years old.

Two treatment-emergent deaths in the voxelotor group occurred on Study Days 21 and 63. The other (6/8) of the treatment-emergent fatal cases for the voxelotor group occurred on Study Day 204 or later (up to Study Day 670). All treatment-emergent deaths occurred in participants in SSA countries. Causes of death were reported as follows: SCA with crisis (2), pyrexia (1), anaemia/SCA with crisis (1), anaemia (1), pyrexia/SCA/diarrhoea/septic shock (1), malaria/SCA/seizure (1), abdominal pain/abdominal tension/SCA (1).

The two deaths in the placebo group occurred on Study Days 35 and 71. The causes of death were cerebrovascular accident (1) and anaemia/cardiac failure/malaria (1).

SCD-related TEAEs, in particular SCA with crisis, contributed to 6 deaths in the voxelotor group; SCD-related TEAEs did not contribute to the deaths of the placebo participants. In the final dataset in 2 (1 voxelotor, 1 placebo) of the 10 TEAE deaths the participant experienced a fatal TEAE of malaria. One additional participant in the voxelotor group had malaria at the time of their death, though it was not listed as a fatal event. Five (5)/10 participants with fatal TEAEs were being treated for malaria as part of the fatal event (4 in the voxelotor group and 1 in the placebo group) as assessed by clinical review of the narratives. From case narratives, particularly in Nigeria, it was observed that Hb level was relatively low at baseline, <8 g/dL. The majority had no VOC within the 12 months prior to study entry. At study entry, in 8 cases of death observed no HU was used (6/8 deaths in patients on voxelotor and 2/2 death in patients on placebo), and half of the patients used proguanil.

Dosing appeared to follow the dose instructions (based on body weight for participants aged below 12 years), however in one case dose was reduced due to SAE, and in half of the cases missed doses were reported. Pharmacokinetics (Pk) findings suggested possible non-compliance with treatment in two of the voxelotor participants who experienced fatal events, as well as in one placebo participant who had detectable level of voxelotor.

In addition to the deaths noted above, 2 additional participants in the previous voxelotor group had a treatment-emergent fatal event after the data cut-off (at 3 and at 5 months after discontinuation, respectively).

2.2.2. Study GBT440-042 (RESOLVE, C5341026)

Study design and baseline characteristics

Study GBT440-042 was a post-marketing, Phase III, multicentre, randomised, double-blind, placebo-controlled study (in addition to standard of care (SoC)) with a duration of 12 weeks. It was initiated on 30 May 2022 and terminated on 25 September 2024 per sponsor decision. The interim and final CSR became available during the procedure.

The aim of the study was to evaluate voxelotor for the treatment of active leg ulcers in patients with SCD, who have at least 1 cutaneous ulcer(s). At the end of the 12-week randomised treatment period, all participants (except those demonstrating initial ulcer re-epithelialization at Week 12) received open-label voxelotor and SoC for a minimum of 12 weeks.

The primary objective of the controlled part of this study was to assess the effect of voxelotor and SoC compared to placebo and SoC on leg ulcer healing in participants ≥12 years of age with SCD, as measured by the proportion of participants achieving resolution of target ulcer(s) in each treatment group by Week 12. In this study, VOCs were not assessed as part of the primary efficacy outcomes, but events were collected from the safety perspective to assess the safety and tolerability of voxelotor compared to placebo based on AEs, including SCA with crisis and ACS.

Study GBT440-042 enrolled 88 participants of 12 years of age and older, 45 randomised to voxelotor and 43 randomised to placebo. Participants had to have at least 1 cutaneous ulcer(s) on the lower extremity (leg, ankle, or dorsum of foot) that had a duration ≥2 weeks and <6 months at screening and was >2 cm^2 in size prior to randomisation. Participants who completed 12 weeks in the open-label treatment period could continue to receive voxelotor until the participant had access to voxelotor from an alternative source, i.e., enrolment in the open label extension (OLE) study GBT440-038, commercialised product, expanded access program (EAP).

During the randomised treatment period, participants received 1500 mg of voxelotor once daily or matching placebo. All participants received 1500 mg of voxelotor during the open-label treatment period. As with study GBT440-032, the majority of participants were enrolled in SSA countries (79/88; 89.8%); Nigeria n=17, Kenya n=62. The remaining participants were from Brazil (n=9).

Baseline leg ulcer characteristics were generally similar in the voxelotor group and the placebo group. Mean (SD) number of target leg ulcers at baseline was 1.3 (0.60) in the voxelotor group and 1.5 (0.80) in the placebo group. The mean (SD) total surface area was 21.19 (25.765) cm^2 and 25.86 (32.121) cm^2, respectively and the maximum duration of the target leg ulcer(s) was 17.85 (8.447) weeks and 16.69 (6.778) weeks, respectively.

A higher percentage of voxelotor participants used HU at baseline than placebo participants (51.1% vs 32.6%, respectively). 45 (100.0%) of participants in the voxelotor arm and 42 (97.7%) of participants in the placebo arm had HbSS, and 1 (2.3%) patient in the placebo arm had HbSb Thalassemia SCD genotype.

Prior to screening, 42.2% of participants in the voxelotor group (19 out of 45) and 48.8% in the placebo group (21 out of 43) had not experienced any VOCs within the preceding 12 months. In contrast, 57.7% of participants in the voxelotor group (26 out of 45) and 51.1% in the placebo group (22 out of 43) had experienced at least one VOC during that same period.

The duration of exposure during the placebo-controlled phase was comparable between treatment groups. During the randomised treatment period, the mean duration of study intervention exposure was 12.09 weeks in the voxelotor group and 12.32 weeks in the placebo group.

Results

An imbalance in non-SCD-related and SCD-related AEs was observed during the randomised treatment period, with higher rates in the voxelotor group than in the placebo group, and the percentage of participants with TEAE of SCA with crisis was higher in the voxelotor group than in the placebo group.

During the randomised 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 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.

Non-SCD–related 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 the placebo group (65.1%).

The most frequently reported non-SCD-related TEAEs (experienced in ≥10% participants in either treatment group voxelotor vs. placebo) included anaemia (5 (11.1%) versus 8 (18.6%)), malaria (7 (15.6%) versus 8 (18.6%)), arthralgia (8 (17.8%) versus 1 (2.3%)), pain in extremity (8 (17.8%) versus 1 (2.3%)), headache (5 (11.1%) versus 3 (7.0%)), skin ulcer (9 (20.0%) versus 10 (23.3%)), and venous ulcer pain (5 (11.1%) versus 3 (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 rate of participants having at least one episode of malaria was lower if they were on HU during the 12-week double blind period in the voxelotor arm (no: 22.7% (5/22 vs. yes: 8.7% (2/23)), as well as in the placebo-arm (no: 24.1% (7/29) vs. yes: 7.1% (1/14)).

SCD–related TEAEs included VOCs (acute painful episodes), ACS, pneumonia, pneumonia viral, priapism, dactylitis, splenic sequestration, hepatic sequestration, and osteonecrosis.

The percentage of participants with SCD-related TEAEs, none considered to be treatment-related by the investigator, was higher in the voxelotor group (23 (51.1%)) than in the placebo group (11 (25.6%)).

The most frequently reported SCD-related TEAE (experienced in ≥10% participants in either treatment group) was any SCA with crisis, with a higher incidence in the voxelotor group (19 (44.4%)) than in the placebo group (11 (25.6%)). The incidence of ACS was 4 (8.9%) in the voxelotor arm versus 1 (2.3%) in the placebo arm.

The most frequently reported (≥5% in either treatment group) SCD-related serious TEAEs were VOCs/SCA with crisis (28.9% versus 20.9%) in the voxelotor and placebo groups, respectively.

By malaria status subgroups among participants who experienced at least one malaria event by Week 12, the percentage of participants with SCD-related TEAEs was similar between the treatment groups.

SCD-related TEAEs incidence based on VOCs prior to screening:

- Of 19 participants in the voxelotor group and 21 participants in the placebo group who had no VOC within 12 months prior to screening, the percentage of participants with SCD-related TEAEs was 42.1% (8/19) and 28.6% (6/21), and those with SCD-related serious TEAEs was 26.3% (5/19) and 23.8% (5/21) in the voxelotor and placebo groups, respectively.

