16 December 2021
EMA/102184/2022
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Oxbryta

International non-proprietary name: voxelotor

Procedure No. EMEA/H/C/004869/0000

Note

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

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List of abbreviations

Abbreviation	Definition
ACS	acute chest syndrome
ADR	adverse drug reaction
AE	adverse event
ALK	alkaline phosphatase
ALT	alanine transaminase
CB	Common Blend
CI	confidence interval
CKD	chronic kidney disease
CGI-C	Clinical Global Impression of Change
CGI-I	Clinical Global Impression of Improvement
C_{max}	maximum blood or plasma concentration
C_{min}	minimum blood or plasma concentration
CSR	Clinical Study Report
CSSCD	Cooperative Study of Sickle Cell Disease
CYP	cytochrome P450
DDI	drug-drug interaction
EAP	Expanded Access Programme
ECG	electrocardiogram
EHA	European Hematology Association
EMA	European Medicines Agency
EU	European Union
F	Formulation
FDA	Food and Drug Administration
FIH	first-in-Human
GI	gastrointestinal
GBT	Global Blood Therapeutics, Inc.
Hb	haemoglobin
HbF	fetal haemoglobin
HbS	sickle haemoglobin
HbSβ^0thalassemia	sickle haemoglobin (S) and 1 beta zero thalassemia gene
HbSβ^+thalassemia	sickle haemoglobin (S) and 1 beta plus thalassemia gene
HbSC	haemoglobin sickle cell disease with 1 HbS sickle cell gene and 1 haemoglobin C (HbC) gene
HbSS	haemoglobin sickle cell disease with 2 sickle cell genes (SS)
HRQoL	health-related quality of life
%HbMOD	Percentage Hb modification
HU	hydroxycarbamide (hydroxyurea)
IPF	idiopathic pulmonary fibrosis
IR	incidence rate
ITT	Intent-to-Treat
LDH	lactate dehydrogenase
LS	least-squares

Abbreviation	Definition
MAA	marketing authorisation application
MATE	multidrug and toxin extrusion
MMRM	mixed-effect model for repeated measures
NHLBI	National Heart, Lung, and Blood Institute
NO	nitric oxide
OAT	organic anion transporter
OATP	organic anion-transporting polypeptide
OLE	open-label extension
P-gp	P-glycoprotein
PASP	pulmonary artery systolic pressure
PBPK	physiologically based PK
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PPK	population pharmacokinetic(s)
PPPY	per patient per year
PRF	Patient Record Form
PT	Preferred Term
QD	once daily
QTc	corrected QT
RBC	red blood cell
RR	relative risk
SAE	serious adverse event
SCD	sickle cell disease
SCI	silent cerebral infarction
SD	standard deviation
SE	standard error
SOC	System Organ Class
STOP	Stroke Prevention in Sickle Cell Anemia
$t_{½}$	half-life
TCD	transcranial Doppler
TEAE	treatment-emergent adverse event
TQT	thorough QT
UGT	uridine 5'-diphospho-glucuronosyltransferase
US	United States
VOC	vaso-occlusive crisis
WBC	white blood cell

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Global Blood Therapeutics Netherlands B.V. submitted on 23 December 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Oxbryta, through the centralised procedure falling within Article 3(1) and point 4 of Annex I of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 June 2017.

Oxbryta was designated as an orphan medicinal product EU/3/16/1769 on 18 November 2016 in the following condition: Treatment of sickle cell disease.

The applicant initially applied for the following indication:

"Oxbryta is indicated for the treatment of haemolytic anaemia in adults and paediatric patients 12 years of age and older with sickle cell disease (SCD). Oxbryta can be administered alone or in combination with hydroxycarbamide."

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Oxbryta as an orphan medicinal product in the approved indication. More information on the COMP's review can be found in the Orphan maintenance assessment report published under the 'Assessment history' tab on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Oxbryta

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included EMA Decision P/0489/2020 dated 21 December 2020 on the agreement of a paediatric investigation plan (PIP) and on the granting of a waiver and a deferral for voxelotor in accordance with Regulation (EC) No 1901/2006 of the European Parliament and of the Council.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Applicant's requests for consideration

1.5.1. Accelerated assessment

The applicant requested accelerated assessment in accordance with Article 14(9) of Regulation (EC) No 726/2004. Upon examination of the request the CHMP concluded that the unmet medical need in patients with haemolytic anaemia associated with SCD is acknowledged, the innovative character of the mechanism of action is recognised and the provided evidence indicate that the drug has an effect on anaemia and haemolysis markers. However, provided data do not allow to assess to what extent the pivotal trial population represents the population with high unmet medical need. This precludes the assessment of the potential of the product to address the major public health interest and to provide major therapeutic innovation. Therefore the CHMP did not agree to the request for an accelerated assessment, as it was considered not sufficiently substantiated.