- Of 26 participants in the voxelotor group and 22 participants in the placebo group who had ≥1 VOCs within 12 months prior to screening, the percentage of participants with SCD-related TEAEs was 57.7% (15/26) and 22.7% (5/22), and those with SCD-related serious TEAEs was 34.6% (9/26) and 18.2% (4/22) in the voxelotor and placebo groups, respectively.
- Of 21 participants in the voxelotor group and 15 participants in the placebo group who had ≥2 VOCs within 12 months prior to screening, the percentage of participants with SCD-related TEAEs was 52.4% (11/21) and 33.3% (5/15), and those with SCD-related serious TEAEs was 33.3% (7/21) and 26.7% (4/15) in the voxelotor and placebo groups, respectively.

By country subgroups, the percentage of participants with SCD-related TEAEs was higher in the voxelotor group compared to the placebo group.

- Of 8 participants in the voxelotor group and 9 participants in the placebo group who were treated in Nigeria, the percentage of participants with SCD-related TEAEs was 37.5% (3/8) and 11.1% (1/9), and those with SCD-related serious TEAEs was 37.5% (3/8) and 11.1% (1/9) in the voxelotor and placebo groups, respectively.
- Of 33 participants in the voxelotor group and 29 participants in the placebo group who were treated in Kenya, the percentage of participants with SCD-related TEAEs was 33.3% (11/33) and 27.6% (8/29), and those with SCD-related serious TEAEs was 33.3% (11/33) and 27.6% (8/29) in the voxelotor and placebo groups, respectively.
- Of 4 participants in the voxelotor group and 5 participants in the placebo group who were treated in Brazil, none experienced SCD-related TEAEs.

During the open-label treatment extension period, the overall incidences of TEAEs were comparable between the voxelotor and delayed voxelotor groups (the group which received open-label voxelotor only after the end of the 12-week randomised treatment period during which it received placebo), though the incidence of discontinuation due to TEAEs and number of deaths were higher in the voxelotor group than in the delayed voxelotor group.

Deaths

In the final dataset 11 deaths occurred in patients receiving voxelotor and none in the placebo arm. One death due to SCA with crisis occurred in the voxelotor group during the randomised treatment period. 8 deaths occurred in the open label follow-up and 2 additional deaths occurred after the pause of study intervention:

- 5 deaths in the voxelotor group: Causes of death included: 1 due to bacteraemia and malaria, 2 due to malaria, 1 due to cholelithiasis, hypovolaemic shock, sepsis, and VOCs/SCA with crisis, 1 due to pulmonary embolism.
- 3 deaths in the delayed voxelotor group: 1 due to hyperkalaemia, 1 due to dengue haemorrhagic fever, 1 due to acute pulmonary oedema.
- 2 deaths after the pause of the study: 1 due to complicated malaria with acute pulmonary oedema 11 days after discontinuation, and the other due to bacterial sepsis, limb injury, and VOCs/SCA with crisis 119 days after discontinuation.

2.2.3. Study GBT440-031 (HOPE, C5341043)

Study design and baseline characteristics

Study GBT440-031 was a phase III, randomised, double-blind, placebo-controlled study to assess the efficacy and safety of voxelotor in participants aged 12 to 65 years with SCD. This study was pivotal in the marketing authorisation application of Oxbryta in the EU.

The primary objective was to assess the effect of voxelotor compared with placebo on improvement in Hb. The primary efficacy endpoint was Hb response at Week 24. Hb response was based on the difference between the average value of Hb levels at Week 20 (Hb20) and Week 24 (Hb24) compared to baseline haemoglobin level (HbB). A subject was considered to be a Hb responder if [mean (Hb20, Hb24) – HbB] > 1 g/dL. If Hb20 or Hb24 was missing, then the calculation used the non-missing Hb level. Regardless of calculated difference, subjects were classified as non-responders if any of the non-responder criteria were met.

The key secondary efficacy endpoint included changes from baseline in Hb at Week 24.

In this study, VOC was defined as a composite of acute painful crisis (including ACS and priapism) for which there was no explanation other than VOC, with moderate to severe pain lasting at least 2 hours and requiring analgesics from an HCP. Contact with a physician within 1 business day of the event had to be documented in the medical record.

The study enrolled 274 participants who were randomised on a 1:1:1 basis. During the treatment period, participants received voxelotor 1500 mg (n=90), voxelotor 900 mg (n=92), or placebo (n=92) once daily administered as 300 mg oral tablets for up to 72 weeks. In total, 63.0%, 68.5%, and 64.4% of patients in voxelotor 900 mg, 1500 mg, and placebo concomitantly used hydroxyurea (HU), respectively.

In total, 38.3% (105/274) of participants were included at sites in North America, 20.4% (56/274) at sites in Europe (includes Turkey), and 41.2% (113/274) at sites in other countries (includes: Egypt, Jamaica, Kenya, Lebanon, Oman). Among the latter, forty-nine (49) participants were at sites in Kenya.

Overall, the mean HbB was 8.5 g/dL, and the majority of participants had SCD genotype HbSS (75.2%) or HbSβ^0 thalassemia (19.7%). The percentage of mean HbF was 10.4%, 9.9%, 9.3% in the voxelotor 1500-mg, 900-mg, and placebo groups respectively. Fifty-eight percent (58.0%) of participants had at least 2 VOCs in the 12 months prior to screening. Overall, at least 1 episode of ACS within the 12 months prior to screening was reported by 8.4% of participants and was more common in the voxelotor 1500-mg group (11.1%) and the voxelotor 900 mg group (10.9%) than in the placebo group (3.3%). Of patients aged 12 to < 18 Years, 17, 15, and 14 (total 46) patients were included in the 900 mg, 1500 mg, or placebo arms, respectively.

Results

Most of the subjects in the study GBT440-031 experienced at least 1 non-SCD-related adverse event (AE): 90.1% in the placebo group, 93.5% in the voxelotor 900 mg group and 96.6% in the voxelotor 1500 mg group. Of these, 26.4% in the placebo group, 32.6% in the voxelotor 900 mg group and 39.8% in the voxelotor 1500 mg group were assessed as related to voxelotor. Number of subjects with any serious non-SCD-related TEAEs ranged between 22-28%.

Non-SCD–related TEAEs

The most common non-SCD–related TEAEs within voxelotor 1500 mg group with incidence higher than in placebo group were headache (31.8% vs 25.3%), diarrhoea (22.7% vs 11%), arthralgia (21.6% vs 14.3%), pyrexia (14.8% vs 7.7%) and nausea (19.3% vs 9.9%).

SCD–related TEAEs

Similar number of subjects in every group experienced at least one SCD-related adverse event (75-80%). The majority of SCD-related TEAEs in each treatment group were Grade ≤ 3. The number of subjects who experienced severe SCD-related AEs was high but similar across the groups (52%). However, in a somewhat higher number of subjects in the voxelotor 1500 mg group (4.5%), SCD-related SAE was attributed to the study drug compared to placebo or voxelotor 900 mg group (1.1% each). The majority of SCD-related TEAEs were SCA with crisis. The incidence of TEAE SCA with crisis was evenly balanced across groups, and its occurrence was widely distributed throughout the study (76-79%).

Although no statistically significant difference was observed in the annualised incidence rate of on-treatment VOCs between the voxelotor 1500 mg group (2.4 events/year; 219 events) and the placebo group (2.8 events/year; 293 events), the study was not powered to detect a difference.

ACS events occurred less frequently than acute painful crisis events, with a higher number of events in the voxelotor groups than in the placebo group: voxelotor 1500 mg (13.6% [12/88 subjects]), voxelotor 900 mg (8.7% [8/92 subjects]), and placebo (6.6% [6/91 subjects]). Priapism occurred infrequently in the study, with a total of 11 subjects experiencing at least 1 event. There was an imbalance in events, numerically higher in the voxelotor groups, that did not appear to be dose-related: 4 subjects in the voxelotor 1500-mg group, 6 subjects in the voxelotor 900-mg group, and 1 subject in the placebo group.

Deaths

There was a total of 6 deaths reported with 9 AEs with fatal outcomes (2 in each treatment group); all deaths were assessed as not related to voxelotor.

2.2.4. Other studies

All other newly available study data came from uncontrolled open label studies. Namely studies GBT440-007, GBT440-038 and the final CSR of the two registry RWE studies (RETRO and PROSPECT) including the corrected analyses. Previously available data from study GBT440-034 was also considered. These were considered as supportive evidence.