1.5.2. New active substance status

The applicant requested the active substance voxelotor contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. PRIME

Voxelotor was granted eligibility to PRIME on 23 June 2017 in the following indication: Sickle Cell Disease.

Eligibility to PRIME was granted at the time in view of the following:

- The unmet medical need has been justified on the basis of reduced survival of affected patients, clinical complications and morbidity;
- The potential to significantly address the unmet medical need has been justified on the basis of preliminary clinical observations, supporting that treatment with the proposed product may result in reduced haemolysis and improvements in haemoglobin levels.

Upon granting of eligibility to PRIME, Paula van Hennik was appointed by the CHMP as rapporteur.

A kick-off meeting was held on 22/01/2018. The objective of the meeting was to discuss the development programme and regulatory strategy for the product. The applicant was recommended to address the following key issues through relevant regulatory procedures:

- clinical aspects including the statistical analysis plan for the main population analysis in study GBT440-031 and use of patient-reported outcome measures;
- the paediatric investigation plan and specifically the design of study GBT440-032 including enrolment of younger children and bracketing of the 6 to <12-years cohort;
- plans for an expanded access programme and the design of a registry for sickle cell disease;
- quality aspects including the definition of starting material, control strategy for potentially genotoxic impurities, the GBT440 drug product stability study plan for primary stability batches and bracketing strategy.

1.7. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
14 December 2017	EMEA/H/SA/3670/1/2017/PA/PR/II	Dr Pierre Demolis, Dr Hans Ovelgönne and Dr Armando Magrelli
26 March 2020	EMEA/H/SA/3670/1/FU/1/2020/PA/PR/II	Dr Pierre Demolis and Dr Peter Mol
25 June 2020	EMEA/H/SA/3670/2/2020/PA/PR/I	Ms Audrey Sultana and Dr Peter Mol

The applicant received protocol assistance on three occasions as mentioned in the table above for the development of Oxbryta for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide. The protocol assistance pertained to the following quality and clinical aspects:

Quality:

- API starting materials for the commercial manufacturing of drug substance.
- Proposed control strategy for the potentially mutagenic impurities assessed in the manufacturing process.
- Proposed stability plan and dissolution method to support the shelf life of one of the strengths intended for commercial use.

Clinical:

- Design of the Phase 3 study GBT440-031, specifically the appropriateness of the study population, sample size, study duration and the primary and key secondary endpoints to support a MAA in adults and adolescents.
- Acceptability of the proposed single Phase 3 study GBT440-031 together with supportive evidence from the Phase 1/2 programme including studies GBT440-001/GBT440-024 and GBT440-007 to support a MAA in adults and adolescents.
- Paediatric development.

- Acceptability of the safety database for the initial MAA.
- Agreement that haemoglobin polymerisation leading to haemolytic anaemia is a key pathophysiologic hallmark of sickle cell disease and driver of progressive end-organ damage, morbidity and mortality.
- Agreement that an increase in haemoglobin and decrease in haemolysis, if maintained over long-term, is a suitable endpoint to demonstrate clinical benefit of voxelotor in patients with SCD.
- Discussion concerning the overall development programme and whether it provides a sufficient basis to evaluate the benefit-risk profile of voxelotor for the treatment of SCD in adults and paediatric patients 12 to 17 years of age.

1.8. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Paula Boudewina van Hennik Co-Rapporteur: Alexandre Moreau

The application was received by the EMA on	23 December 2020
The procedure started on	21 January 2021
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	13 April 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	14 April 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	26 April 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	06 May 2021
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	20 May 2021
The applicant submitted the responses to the CHMP consolidated List of Questions on	13 August 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	27 September 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	30 September 2021
The CHMP agreed on a list of outstanding issues to be sent to the applicant on	14 October 2021

The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 November 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	09 December 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Oxbryta on	16 December 2021
The CHMP adopted a report on similarity of Oxbryta with Adakveo on (see Appendix on similarity)	16 December 2021
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	16 December 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

The applicant initially proposed the following indication:

Treatment of haemolytic anaemia in adults and paediatric patients 12 years of age and older with sickle cell disease (SCD). Oxbryta can be administered alone or in combination with hydroxycarbamide.