Open-label extension (OLE) study GBT440-034 (C5341022)

Study GBT440-034 was an open-label, multicentre extension study conducted globally for adult and paediatric participants with SCD who completed 72 weeks of treatment in study GBT440-031. All subjects who enrolled in study GBT440-034, regardless of treatment received in study GBT440-031 (i.e., voxelotor 1500 mg, voxelotor 900 mg, or placebo), received voxelotor 1500 mg once daily and were evaluated for safety according to the protocol-specified schedule of assessments.

The primary objective of this OLE study was to assess the long-term safety and treatment effect of voxelotor in participants who have completed treatment in study GBT440-031, using the following parameters:

• Safety based upon AEs, clinical laboratory tests, physical examinations (PE) and other clinical measures.

• Frequency of sickle cell disease-related complications.

• Haemolytic anaemia as measured by haematological laboratory parameters (e.g. haemoglobin, reticulocytes and unconjugated bilirubin).

The study was conducted in Canada, Egypt, France, United Kingdom (UK), Italy, Kenya, Lebanon, Netherlands, Oman, Turkey, United States of America (USA). Of the 199 subjects who completed study GBT440-031, 179 participants (90%) were enrolled in the OLE study GBT440-034, and 178 received treatment with voxelotor (one participant withdrew consent prior to starting treatment).

A total of 60.7% (108/178) of subjects were taking concomitant HU at baseline.

The mean duration of exposure to voxelotor in study GBT440-034 was 138 weeks.

Among the 178 subjects, 157 (88.2%) experienced a non-SCD-related AE. Overall, most non-SCD-related AEs were grade 1 or 2. Forty-four (24.7%) subjects had grade 3 non-SCD-related AEs, 4 (2.2%) subjects had grade 4 non-SCD-related AEs, and 5 (2.8%) subjects had grade 5 non-SCD-related AEs. Forty-four (24.7%) subjects experienced non-SCD-related SAEs. Three (1.7%) subjects had SAEs assessed by the investigator as related to study drug. Non-SCD-related SAEs were reported in 24.7% (44/178) of subjects. The most frequently reported non-SCD-related SAE was anaemia (4.5%, 8/178).

A total of 129/178 (72.5%) subjects experienced an SCD-related AE (SCD-related events include SCA with crisis, ACS, pneumonia, COVID-19 pneumonia, priapism, and osteonecrosis). Eighty (44.9%) subjects had grade 3 SCD-related AEs, 5 (2.8%) subjects had grade 4 SCD-related AEs, and 4 (2.2%) subjects had grade 5 SCD-related AEs. SCD-related SAEs were reported in 50.6% (90/178) of subjects (SCD-related events include SCA with crisis, ACS, pneumonia, COVID-19 pneumonia, priapism, and osteonecrosis). The only SCD-related SAE considered by the investigator as related to voxelotor was priapism, which was reported in 1 subject.

Nine fatal SAEs were reported prior to the data cutoff date. These were SCA with crisis (3 subjects), and one subject each with sepsis, dyspnoea, pyrexia, COVID-19, ACS, and anaemia. None of the fatal SAEs were considered by the investigator as related to voxelotor. One additional death occurred after the data cutoff date and prior to the end of the study.

The annualized IR of on-treatment VOC events was 1.02 events/year.

Open label Study GBT440-007 Parts C-D (C5341020)

Study GBT440-007 was an integrated Phase IIa, multicentre, open-label study consisting of 4 parts. Parts C and D explored single and multiple doses of voxelotor in paediatric participants with SCD. The study was performed in the US, UK, and Lebanon.

Part C of the study was designed to assess the safety, tolerability, PK, and efficacy, as well as the haematological effects and the effect on TCD flow velocity of multiple doses of voxelotor administered for up to 48 weeks in paediatric subjects 4 to 17 years old with SCD. The primary objective of Part C was to evaluate the effect of voxelotor on cerebral hemodynamic in paediatric participants with SCD with elevated or conditional TCD flow velocity as assessed by TCD ultrasonography. The secondary objectives included the evaluation of the effect of voxelotor on clinical measures of anaemia and haemolysis, as well as on the incidence of stroke and VOC.

Part C was completed and enrolled a total of 62 participants: 51 patients aged 4–11 years and 11 patients aged 12–17 years. Prior to study initiation, the mean (SD) number of VOCs was 1.3 (2.02) in

the 4–11 age group, 1.5 (2.02) in the 12–17 age group, and 1.3 (2.01) across all participants. The study was conducted in US, UK, and Lebanon.

The analysis of VOCs showed that over 50% of participants did not experience any VOC events during the study. Among those who did, most reported only 1–2 events. The mean (SD) duration of the treatment period was 0.7 years (0.36).

In the 4–11 age group, a total of 46 VOC events were reported, corresponding to an annualised incidence rate of 1.25 events/year (95% CI: 0.912–1.662).

In the 12–17 age group, 11 VOC events were reported, with an annualised incidence rate of 2.25 events/year (95% CI: 1.123–4.025).

No events of stroke were reported in Part C of the study.

Part D of the study was designed to assess the safety, tolerability, and PK of multiple doses of voxelotor administered up to 48 weeks in paediatric participants of 6 months to <4 years of age with SCD. The primary objective was to evaluate the safety and tolerability of voxelotor in paediatric participants with SCD aged 6 months to < 4 years. The secondary objectives included the evaluation of the effect of voxelotor on clinical measures of anaemia and haemolysis and as well as on the incidence of stroke and VOC.

Part D was terminated on 25 September 2024.

The study enrolled 32 participants, 16 participants were at sites in Lebanon, 12 in the US and 4 in the UK. Overall, the number of study drug-related AEs was low. 40.6% of participants reported no VOCs. The annualized incidence of VOCs was 1.399 events/year (95% CI: 0.914, 2.050) in participants aged 2 to <4 years.

Open-label extension (OLE) Study GBT440-038 (C5341023)

Study GBT440-038 was an OLE study of voxelotor administered orally to paediatric and adult participants with SCD aged 2 years and older, who had participated in previous voxelotor clinical trials, including participants who completed studies GBT440-032, GBT440-042 and part C and D of study GBT440-007.

The primary objective was to assess the safety, and SCD-related complications, of long-term treatment with voxelotor based on the following parameters:

- AEs, clinical laboratory tests, physical examinations, and other clinical measures
- Frequency of SCD-related complications

In participants who enrolled from studies GBT440-032 and GBT440-042, dosing was paused at the same time as the parent studies. Dosing continued for participants who enrolled from Study GBT440-007 until 25 September 2024, when all voxelotor trials were terminated.

The study was conducted in the UK, US, Egypt, Lebanon and Nigeria. At study termination, 162 participants had enrolled in GBT440-038: 97 from GBT440-032, 11 from GBT440-042 and 54 from GBT440-007. The mean (SD) duration of exposure to study drug was 48.0 (46.78) weeks in the study population overall.

Non-SCD related TEAEs:

In total, 95 participants (58.6%) had at least 1 non-SCD related TEAE. The most common non-SCD-related TEAEs were pyrexia (14.2%), anaemia (12.3%) and malaria (8.6%). Most of the events were Grade 1 or 2; 23.5% (38/162) had at least 1 non-SCD-related TEAE Grade 3 or higher. The percentage

of participants with TEAEs considered related to study drug was 3.7%. The percentage of participants experiencing a non-SCD related SAE was 24.1% (39/162). One participant discontinued due to liver function test increased.

SCD-related TEAEs:

In total, 57 participants (35.2%) had at least 1 TEAE; VOC/SCA with crisis was the most common event (32.7%). Of the 57 participants, 35 had Grade 3 events and 2 had Grade 4 events. The percentage of participants with SCD-related TEAEs considered related to study drug was 1.2%. The percentage of participants experiencing a serious SCD-related TEAE was 24.7% (40/162). There was one death in the study further to an acute haemolytic transfusion reaction.

Studies GBT440-4R1 and GBT440-4R2 (RETRO (C5341018) and PROSPECT (C5341019)) registry studies

These studies provide information about voxelotor treatment patterns and clinical outcomes in a real-world setting in the USA. The concerns identified in the exploratory interim analysis provided in early in the procedure, were not replicated in the corrected analyses of the final study reports.

Study GBT440-4R1 (RETRO) was a post-authorisation multicentre, retrospective registry study to characterise health outcomes in 216 participants with SCD aged ≥12 years, who have been treated with voxelotor as part of their usual care. The mean duration was 13.09 months and 83.3% of participants completed the study. Mean age was 33.1 years, most were black or african american (87.5%), and 62.0% were taking HU at baseline. The most common SCD complication pre- (12 months prior to treatment) and post-voxelotor was acute pain crisis (VOCs) (41.2% [89/216] and 55.6% [120/216], respectively). The annualised IR of acute pain crisis (VOCs) was 1.33 events/patient-year prior to voxelotor initiation and 1.54 events/patient-year after voxelotor treatment. There were 5 deaths reported, of which most were accompanied with multiple SCD-related medical conditions. None of the deaths were considered related to voxelotor.