The applicant subsequently adjusted the initial wording of the indication as requested by the Rapporteurs, in order to be more specific on the origin of haemolytic anaemia; the approved indication is:

"Oxbryta is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide."

2.1.2. Epidemiology and risk factors

Sickle cell disease (SCD) is an orphan disease in the European Union (EU) which affected 2.6 in 10,000 people in the EU in 2017 (EHA, 2019). SCD is the most prevalent genetic disease in France and the UK, and its frequency is steadily rising in many other countries of Central and Southern Europe (Colombatti, 2016; Thalassaemia International Federation, 2013). Approximately 50% of individuals afflicted with SCD are younger than 18 years of age (based on United States [US] epidemiological data), with clinical manifestations occurring across all paediatric age groups including in children < 1 year of age (Brousseau, 2010; Ansa, 2012).

Importantly, the prevalence of SCD in Europe is rising due to migration to Europe from countries with high SCD prevalence (Angastiniotis, 2013; Colombatti, 2016; EHA, 2019). For example, approximately 4.8% of immigrants in France are from at risk populations (Thalassaemia International Federation, 2013), and the number of migrants and migrant newborns with HbSS (sickle Hb with two sickle Hb genes) in Germany increased by 60% between 2007 and 2015 (Kunz, 2017).

2.1.3. Aetiology and pathogenesis

Sickle cell disease (SCD) is a group of autosomal recessive inherited disorders caused by mutations in HBB, which encodes haemoglobin subunit β, resulting in the presence of a mutated form of haemoglobin, haemoglobin S (HbS). The most common form of SCD found is homozygous HbS disease (HbSS). In SCD, a single amino acid substitution in the β-globin chain leads to polymerisation of mutant haemoglobin S (HbS), impairing erythrocyte rheology and decreasing RBC survival to about 10-20 days. Erythrocytes that contain mostly haemoglobin polymers assume a sickled form and are prone to haemolysis. These erythrocyte abnormalities in SCD manifest in haemolytic anaemia.

The polymerisation of deoxy HbS is the primary and indispensable event in the molecular pathogenesis of sickle cell disease. However, polymerisation, although the primary pathophysiologic event, alone does not account for all of the pathophysiology of sickle cell disease. Downstream events following polymerisation, including changes in red cell membrane structure and function, disordered red cell volume control, increased red cell

adherence to vascular endothelium, misregulation of vasoactivity, and inflammation contribute to vaso-occlusive crises (VOC) and haemolysis that are the hallmarks of sickle cell disease (UpToDate 2021, Piel et al, NEJM 2017).

VOCs occur due to adhesive events among red blood cells and other cell types, obstructing the vasculature that accompanies with episodes of pain. Triggers for VOC vary and can include inflammation, stress, increased viscosity, decreased flow, haemolysis, or a combination of factors.

With **haemolysis**, i.e. intravascular destruction of sickle erythrocytes, the products of haemolysis (cell-free haemoglobin, arginase 1, asymmetric dimethylarginine, and adenine nucleotides) are released which damage the vascular system. This is associated with an increased risk of developing specific clinical complications of pulmonary and systemic vasculopathy, including pulmonary hypertension, leg ulcers, priapism, chronic kidney disease and large-artery ischemic stroke (Kato et al, 2012).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

SCD causes significant morbidity and mortality. Morbidity, frequency of crisis, degree of anaemia and the organ systems involved vary considerably from individual to individual. Screening for HbS at birth is currently mandatory. For the first 6 months of life, infants are protected largely by elevated levels of Hb F. SCD usually manifests early in childhood, in the following ways:

Signs and symptoms

- VOC: Approximately half the individuals with homozygous HbS disease experience VOC. The frequency of crises is highly variable. Some individuals have as many as 6 or more episodes annually, whereas others may have episodes only at great intervals or none at all. Each individual typically has a consistent pattern for crisis frequency.
- *Acute and chronic pain*: Pain episodes are the most distinguishing clinical feature of SCD and are typically associated with VOC. Also, chronic pain can develop as sequalae of vaso-occlusive events.
- *Anaemia*: Universally present, chronic and haemolytic in nature.
- *Acute chest syndrome*: Young children present with chest pain, fever, cough, tachypnea, leukocytosis, and pulmonary infiltrates in the upper lobes; adults are usually afebrile, dyspneic with severe chest pain, with multilobar/lower lobe disease.
- *Pulmonary hypertension*: Increasingly recognised as a serious complication of SCD.
- *Splenic sequestration*: Characterised by the onset of life-threatening anaemia with rapid enlargement of the spleen and high reticulocyte count.
- *Infection*: Organisms that pose the greatest danger include encapsulated respiratory bacteria, particularly Streptococcus pneumoniae; adult infections are predominantly with gram-negative organisms, especially Salmonella.
- *Central nervous system (CNS) involvement*: Most severe manifestation is stroke.
- *Hand-foot syndrome*: This is a dactylitis presenting as bilateral painful and swollen hands and/or feet in children.

- *Genitourinary involvement*: Kidneys lose concentrating capacity; priapism is a well-recognised complication of SCD
- *Dermatologic involvement*: Leg ulcers are a chronic painful problem

Further, manifestations such as aplastic crisis, growth retardation, delayed sexual maturation, bone pain, avascular necrosis of the femoral or humeral head, ophthalmologic involvement, cardiac involvement, gastrointestinal involvement may occur.

(Medscape, UpToDate, Nature: https://www.nature.com/articles/nrdp201810).

2.1.5. Management

Available therapies in SCD

There are multiple components to the management of SCD, including the prevention and treatment of the complications of SCD, as well as the potential cure for this illness.

The only curative treatment currently available for SCD is bone marrow transplantation. This treatment is primarily limited to children and adolescents, with use of a matched sibling donor and a myeloablative conditioning regimen.

Therapies to prevent VOC and associated pain episodes in SCD:

Hydroxycarbamide (hydroxyurea [HU]) (Siklos, 2017; Xromi, 2019) and Adakveo (crizanlizumab) (Adakveo, 2020) are approved therapies in Europe for patients with SCD.

- Hydroxycarbamide reduces DNA synthesis, which shifts the haematopoiesis from HbS to HbF production. The HbF suppresses polymerisation of HbS.
    - Siklos {HU) is indicated for the prevention of recurrent painful vaso-occlusive crises (VOCs) including ACS in adults, adolescents and children older than 2 years suffering from symptomatic Sickle Cell Syndrome (Siklos, 2017)
    - Xromi (HU) is indicated for the prevention of VOC complications of SCD in patients over 2 years of age (Xromi, 2019).
- Adakveo (crizanlizumab), a monoclonal antibody directed against P selectin, which was granted conditional marketing authorisation in October 2020 for the prevention of recurrent VOCs, or pain crisis, in patients with SCD aged 16 years and older (Adakveo, 2020).

Therapy to treat haemolytic anaemia in SCD

There is currently no EU approved therapy for the treatment of haemolytic anaemia associated with SCD, though transfusions are applied.

- Transfusions
    - Regularly scheduled blood transfusion therapy (also called chronic, prophylactic or preventive transfusion) involves periodic transfusion of the patient at regularly scheduled intervals, with the frequency guided by the patient's symptoms, haemoglobin (Hgb), and percent sickle Hgb (HgbS). This strategy could be effective in reducing morbidity of most complications of SCD. Regular

transfusions are used in the secondary prevention of stroke, acute chest syndrome (ACS), painful events, priapism and pulmonary hypertension. Potential benefit of transfusion therapy must be weighed against potential risks, including transfusion reactions, blood-borne viral infection, iron overload and alloimmunisation.

  - Prophylactic transfusion is used to reduce perioperative complications in patients with SCD undergoing surgery and to reduce the incidence of a range of vaso-occlusive complications of SCD.

- Erythropoietin is used off-label in patients with SCD primarily in the setting of chronic kidney disease (CKD) (Epogen, 2018; NHLBI, 2014). However, the clinical efficacy has not been established.

Unmet medical need

There is an unmet medical need in SCD for new targeted, mechanism based, preventive and potentially disease modifying therapies. These includes therapies to address haemolytic anaemia in SCD. To date, no drugs have been approved that specifically and directly target HbS polymerisation, the underlying mechanism of SCD.

The unmet medical need, extent of the disease burden as well as limitations of the available treatment options are also supported by the Pilot "CHMP early contact with patient organisations" that is described below.