Study GBT440-4R2 (C5341019, PROSPECT) was a post-registration, prospective, open-label, multicentre, registry study. Eligible participants received treatment with voxelotor as prescribed by their physician, as part of their usual care. The study collected data recorded in the participants' medical records and these data were entered in case report forms (CRFs) by the site study staff. A total of 265 participants with SCD (all genotypes) aged ≥5 years were enrolled. The mean (SD) duration of voxelotor treatment was 143.18 (65.588) weeks. The most common (>6% participants) SCD complications were acute pain crisis (VOCs) (71.9%; 187/260 participants), ACS (28.8%; 75/260 participants), pneumonia (7.7%, 20/260 participants), and avascular necrosis (6.2%; 16/260 participants). The annualised IR of acute pain crisis (VOCs) was 4.78 events/patient-year prior to voxelotor initiation and 3.15 events/patient-year after voxelotor treatment. A total of 6 deaths were reported and occurred during the study, none of the deaths were considered related to voxelotor.

Limitations of registries studies

Limitations are generally inherent with RWE studies. Beyond this, additional limitations for RETRO and PROSPECT are noted and the results of these studies are considered supportive only:

- RETRO and PROSPECT were not designed to assess VOCs, which were defined as "acute pain crisis" in these studies, and the number of VOCs during the pre-voxelotor period was not an eligibility criterion. The VOC events were collected as patient-reported data and were entered into the system by site staff based on the participants' medical records. Events that occurred in other settings (e.g., home, hospital, other SCD clinics, emergency room) may not have been recorded in the medical record. In RETRO no source verification or adjudication took place, while in PROSPECT VOC events

were source verified, but not adjudicated. Exacerbations of acute or chronic pain episodes could have been counted as multiple VOC events.

- In RETRO, the data collection method used all occurrences of SCD complications (VOCs) prior-voxelotor that needed to be entered individually, which may have resulted in underreporting. In addition, there could be recall bias of pain episodes, especially to distinguish chronic pain from acute events. In PROSPECT, participants were followed prospectively and may have been followed more closely by healthcare providers, which could have resulted in more reported events, including VOCs, than in the pre-voxelotor period.
- The COVID-19 pandemic at time of the studies may have had a confounding effect on healthcare utilisation.
- Investigators provide standard care, and there is no close monitoring of the participants' drug compliance or changes in medications such as HU are potential confounders of the observed results.
- The laboratory values captured from participants' medical records may include those collected during acute visits (e.g. emergency room, hospitalisation, infusion center) or during occurrence of SCD complications, which could have confounded the pre- and post-voxelotor values. Additionally, timing of recorded laboratory values may vary since this registry was conducted under the direction of the investigator's "standard of care". No set visits were required per the protocol. Assessments and laboratory measurements recorded were over a period of time, and do not reflect the specific post-voxelotor visit timepoint.

2.2.5. Other post-marketing data

A cumulative review of the MAH safety database and of the literature, related to the utilisation of voxelotor and its association with incidents of VOCs/SCA with crisis and death was performed. In particular, in an oral explanation the MAH presented a high-level summary of findings from four investigator-led observational studies. Specifically, Muschick et al. (Eur J Haematol, 2022), De Luna et al. (Eur J Haematol, 2025), Bade et al. (Transfusion, 2022), and Curtis et al. (Am J Hematol, 2022). The summary reflects use of Oxbryta in 147 patients aged 18 years and older across the four studies. Approximately 112 of those participants were also treated with HC, representing between 61% and 100% of participants per study. Treatment duration ranged from three months to one year. No signals for VOC were reported; two deaths occurred in the De Luna study, neither considered related to voxelotor by the author. Adverse events were generally mild and resolved with dose modification, with occasional mild elevation of alanine aminotransferase (ALT) noted.

2.2.6. Discussion on safety

New important safety issues with voxelotor were identified based on the data from the post-authorisation studies GBT440-032 and GBT440-042, in particular an imbalance in fatal cases and VOCs/SCA with crisis.

With respect to deaths, an imbalance was observed in the blinded randomised controlled period of study GBT440-032 and a higher-than-expected number of deaths in the open-label uncontrolled follow-up period of study GBT440-042 in patients aged 12 years and older, both performed post-marketing, and predominantly in SSA area. In study GBT440-032, performed in paediatric patients, 8 deaths were observed in voxelotor treated participants compared to 2 deaths in the placebo arm. Many of the fatal cases described incidence of infection, including 2 patient who developed (fatal) malaria (1 voxelotor, 1 placebo) and 1 septic shock (voxelotor). In study GBT440-042, performed in patients with leg ulcers, in the placebo-controlled period of 12 weeks, 1 death occurred in voxelotor arm and none in

the placebo arm; and 8 deaths in patients using voxelotor during the open-label extension of an additional 12 weeks or longer.

Regarding VOCs, in study GBT440-32, based on a total person-years of 171.3 versus 160.2, the adjusted annualised incidence rate of VOCs was low in both treatment groups, but in the voxelotor group, a higher percentage of patients experienced at least 1 VOC compared to the placebo group and the adjusted annualised incidence rate was higher in the voxelotor group: adjusted annualised VOC rate: 1.098 (95% CI: 0.869, 1.387) voxelotor; 0.580 (95% CI: 0.439, 0.765) placebo, IRR: 1.894 (95% CI: 1.318, 2.722); 2-sided p=0.0006. In study GBT440-042 no annualised incidence rate for VOCs has been evaluated.

With respect to the rates of SCD-related TEAE SCA with crisis, the rates were higher in the voxelotor arm, compared to placebo. In study GBT440-032 the rate was 59.2% (71/120) in the voxelotor arm vs 37.9% (44/116) in the placebo arm; and in study GBT440-042, 44.4% (19/45) in the voxelotor arm vs 25.6% (11/43) in the placebo arm during the 12-week randomised treatment period of GBT440-042.

Also, a trend to a higher number of ACS events on voxelotor was noted in study GBT440-042, with 8.9% in the voxelotor arm and 2.3% in the placebo arm. This issue was also discussed during the initial marketing authorisation application (MAA), as in study GBT440-031 a higher percentage of patients on voxelotor developed ACS compared to placebo (13.6% vs 6.6%). In study GBT440-032, the rates of ACS between arms were rather similar (7.5% voxelotor vs 6.9% placebo).

There was also a trend for a higher rate of SoC infections and infestations in study GBT440-032 (59.2% in the voxelotor arm vs. 50.0% in the placebo arm). Further, there was an imbalance between voxelotor and placebo arms in serious infection rates, primarily due to higher rates of malaria (27.5% vs. 24.1%), upper respiratory tract infection (12.5% vs. 6.0%) and sepsis (7.5% vs. 3.4%) in the voxelotor arm compared to the placebo arm, respectively.

On the contrary, in the pivotal study supporting the initial marketing authorisation, GBT440-031, no imbalance in deaths was observed, with 2 deaths reported in each treatment arm during the placebo-controlled treatment phase of 72 weeks. No detrimental effect on VOCs were noted either, with even a slight positive trend for VOCs in the voxelotor arm versus placebo. The difference between the treatment groups was not statistically significant; however, the study was not powered to detect a difference. Further, the rates of SCD-related TEAE SCA with crisis were similar in both groups (79.1% in placebo and 76.1% in voxelotor arm) in that study.

Therefore, possible explanations as to why voxelotor would lead to higher VOCs/SCA with crisis rates and possibly death in the settings of studies GBT440-032 and GBT440-042 but not of GBT440-031 were investigated.

Relevance of the results from studies GBT440-032 and GBT440-042 on the authorised use of Oxbryta

The cause of the deaths and VOC imbalance in studies GBT440-032 and GBT440-042, which had not been observed in study GBT440-031, was investigated. Possible risk factors or contributors to the imbalance in deaths, included concomitant malaria infection, concomitant HU use, treatment adherence, geography, young age, haemoglobin response, and impact of immunosuppression associated with SCD particularly in young children. The possible role of hampered release of oxygen in tissues from stabilised HbS on susceptibility to VOC, infections and overall immunity was considered too.

Key differences are noted between the pivotal study supporting the initial marketing authorisation, i.e., study GBT440-031, and the post-authorisation studies GBT440-032 and GBT440-042:

- The trial populations were enriched for different factors (VOCs in study GBT440-031, TCD velocity in study GBT440-032 and leg ulcers in study GBT440-042).
- The age of patients in the study GBT440-032 was younger (2 to <15 years of age), while in the studies GBT440-031 and GBT440-042 adults ≥ 12 years of age were included.
- The geographical area where the studies were conducted was different, study GBT440-031 was performed mostly in Europe and USA and studies GBT440-032 and GBT440-042 were performed predominantly in SSA area.
- Annualised incidence rate of VOCs was not a primary endpoint in studies GBT440-032 and GBT440-042 and the events were not adjudicated.

Recognising these differences, the CHMP also noted that the study population in GBT440-042 (≥12 years) overlaps with that of GBT440-031 (12 to 65 years), as well as with the authorised indication for Oxbryta (≥12 years). Additionally, the paediatric population in study GBT440-032 shows a partial overlap with GBT440-031 and the approved indication, given that 29 out of 236 children enrolled in GBT440-032 were aged 12–15 years. Although the number of patients aged 12–15 years included in study GBT440-032 is relatively low, the severity of the safety concerns makes the overlap between populations highly relevant. Data from all ages are therefore considered relevant for the authorised indication. While it is acknowledged that infections may be more common in children, no risk factors emerge from the randomised studies that are age dependant.

The impact of voxelotor on susceptibility for infections/immunity is likely to have more severe consequences in areas with high background infection rates and with a lower degree of medical care compared to the EU. Due to functional asplenia related to SCA causing immune deficiency, the increased risk of infections particularly in children and/or endemic disease in the SSA region could be considered a contributing factor to the differences observed in study GBT440-032 versus studies GBT440-031 and GBT440-042. Importantly, infections are known to increase the risk of VOCs. In this regard, differences in certain AEs related to infections were observed in the voxelotor arm compared to placebo (malaria, sepsis, pyrexia, upper respiratory tract infection), and the majority of death cases in the voxelotor arm were concurrent with ongoing infections. Moreover, clear immunosuppressive effects of voxelotor were observed in rat and monkey studies, at the time of the MAA. Collectively, the clinical data show that voxelotor might possibly increase susceptibility to (severe) adverse events in certain groups of patients. However, the CHMP and the ad hoc expert group (AHEG) agreed that the geographical area of the trials alone does not account for the observed imbalance in VOCs/SCA with crisis and deaths between voxelotor and placebo in studies GBT440-032 and GBT440-042. While it is acknowledged that factors such as endemic diseases (including malaria), malnutrition, and limited access to healthcare associated to the SSA region may contribute to more severe manifestations of SCD, both studies conducted in SSA were double-blinded, randomised controlled trials. These contextual factors would therefore be expected to affect both treatment arms equally and cannot fully explain the discrepancies in VOCs/SCA with crisis and deaths between both arms. Further, while an increased rate of malaria or other infections in the voxelotor arm could have potentially contributed to the increased VOC rates, in the context of a randomised controlled trial, the differential occurrence of infection events may likely be attributed to the randomised treatment.

Therefore, none of these factors could be clearly identified as a single causal factor responsible for the deaths, VOCs and/or the higher incidence of SCA with crisis observed in the voxelotor arm in both studies. This view was shared by the AHEG. Although study GBT440-031 did not show any detrimental effect on VOC incidence, the results collected in the two studies performed in the SSA cannot be disregarded and it remains unclear what risk factors or mechanisms led to the observed detrimental effects of the treatment in the two studies conducted in the SSA (GBT440-032 and GBT440-042).

In addition, real word data available from the two registry studies conducted in the USA did not provide reassurance regarding the risk of increased VOCs with voxelotor. These studies present a number of limitations and should be considered with caution. Likewise, newly available data coming from study GBT440-007 Parts C-D and the OLE studies showed no clinically relevant signal of VOCs or deaths, but do not provide additional reassurance regarding the safety of Oxbryta considering their open label, uncontrolled design.

A cumulative review of the MAH safety database and of the literature, related to the utilisation of voxelotor and its association with incidents of VOCs/SCA with crisis and death did not bring significant additional information. The investigator-led observational studies suffer from the same limitations as the MAH sponsored open label studies.

In conclusion, given that the causes of the increase in deaths and VOCs/SCA with crisis are unknown and the at-risk populations cannot be identified, the identified risks of death and VOCs/SCA with crisis are considered to be of relevance also to the EU population.

Other issues

Clear trends indicating an increase in VOC/SCA with crisis, pyrexia, and arthralgia with voxelotor compared to placebo were observed in the two the post-authorisation randomised controlled trials (RCTs). However, it is noted that these adverse events are not currently included in section 4.8 of the Summary of Product Characteristics (SmPC).

Additionally, the SmPC does not provide guidance on several key aspects of dose management, including a temporary dose reduction in case of adverse events, a de-escalation/dose tapering strategy upon treatment discontinuation, and dose escalation at treatment initiation and warning regarding ADRs due to abrupt discontinuation of voxelotor. It should be noted that the impact of abrupt discontinuation versus gradual tapering was not formally studied in any of the clinical studies. Although 2 deaths and a number of VOCs were reported following treatment discontinuation, the available data do not support the implementation of specific recommendations in this regard. However, as reported in an AHEG meeting, following the withdrawal and market recall of the product by the MAH in 2024, which resulted in the absence of treatment availability for patients, the effects of abrupt withdrawal varied among patients. While some patients did not experience adverse effects related to abrupt discontinuation, others developed severe crises. These findings suggest a potential need for a gradual dose reduction strategy when discontinuing treatment, as well as a titration approach at treatment initiation based on gastrointestinal tolerability.

2.3. Data on efficacy

2.3.1. Study GBT440-031 (HOPE, C5341043)

The clinical efficacy of voxelotor in the authorised indication was established during the initial marketing authorisation application based on the assessment of data from the pivotal Phase III study GBT440-031 (HOPE, C5341043).

In subjects receiving voxelotor 1500 mg or 900 mg respectively, 51.1% (46/90) and 32.6% (30/92) of subjects achieved an Hb response (> 1 g/dL increase in Hb from baseline) at Week 24, compared with 6.5% (6/92) of the subjects receiving placebo ($p < 0.001$ for both voxelotor dose groups vs placebo).

A dose-dependent increase in Hb was observed, with mean change from baseline at Week 24 of 1.13 g/dL for the voxelotor 1500-mg group, compared with 0.58 g/dL for the voxelotor 900 mg group and -0.10 g/dL for the placebo group. The increase in Hb levels (on average) was readily observable after 2 weeks of voxelotor administration and was sustained through 72 weeks.

Concurrent with a mean increase in Hb, voxelotor also decreased clinical measures of haemolysis on average, in a dose-dependent manner. This decrease was observed beginning at Week 2 and generally maintained through 24 weeks in the voxelotor 1500 mg treatment group. The significant difference between voxelotor 1500 mg and placebo groups was sustained at Week 72 for indirect bilirubin.

2.3.2. Study GBT440-032 (HOPE KIDS 2, C5341021)

The primary efficacy endpoint of change from baseline at 24 weeks in TAMMV arterial cerebral blood flow, as measured by TCD was met. Treatment with voxelotor resulted in a statistically significant reduction in TCD flow velocity compared to placebo at Week 24. These reductions were sustained at Week 48, meeting the key secondary endpoint.

Specifically, the adjusted mean (SE) change in TCD flow velocity at Week 24 was -12.06 (1.916) cm/sec for the voxelotor group and −4.29 (1.983) cm/sec for the placebo group, resulting in a treatment difference of 7.77 cm/sec (95% CI: -13.18 to -2.37; 2-sided p = 0.0048).

Treatment with voxelotor also showed improvements in other secondary endpoints, including Hb levels, and clinical markers of haemolysis such as LDH, reticulocytes, and specifically indirect bilirubin. A higher proportion of participants in the voxelotor group achieved an Hb response (defined as ≥1 g/dL increase from baseline) compared to placebo at both Week 24 (42.6% vs 9.1%) and Week 48 (37.4% vs 11.2%), with statistically significant differences at both timepoints ($p < 0.0001$).

2.3.3. Study GBT440-042 (RESOLVE, C5341026)

The study did not meet its primary endpoint of achieving resolution of the target ulcer(s) by Week 12. 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 Cochran–Mantel–Haenszel (CMH) proportion between the voxelotor and placebo groups was 0.3% (95% 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 favouring the placebo group.