Pilot "CHMP early contact with patient organisations"

Feedback was collected from the network of sickle cell disease organisations who surveyed their members, as well as through direct interviews by Eurordis. Among others, feedback was received from the French patient organisation SOS-Globi, the Dutch patient organisation "Oscar Nederland", Thalassemia International Federation that includes patient groups representing SCD. In total 46 patients responded to the survey and one additional patient provided his view outside the survey.

The results of the survey summarised below should however be interpreted with caution due to the limited sample size and limited number of treatment centres and countries participating. In addition, respondents included a significant number of patients who were more severely affected than the population investigated in the Oxbryta pivotal trial, judging by the annual rate of VOC and number of patients who received RBC transfusions in the pivotal study.

Results

Disease experience

Fatigue caused by chronic anaemia and pain are noted as main symptoms reported. Patients describe pain as chronic and not localised, but everywhere from the back to their legs, arms, and can be very severe. Painkillers typically have no or little effect (paracetamol, tramadol, nefopam, caffeine, morphine derivatives, non-steroidal anti-inflammatory drugs).

Impact on daily life

The impact of the disease on patient's life can be considerable, the patient/family might even decide to relocate near to a care centre. Focus on the onset of a crisis prevails. The lives of patients and their relatives are subject to many restrictions: the impossibility of practicing many physical activities (skiing, swimming or other), difficulties to go on vacation, limitation of social life. The patient must adapt his professional life according to the fatigue.

Treatments

Based on the Dutch survey (17 patients), most of the SCD patients use medications daily. Most commonly used medications are medicines for pain, to reduce crises frequency (hydroxycarbamide), to reduce anaemia, to treat or prevent infections. When anaemia is severe, hydroxycarbamide is used. However, adverse reactions, such as severe headache is the limiting factor for hydroxycarbamide use. In general, there is limited choice in treatment options, and substantial part of the patient population are not satisfied with their treatment and consider the beneficial effects to be of limited size and/or duration. Currently the ultimate treatment is bone marrow transplant. The main limiting factor is the availability of a donor.

Of note, Adakveo (crizanlizumab) was not mentioned in the discussions, probably as very recently authorised (October 2020).

Treatment of complications consists of folate, anticoagulant treatment, hydroxycarbamide, painkillers, and erythrocytapheresis.

Patients expectations from a new treatment (ranked)

- a treatment that reduces the frequency of crisis;
- a treatment which would increase timing between erythrocytapheresis treatments;
- a treatment which would reduce pain;
- a treatment which reduces the risk of infections;
- a treatment which does not expose to pain as a side-effect (headaches).

2.2. About the product

Mode of action

Sickle cell disease (SCD) is a group of inherited disorders caused by mutations in HBB, which encodes haemoglobin subunit β, resulting in the presence of a mutated form of haemoglobin, haemoglobin S (HbS). The primary cause of sickle cell anaemia is that HbS, when deoxygenated in the venous capillaries of peripheral tissue, has the capacity to polymerise. HbS polymers injure the sickle erythrocyte, leading to increased density, reduced deformability, increased adhesivity, and a shortened Red Blood Cell (RBC) life span, leading to haemolytic anaemia. Due to the chronic anaemia, O2-carrying capacity is decreased, which limits the total amount of O2 that can be carried to tissues (Kato, 2018). In addition, Hb-O2 affinity is decreased due to increased 2,3-DPG concentrations in sickle RBCs. In patients with SCD, O2 extraction (ie, tissue extraction of Hb-bound O2) is preserved but limited by reduced O2 content and impaired O2 delivery. With increased metabolic demand (ie, stress situations or exercise), O2 delivery may therefore be insufficient.

Voxelotor (GBT440) is an orally bioavailable small molecule which acts as HbS polymerisation inhibitor. Voxelotor inhibits the process of polymerisation by allosterically stabilising the oxygenated state of HbS by means of increasing the Hb-oxygen (Hb-O2) affinity. This stabilisation increases the ratio of oxygenated HbS

to deoxygenated HbS. This would provide a sufficiently prolonged delay time for RBCs to pass through the hypoxic environment of distal capillaries and arterioles without sickling prior to reoxygenation in the lungs (Oksenberg, 2016).