At Week 12, the mean change from baseline (CFB) in Hb was 1.9 g/dL in the voxelotor and -0.0 g/dL in the placebo arm; and the mean CFB in indirect bilirubin was -29.5 µmol/L in the voxelotor arm and 2.8 µmol/L in the placebo arm.

2.3.4. Other studies

Participants who previously received placebo in study GBT440-031 had an improvement in Hb over time and improvement of clinical markers of haemolysis in study GBT440-034 compared to baseline. Those who received voxelotor in study GBT440-031 experienced durability of response in study GBT440-034.

In study GBT440-007 part C, no subject converted to an abnormal TCD during the course of the study and treatment with voxelotor was shown to improve anaemia and reduce clinical measures of haemolysis in participants aged 4 to 11 years with SCD. In study GBT440-007 part D, treatment with voxelotor was shown to improve anaemia and reduce clinical measures of haemolysis in participants aged 2 to <4 years. Overall, in both parts, efficacy in participants aged 4 to 11 years and 2 to <4 years, respectively, was consistent with that previously observed in adults and paediatric participants aged 12 years and older.

In the registry studies RETRO and PROSPECT, the results also suggest comparable effectiveness with regard to Hb increase and decrease in haemolytic markers. In RETRO study, mean (SD) of the maximum increase in Hb from baseline was 1.3 g/dL (1.57) (from 7.8 g/dL [SD 1.51] to 9.2 g/dL [SD 2.01]); Hb remained increased compared to baseline over the 12-month treatment period. In PROSPECT study, the mean (SD) of the maximum change in Hb from baseline (pre-voxelotor) was 2.0 g/dL (1.62) (from 7.8 g/dL [SD 1.36] to 9.8 g/dL [SD 1.81]).

Per protocol, the open-label extension study GBT440-038 did not collect efficacy outcomes.

2.3.5. Discussion on efficacy

In the pivotal study of the MA (study GBT440-031), a significant Hb response was observed, with 51.1% of patients in the Oxbryta arm achieving the predefined increase in Hb levels, compared to 6.5% in the placebo group, showing improvement in haemolytic anaemia in patients with SCD. Overall, long-term efficacy data is limited to data generated from GBT440-031 and its subsequent OLE study GBT440-034.

The CHMP recognises the haemolytic benefit of voxelotor across studies and populations, including improvements in Hb levels and haemolysis markers as demonstrated at the time of the MA and confirmed in studies GBT440-032 and GBT440-042.

Additional potential benefits were also noted from study GBT440-032. Indeed, in this study a reduction is seen in TCD flow velocity at Week 24, with a least squares mean (±SE) change from baseline of -12.15 (±1.881) cm/sec in the Oxbryta group versus -4.51 (±1.945) cm/sec in the placebo group. This reduction in TCD flow velocity may reflect a potential benefit in reducing cerebrovascular risk. TCD velocity is known to be a predictor for risk of stroke in paediatric patients.

However, while improvements in leg ulcers were observed in a small number of patients in study GBT440-031, study GBT440-042 failed to confirm those findings. The impact on leg ulcer resolution was low and not different from placebo.

The CHMP also noted the supportive evidence coming from the open labelled study GBT440-007 and the corrected analyses in the final CSR of the two registry RWE studies (RETRO and PROSPECT), which showed comparable efficacy outcomes and no clinically relevant imbalance in VOCs and deaths.

Several experts of the AHEG acknowledged that the increase in Hb observed with voxelotor may offer clinical benefit, particularly in addressing the burden of chronic haemolytic anaemia and reducing fatigue. However, they emphasised the need for additional clinical data to assess the impact of voxelotor on other complications, using robust clinical endpoints.

Therefore overall, even though the efficacy of voxelotor to treat haemolytic anaemia is not disputed (demonstrated by Hb response rate from baseline to Week 24), the clinical relevance of observed increase in Hb and decreases in haemolysis parameters for the occurrence of (long-term) complications due to SCD was not studied. Indeed, Hb level or haemolytic activity are not accepted surrogates for other outcomes.

2.4. Non-clinical aspects

At the time of the MA, non-clinical data showed decreased humoral immune response to antigens, changes in the relative lymphocyte distribution in both rats and monkeys and gastrointestinal effects possibly caused by opportunistic infections in monkeys. These effects were seen at the exposure multiple of the anticipated clinical exposure ~0.6 in monkeys and ~4.0 in rats based on plasma Cmax value. The known decreased humoral immune response to antigens of voxelotor links to the concern

arising from the post-authorisation clinical data showing that voxelotor might possibly increase susceptibility of patients to (severe) infections, particularly in children, and an active infection may have been contributory to the confluence of events that lead to fatal outcomes or VOCs.

No new non-clinical studies have been conducted since the MA, and no non-clinical literature related to voxelotor and immune suppression was identified. Additionally, the role of underlying malaria in the observed imbalances remains currently unclear and non-clinical data investigating the possibility of an interaction between malaria parasite and voxelotor mechanism of action is missing. It is understood from the MAH that non-clinical studies may be ongoing to assess the interplay of voxelotor and malaria in both in vitro and in vivo assays.

3. Expert consultation

The CHMP consulted an ad hoc expert group (AHEG) on several questions. The AHEG was composed of haematologists, tropical medicine experts and patients' representatives. In addition, the CHMP sought the advice from the Pharmacovigilance Risk Assessment Committee (PRAC). Their respective advice are provided below.

1. AHEG

Question 1. Please comment on the medical need for voxelotor based on the available data and your clinical experience with voxelotor in its approved indication, particularly in managing haemolytic anaemia and reducing sickle cell disease (SCD) complications.

Overall, the experts consistently highlighted the need for therapeutic options for patients with SCD. The experts who had direct experience with voxelotor, reported mixed clinical outcomes in patients who had different SCD treatment needs.

Several experts acknowledged that the increase in Hb observed with voxelotor may offer clinical benefit, particularly in addressing the burden of chronic haemolytic anaemia and reducing fatigue. However, they emphasised the need for additional clinical data to assess the impact of voxelotor on other complications, using robust clinical endpoints.

There was a consensus among the experts that the safety signals (e.g. deaths and VOCs) observed in the post-marketing studies GBT440-032 and GBT440-042 must be taken seriously.

The patient representatives stressed the importance for safe, effective, and accessible treatments for SCD. One patient representative stressed that in Europe seasonal illnesses such as flu pose significant risks for patients in the absence of adequate SCD treatment.

Question 2. In the context of conflicting data on vaso-occlusive crisis (VOC) and death observed across the randomised controlled studies (RCT) C5341043/GBT440-031, C5341021/GBT440-032 and C5341026/GBT440-042 with voxelotor, the experts are asked to comment on:

a. the likely mechanism(s) involved;

Experts noted that the studies had a randomised controlled study design, and therefore they were not designed to identify such mechanisms or risk factors making the task rather difficult, and quite speculative.

No definite mechanism could be agreed by the experts. One expert suggested that the profile of initial Hb rise upon initiation of treatment with voxelotor might be particularly relevant in patients with VOC phenotype, as it could potentially lead to an increased frequency of VOC episodes in this group compared to those with a haemolytic phenotype. This was supported by the fact that upon transfusion the target Hb values are always below the normal range to reduce complications such as stroke. Another expert noted however that no correlation was seen between increased Hb values and cumulative risk of VOC in study GBT440-031. The possible decrease in peripheral tissue oxygenation which may be related to voxelotor treatment, was also suggested by an expert as a possible mechanism.

Experts highlighted the need to clarify the causes of the imbalance in deaths and to consider possible confounding factors, such as nutritional status, geographical location, malaria prophylaxis, regional healthcare disparities, disease heterogeneity and social vulnerabilities, in both sub-Saharan and European contexts. One expert highlighted that vulnerable populations in Europe, such us paediatric patients, refugees and individuals with limited access to healthcare and poor nutrition may also be at increased risk.

The experts broadly agreed that more data is needed to understand the interaction between voxelotor and malaria in patients with SCD.

b. the potential risk factors that could explain the increased rates of VOCs and deaths in the C5341021/GBT440-032 and C5341026/GBT440-042 trials;

The experts could not reach a conclusion on specific risk factors due to several limitation identified. While several potential risk factors in the SSA population were raised during the discussion by several experts, these were acknowledged to be speculative and not supported by conclusive evidence.