Voxelotor is claimed to bind covalently and reversibly via a Schiff-base to the N-terminal valine of one of the α-chains of Hb (Metcalf, 2017). It is claimed a dose-dependent pharmacodynamic effect of increasing affinity of Hb for oxygen (Hb-O2 affinity). By this, it expects to prevent RBC sickling, haemolysis and the resulting end-organ damage and morbidity.

The agreed indication is as follows:

"Oxbryta is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) *in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide."*

The recommended dosage of voxelotor is 1500 mg taken orally once daily (QD) with or without food.

For patients with severe hepatic impairment (Child Pugh C), the recommended dosage of voxelotor is 1000 mg taken QD with or without food. No dosage adjustment of voxelotor is required for patients with mild or moderate hepatic impairment.

Paediatric population

The recommended dosage of Oxbryta in patients 12 to < 18 years of age is the same as for adults; 1500 mg dose (three 500 mg film-coated tablets) taken orally once daily with or without food.

The safety and efficacy of Oxbryta in paediatric patients below the age of 12 years have not been established yet.

2.3. Type of application and aspects on development

The applicant submitted a request for an accelerated assessment. Upon examination of the request the CHMP concluded that the unmet medical need in patients with haemolytic anaemia associated with SCD is acknowledged, the innovative character of the mechanism of action is recognised and the provided evidence indicate that the drug has an effect on anaemia and haemolysis markers. However, provided data do not allow to assess to what extent the pivotal trial population represents the population with high unmet medical need. This precludes the assessment of the potential of the product to address the major public health interest and to provide major therapeutic innovation. Therefore the CHMP did not agree to the request for an accelerated assessment, as it was considered not sufficiently substantiated

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as film-coated tablets containing 500 mg of voxelotor.

Other ingredients of the tablet core are: microcrystalline cellulose (E460), croscarmellose sodium (E468), sodium laurilsulfate (E487), silica, colloidal anhydrous (E551) and magnesium stearate (E470b). Ingredients of the film-coating are: polyvinyl alcohol (E1203), titanium dioxide (E171), polyethylene glycol (E1521), talc (E553b) and iron oxide yellow (E172).

The product is available in high-density polyethylene (HDPE) bottle with a polypropylene child-resistant cap and an aluminium induction seal. The bottle also contains a silica gel desiccant canister and polyester coil. as described in section 6.5 of the SmPC.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of voxelotor is 2-hydroxy-6-((2-(1-isopropyl-1*H*-pyrazol-5-yl)pyridin-3-yl) methoxy)benzaldehyde corresponding to the molecular formula $C_{19}H_{19}N_3O_3$. It has a molecular weight of 337.4 g/mol and the following structure:

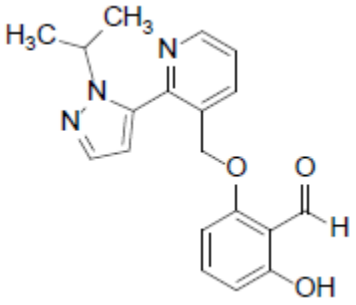


Figure 1 Active substance structure

The chemical structure of voxelotor was elucidated by a combination of mass spectrometry, nuclear magnetic resonance spectroscopy, infrared spectroscopy and ultraviolet spectroscopy The solid state properties of the active substance were measured by single crystal X-ray crystallography. Voxelotor has a non - chiral molecular structure.

The active substance is a white to yellow to beige non-hygroscopic solid. Based on the Biopharmaceutics Classification System (BCS), voxelotor is classified as a Class 2 compound. Voxelotor has low aqueous solubility and high permeability as demonstrated in an in vitro study. Since voxelotor aqueous solubility is not high in most ingested conditions, a conventional-release tablet was formulated consistent with rapid disintegration for maximal absorption in the gastrointestinal tract.

Polymorphism has been observed for voxelotor. Form II has been selected for clinical and commercial use and has been consistently produced by the manufacturing process. It has been demonstrated that there is no polymorph conversion during the finished product manufacturing.

2.4.2.2. Manufacture, characterisation and process controls

Voxelotor is synthesised in six main steps via a convergent route using well defined starting materials with acceptable specifications.

A comprehensive overview of all development activities regarding the manufacturing process, the various control strategies (organic impurities, potentially mutagenic impurities, nitrosamine impurities, elemental impurities, inorganic impurities, residual solvents / organic volatile impurities, polymorphic form, particle size,

selection and justification of the starting materials, risk assessment and determination of critical process parameters, has been provided and found acceptable. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented. Based on provided studies, proven acceptable ranges have been defined. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

2.4.2.3. Specification

The active substance specification includes tests for: appearance, identification (IR, HPLC), polymorph identification (XRPD), assay (HPLC), impurities (HPLC), residual solvents (GC), palladium content (ICP-MS), water content (KF), residue on ignition (Ph. Eur.) and particle size (laser diffraction).