Discussion focused on study limitations such as inconsistent use of hydroxyurea (HU), possible differences in access to optimal health systems, uncertainties in criteria to characterise VOCs, or possible difficulties in determining the exact cause of death, lack of information on how voxelotor was withdrawn in the studies upon occurrence of adverse events and the fact that there was limited information regarding possible interactions between malaria and voxelotor. Based on the oral presentation from the MAH, there was apparently uncertainties regarding the handling of study participants who contracted infections, in particular malaria.

c. whether a specific subset of the patient population for which voxelotor is authorised in the EU can be identified for whom the potential and identified risks with voxelotor could be effectively mitigated.

The group agreed that safety concerns remain. The majority of the experts stated that adult patients treated with HU and taking prophylactic treatment for malaria when travelling to endemic regions might qualify for treatment, although a general apprehension remained in connection to the safety concerns. Acknowledging the medical need in children (<18 years) and patients not taking HU, several experts raised concerns regarding the use of voxelotor in these groups before the safety profile is further ascertained.

One expert was of the opinion that in the EU, voxelotor treatment might be reserved to patients really needing Hb increase, such as those who lack access to regular blood transfusions.

Question 3: Please describe the current clinical practices for routine monitoring of patients with SCD, including those pertaining to the identification and management of VOC events and infections.

The experts limited their response to this question to European countries. Monitoring is generally guided by established clinical guidelines and, overall, the approach to outpatient treatment seems harmonised across the countries of the experts, with minor differences.

Experts described that the periodicity of the monitoring is tailored to the severity of patients' conditions. Generally, adult patients not on HU on a steady state are monitored every 6 months, whilst patients on HU are monitored on a 2-3 months' basis and patients under transfusion and pregnant patients are monitored more closely. Paediatric patients are generally monitored more frequently, usually every 2-3 months after time of diagnosis (depending on whether there are newborn screening programs in place) and later every 6 months. At least once a year blood tests and other additional tests are performed to assess end organ damage. Notably, monitoring is performed by specialists (such as paediatricians and haematologists) and seldom by the patients' general practitioners.

Important points highlighted by different experts or patient representatives:

- Patients communicate directly with physicians for symptoms to be assessed remotely, they also have direct phone contact with haematology teams, especially during VOC episodes or infections. Rapid response and hospital admission are common when symptoms escalate;
- Patients are educated regarding risk of VOCs, infections and pain management;
- The need to inform patients to take prophylactic medication when travelling to regions where malaria is endemic was highlighted;
- Travel-related issues (e.g., lack of medication during holidays) were noted as common triggers for crises;
- Children are given penicillin until the age of 5 years, and the completeness of the immunization program is monitored into adulthood.

Question 4: Based on your experience in clinical practice, would you consider any potential optimisation of the dose recommendations (including gradual step-up/step-down) to be appropriate?

Based on the observation from one expert, it was noted that based on gastrointestinal tolerability, a dose titration approach should be used when commencing treatment with voxelotor, gradually increasing the daily dose up to 1500 mg. In case of treatment withdrawal, a gradual step-down approach should be used to avoid the possibility of side effects such as haemolytic crisis.

It was flagged by another expert that when the product was withdrawn and recalled from the market in 2024 with no treatment availability for patients, the effects of abrupt withdrawal varied among patients. Some experienced no clinical manifestations linked to the rapid withdrawal, while others developed severe crises. This supported the likely need to gradually step-down the dose in case of treatment discontinuation.

Question 5: The experts are asked to comment on:

a. the appropriateness of the proposed risk minimisation measures

Several experts also commented on general SCD information leaflet or card already being provided to patients. The patient representatives commented that they find it useful. While no strong objection was raised regarding the introduction of a patient card, its added value in the minimisation of VOC severity and frequency among patients treated with voxelotor was questioned both by experts and patient

representatives. If retained nonetheless, besides formal patient information, the patient card should be specific on vigilance of infections, include information for patients going to malaria endemic regions, risk of death, as well as information on how to proceed in case of treatment withdrawal (i.e. gradual step-down).

The expert group considered that the potential increased risk of VOC is a critical concern and a patient card alone would be insufficient to ensure safe use.

One expert raised concern on the patient card, as appearing to place the responsibility primarily on the patient.

Transparent information to patients and healthcare professionals regarding the studies' results and related uncertainties was considered important, to support informed decisions.

b. whether any other measures would be considered necessary to minimise the risks under evaluation

Additional measures considered necessary by the experts included increased clinician monitoring by higher frequency of visits to identify complications in a timely manner, appropriate infection prophylaxis specially for malaria and, if possible, patients should be under stable HU treatment.

One expert commented as well on the need to have voxelotor prescribed by the specialised centres only.

2. PRAC advice to the CHMP

PRAC advice was sought to identify potential risk minimisation measures that could effectively mitigate the risk of VOC and death observed in the voxelotor treatment arms of studies GBT440-032 and GBT440-042, within any subset of the authorised patient population for Oxbryta.

The PRAC considered that the risk of VOCs is an important identified risk of voxelotor that warrants effective risk minimisation measures (RMMs).

Given that the underlying mechanisms contributing to the increased risk of VOCs/SCA with crisis and death observed in the studies GBT440-032 and GBT440-042 conducted in sub-Saharan Africa (SSA) are not established, the PRAC concludes that no risk factors or specific patient population at increased risk can be identified. Consequently, no targeted RMMs (e.g. warnings, contraindications or restrictions) to exclude such patients from treatment with voxelotor can be proposed.

The PRAC considered the potential effectiveness of a patient card and a Direct Healthcare Professional Communication (DHPC) and noted the latest MAH's proposal for close monitoring for improvement of haemolytic anaemia, a risk awareness dialogue form and a patient diary. It was concluded that these tools would not effectively minimise the risk of VOC and death considering that close routine clinical monitoring is already standard practice for this patient population and more frequent clinical assessment is considered unlikely to be effective for prior detection and prevention of infections or VOCs.

No risk minimisation measures were identified by PRAC that could effectively mitigate the risk of VOC and death in patients treated with voxelotor.

4. Benefit-risk balance

The CHMP critically reviewed all available data in relation to the efficacy and safety of Oxbryta to determine whether there is an impact on the benefit-risk balance of Oxbryta in its authorised indication. This included the pivotal study GBT440-031, two post-authorisation studies (GBT440-032 and GBT440-042), two extension studies (GBT440-034 and GBT440-038), as well as two registry-based studies (PROSPECT and RETRO), in the context of all available data submitted by the MAH in writing and during an oral explanation (OE). The CHMP also consulted an ad hoc expert group (AHEG) and the Pharmacovigilance Risk Assessment Committee (PRAC).

In the pivotal study of the initial marketing authorisation, i.e., study GBT440-031, no detrimental effects on incidence of death or VOCs/SCA with crisis were observed. On the contrary, a slight favourable trend in the rates of VOC was observed following prolonged treatment. However, studies GBT440-032 and GBT440-042 showed an imbalance in the incidence of death (study GBT440-032), a higher-than-expected number of deaths (open-label uncontrolled follow-up period of study GBT440-042), and an imbalance in VOCs (study GBT440-032) and rate of SCD-related SCA with crisis (both studies).

In study GBT440-032, the incidence of SCA with crisis was 59.2% in the voxelotor arm vs 37.9% in placebo. Although absolute VOC incidence remained low, the annualised rate of VOCs showed an imbalance with 1.098 and 0.580 events/year in the voxelotor and placebo arms, respectively. Eight (8) deaths were reported in the voxelotor treatment group, compared to two (2) deaths in the placebo group.

In study GBT440-042, the incidence of SCA with crisis was 44.4% in participants receiving voxelotor vs 25.6% in the placebo arm during the 12-week randomised treatment period. However, no VOC incidence was evaluated. A total of 11 deaths were reported in patients treated with voxelotor, of which one occurred during the placebo-controlled, blinded period, eight occurred during the open-label extension period, and two occurred after the study was paused. No deaths were reported in the placebo group.

The CHMP considered the multiple potential contributing factors to the increased rates of death and VOC/SCA with crisis observed in the voxelotor arms of studies GBT440-032 and GBT440-042, but which were not observed in study GBT440-031. These factors included concomitant infections, concomitant HU use, treatment adherence, geography, young age, haemoglobin response, and impact of immunosuppression associated with SCD. The possible role of hampered release of oxygen in tissues from stabilised HbS on susceptibility to VOC, infections and overall immunity was considered too. The increased number of deaths on voxelotor compared to what was seen in study GBT440-031 could potentially be explained by a suboptimal patient care received during (an) acute event(s) (e.g., VOC, sepsis, or malaria). Nevertheless, no single causal factor could be identified as responsible for the observed differences between the voxelotor arm and the placebo arm in the two post-authorisation studies GBT440-032 and GBT440-042, or between these studies and study GBT440-031. In this respect, it must be noted that these two post-authorisation studies concerned randomised controlled trials, which would correct the influence of any external factors (such as suboptimal patient care) as they would apply equally to both arms.

Moreover, clear immunosuppressive effects of voxelotor were observed in rat and monkey studies, at the time of the MAA. Collectively, the clinical data show that voxelotor might possibly increase susceptibility to (severe) adverse events in certain group of patients. However, possible mechanisms that make a subpopulation more susceptible to these adverse events are unknown. Therefore, it is not possible to identify a specific patient population at increased risk in order to exclude such patients from treatment with voxelotor.

Overall, the safety data presented is of concern. Given that the causes of the increase in deaths and VOCs/SCA with crisis are unknown and the at-risk populations cannot be identified, it is clear that risk factors cannot be mitigated. Therefore, the CHMP considers that the identified risks of death and VOC/ SCA with crisis are of relevance to Oxbryta in its authorised indication in the EU.

Several potential measures to minimise the risks of VOC and death in patients with SCD have been considered. These included increased clinical monitoring, restrictions to the indication, communication about the risks identified and a controlled access programme integrated with a registry to enforce the restricted use and enable the collection of evidence to characterise VOC and death in the EU population.

Following the advice of the AHEG, the MAH proposed to increase the frequency of monitoring for improvement in haemolytic anaemia (laboratory results and clinical status) to, at least every 4 weeks for the first 3 months after treatment initiation, followed by 3-monthly monitoring (following the frequency of routine monitoring in study GBT440-031 and its subsequent open-label extension study). However, as also highlighted by the AHEG, close routine clinical monitoring is already standard practice for this patient population. VOC is the most common and characteristic clinical manifestation of SCD, which is monitored as part of routine clinical practice i.e. reviewing VOC history since last visit, assessing patterns of increased severity or frequency and evaluating the occurrence of chronic pain vs. acute VOCs. Therefore, in the view of CHMP, and as advised by PRAC, more frequent clinical assessment is considered unlikely to be effective for prior detection and prevention of infections or VOCs.

The MAH also proposed restricting the indication to less vulnerable patients or in the absence of alternative treatment options (i.e. restricting only to adults receiving concomitant hydroxycarbamide (HC), or as monotherapy for whom HC is inappropriate or at high risk of blood transfusion complications, and recommending against the use in patients with active leg ulcers). The MAH further proposed to communicate about the risks identified through the addition of warnings and precautions in the product information and the introduction of a patient card, later replaced by the introduction of a controlled access programme aimed at supporting the use in this restricted patient population. This programme would include a Healthcare Professional (HCP) guide to increase awareness of risks, while also supporting therapeutic decisions and counselling on the risks; a HCP checklist to document appropriateness of the prescription; a risk awareness dialogue form to document discussions between prescribers and patients, along with recommended actions should they arise; and a patient diary to capture VOC events for discussion during healthcare visits. The dissemination of a DHPC was also proposed in order to ensure awareness of HCP regarding the new risks and associated measures.

However, since the mechanisms underlying the increased risk of VOCs/SCA with crisis and death observed in studies GBT440-032 and GBT440-042 are unknown, no specific risk factors or patient subgroups at no risk could be identified. The CHMP shares the view of the AHEG regarding the need for therapeutic options for patients with SCD. However, while SCD is recognised as a disease with a high unmet medical need, it is important to note that the authorised indication for voxelotor specifically targets the treatment of haemolytic anaemia resulting from SCD, rather than the disease itself.

The PRAC also advised that, in the absence of an evidence-based strategy to mitigate the risks of VOC and death, and without identification of the risk factors contributing to these adverse outcomes, the risks associated with voxelotor cannot be adequately mitigated. As a consequence, no population within the authorised indication for Oxbryta in the EU at no risk of VOC and death could be identified. Moreover, extensive information is already provided to these patients as part of their ongoing care, and the proposed additional communication tools are not expected to improve the management or otherwise effectively minimise the risks. Likewise, regarding the proposed controlled access programme to support the use of Oxbryta in a restricted patient population, it should be recalled that it

has not been possible to identify a population in which the risk of VOC and death is absent. Therefore, the proposed restricted indication does not differentiate or narrow the population by risk factors. Instead, it focuses on the use of voxelotor as mono or combination therapy with HU, which is not considered to be based on existing robust data given that HU use did not show a consistent effect on deaths and VOCs/SCA with crisis events. In patients with complications from blood transfusions, Oxbyta is neither a life-saving therapy nor has it been evaluated for its impact on Quality of Life. Even under a narrowly defined indication, there are no available measures to mitigate the risks associated with VOCs or SCA with crises, including the potential for fatal outcomes. In addition, the counselling provided in the context of the controlled access programme is not considered to meaningfully contribute to the management of these risks, in view of the extensive information already received by patients treated with Oxbryta. In consequence, while a controlled access programme might in the future yield further insights regarding the occurrence of these events, it would not protect at time of implementation patients exposed to Oxbryta against the risk of VOC and death. Therefore the CHMP, in line with the PRAC, concludes that the measures considered would not adequately minimise the risk, in any of the subsets of the authorised indication.

In conclusion, considering the seriousness of the identified risks, in the context of the benefits of Oxbryta, the CHMP is of the view that the benefit-risk balance of Oxbryta is not favourable in all subsets of the authorised indication.

While it is understood from the MAH that a double-blinded randomised controlled trial to further characterise the risk of VOC may be performed in the USA and Europe, the outcome of such trial remains entirely hypothetical; and this proposal in any event has no bearing on the conclusion based on the data available at present. The same applies to possible alternative study designs considered by the MAH, namely a registry capturing all voxelotor-exposed patients within a controlled access programme, using a matched control design, or a pragmatic randomised controlled trial with a real-world data control arm.

The CHMP, having considered the matter, recommends the suspension of the marketing authorisation for Oxbryta. The CHMP considers that, for the suspension to be lifted, additional robust evidence is needed to define a clinically relevant patient population in which the benefit-risk balance of voxelotor is favourable.

This conclusion is without prejudice to the potential need for other updates to the terms of the marketing authorisation in view of the new data assessed in this procedure (e.g. regarding observed ADRs and gradual dosing reduction strategy when discontinuing treatment, as discussed in section 2.2.5) if the suspension of the marketing authorisation would be lifted.

5. Condition for lifting the suspension of the marketing authorisation

For the suspension to be lifted, the marketing authorisation holder shall submit robust evidence that defines a clinically relevant patient population in which the benefit-risk balance of the treatment is favourable.

6. Grounds for Opinion

Whereas,

- The Committee for Medicinal Products for Human Use (CHMP) considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Oxbryta (voxelotor).

- The CHMP reviewed the data from studies GBT440-032 and GBT440-042, in the context of all available data submitted by the MAH in writing and during an oral explanation, as well as the views expressed by a group of independent experts and patient representatives at an ad hoc meeting (AHEG) and the outcome of a consultation with the Pharmacovigilance Risk Assessment Committee (PRAC).
- The CHMP noted the established efficacy of voxelotor to treat haemolytic anaemia.
- The CHMP noted an increased number of vaso-occlusive crises (VOCs)/sickle cell anaemia (SCA) with crisis and deaths with voxelotor compared to placebo in the randomised controlled studies GBT440-032 and GBT440-042.
- The CHMP noted that the underlying mechanisms that could explain the increased numbers of VOCs/SCA with crisis and deaths following treatment with voxelotor in studies GBT440-032 and GBT440-042 are not established. Therefore, the CHMP considered these important new safety concerns relevant to the authorised use of Oxbryta in the EU.
- In the absence of specific risk factors, the CHMP could not identify any measures that could effectively minimise these risks, nor any subset of patients within the authorised indication in which the benefits of Oxbryta would outweigh the identified risks.

The Committee, as a consequence, considers that the benefit-risk balance of Oxbryta is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the suspension of the marketing authorisation for Oxbryta.

In order for the suspension to be lifted, the MAH shall submit robust evidence that defines a clinically relevant patient population in which the benefit-risk balance of the treatment is favourable.