Consistent with the ICH M7(R1), an assessment of potential mutagenicity for actual and potential impurities that may be present in voxelotor arising from the manufacture and storage of the active substance has been performed. The assessment has identified PMIs. The control strategies for all PMIs has been presented and found acceptable.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurity testing has been presented.

Batch analysis data on nine commercial scale batches of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data on three pilot scale batches of active substance from the proposed manufacturer stored in a container closure system representative of that intended for the market for up to 36 months under long term conditions (25ºC / 60% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Up to 24 months stability data are available for six supportive stability batches of the active substance. Supportive stability batches were manufactured at pilot and production scale by the second proposed manufacturer using the same proposed commercial process.

The following parameters were tested: appearance, polymorph identification, assay, impurities, water content and microbial limits. The analytical methods used were the same as for release with the exception for the impurity reporting. The methods were stability indicating.

All tested parameters were within the specifications on both storage conditions. No trends are apparent under either long-term or accelerated storage conditions.

Photostability testing following the ICH guideline Q1B was performed on one batch.

The photostability and forced degradation studies demonstrate that the voxelotor is insensitive to acid, base, temperature, or light.

The stability results indicate that the active substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period of 36 months with no special storage conditions in the proposed container.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

Voxelotor tablet, 500 mg, is a light yellow to yellow, oval-shaped, biconvex, film-coated tablet of approximately 18 mm × 10 mm, with "GBT 500" debossed on one side. The finished product tablet is developed as an immediate-release oral solid dosage form.

Pharmaceutical development of the finished product contains QbD elements.

Active substance particle size and polymorphic form are the properties extensively evaluated as they may affect the performance of the finished product. The particle size of the active substance can potentially impact the dissolution of finished product. To minimize the particle size impact on the tablet dissolution profile, the particle size distribution control for the active substance was established and controlled via the specifications.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. Each component in the film-coating system conforms to the Ph. Eur., USP-NF compendial standards, and is accepted by E number–Purity Criteria according to Commission Regulation (EU) No. 231/2012 for Food Additives. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report. The chemical compatibility of the active substance with the formulation excipients under accelerated storage condition (40 °C/75% RH) was evaluated. The study results demonstrated that all selected excipients were compatible with the active substance.

The finished product was initially developed in two solid oral dosage forms: capsules and tablets. The capsule dosage forms, including powder in capsule (PIC) and common blend (CB) capsule, were initially developed and used in early clinical studies.

The tablet dosage form was developed to improve the manufacturing process and to support potentially higher clinical doses. A tablet dosage strength of 300 mg was first developed to support clinical studies. Oxbryta tablet, 500 mg, was later developed as the proposed commercial finished product.

Based on the desired daily dose of 1500 mg and the suitable tablet size, voxelotor tablet, 500 mg, was selected as the proposed commercial dosage form. The common blend approach enables the use of the same formulation compositions for the 500 mg dosage strength.

Based on total tablet weight it is assumed that size is rather large. Three such tablets should be taken once a daily. The applicant provided additional details and compares for the two patient population groups other existing products in the market having comparable large tablet sizes.

Elderly patients: The applicant compared the product to five other registered products (4x film-coated tablet, 1x extended release tablet), four of them with a larger length and one with an almost similar length, and two of them with a larger width. Based on the comparison with the five other registered products (four of them via EU centralised procedure), it has been assumed that for the comparably sized proposed tablet the problem of

swallowing for elderly patients is not to be expected. In addition, the proposed oval shape is assumed to improve swallowability of the Oxbryta tablet.

Paediatric patients (adolescents 12 - <18 years old): A metformin 1000 mg tablet of 9.8 x 19.0 mm, meant for children of 10 years above and registered in the UK, slightly larger than the proposed Oxbryta tablet, is the most relevant example of a comparably-sized proposed tablet product. Another EU registered product, Sovaldi film-coated tablet, possesses a larger length (20 mm) but a smaller width (9 mm). Based on the comparison with other registered products (three of them via centralised procedure), it has been assumed that for the comparably sized proposed Oxbryta tablet, the problem of swallowing for adolescents of 12- <18 years old is not to be expected. In addition, this assumption is supported by a literature reference, which suggests that the majority of adolescent patients are capable of swallowing a 22 mm long capsule.

The manufacturing development have been evaluated through the use of risk assessment and design of experiments to identify the critical process parameters. A risk analysis was performed using the failure mode effect analysis (FMEA) method in order to define critical process steps and process parameters that may have an influence on the finished product quality attributes. The risk identification was based on the prior knowledge of products with similar formulations and manufacturing processes as well as on the experience from formulation development, process design and scale-up studies. The critical process parameters have been adequately identified.

The commercial manufacturing process involves standard and conventional pharmaceutical operations, including pre-blending, dry granulation, final blending, tablet compression, film-coating, and packaging. A tablet dosage strength of 300 mg was first developed to support the clinical studies. Voxelotor tablet, 500 mg, was later developed as the proposed commercial finished product presentation.

The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is high-density polyethylene (HDPE) bottle with a polypropylene child-resistant cap and an aluminium induction seal. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The manufacturing process consists of six main steps: pre-blending, dry granulation, final blending, tablet compression, film-coating, and packaging.

Adequate IPCs for compression and for film-coating are applied. CPPs are applied for roller compaction, compression, and film-coating are controlled, ensuring that the quality of the product is maintained.

As the process is considered to be a standard manufacturing process, major steps of the manufacturing process will be validated in line with provided validation protocol, which was found acceptable.

2.4.3.3. Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance, identification (UV, HPLC), assay (HPLC), uniformity of dosage units(HPLC), degradation products (HPLC), dissolution (Ph. Eur., HPLC), water content (Ph. Eur., KF) and microbial purity (Ph. Eur.).

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. The information on the control of elemental impurities is satisfactory.

During the procedure a major objection (MO) was raised on the absence of a risk assessment concerning the potential presence of nitrosamine impurities in the finished product. In response, a risk assessment has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

In accordance with ICH Q3C guideline, the residual solvents are adequately controlled in the active substance and excipients. No solvents are involved in the manufacture of finished product. The daily exposure to the residual solvents through the finished product is within the permitted limits and no routine monitoring of residual solvents in the finished product is proposed and accepted.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis data are provided on 18 commercial scale batches, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification. The methods and specification in place at the time of release for the respective products were appropriate for the stage of development and the intended use of the product.

The finished product is released on the market based on the release specifications, through traditional final product release testing.

2.4.3.4. Stability of the product

Different dosage strengths of the finished product were developed to support clinical and stability studies (300 and 900 mg) and commercialisation (500 mg). Limited batch history and stability data are available for the 500 mg tablet strength. To support the shelf life for the 500 mg commercial dosage strength, a bracketing strategy was utilised in the primary stability studies that are based on ICH Q1D. The design factors in the bracketing strategy include dosage strength, container closure material of construct and size, and fill. Three primary stability lots of each finished product configuration, were fully tested for stability in accordance with the test frequency recommended by ICH Q1A.

Stability data on 3 common blend batches for the 300 mg tablet each manufactured at commercial scale of the finished product stored for up to 12 months under long term conditions (25ºC / 60% RH), for up to 24 under intermediate / long term conditions (30ºC / 75% RH) and for up to 6 months under accelerated conditions (40ºC / 75% RH) according to the ICH guidelines were provided. Further data on 3 supportive batches of 500 mg tablets have been provided. The container closure system used for the stability samples are of the same packaging material used for the proposed commercial finished product with the exception of size as defined in the bracketing strategy.

Samples were tested for appearance, assay, degradation products, dissolution, water content and microbial limits. The analytical procedures used are stability indicating.

No significant changes and no apparent trends were observed under any of the storage conditions.

In addition, one batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The photostability and forced degradation studies demonstrated that the finished product is insensitive to acid, base, temperature, or light.

Considering the amount of stability data available, further data on in use stability were not requested.

Based on available stability data, the proposed shelf-life of 3 years with no special storage conditions as stated in the SmPC (section 6.3) is acceptable.

2.4.3.5. Adventitious agents

No excipients derived from animal or human origin have been used.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. During the procedure a major objection (MO) was raised on the absence of a risk assessment concerning the potential presence of nitrosamine impurities in the finished product. The risk assessment has been performed as requested and, based on the information provided, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.4.6. Recommendations for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

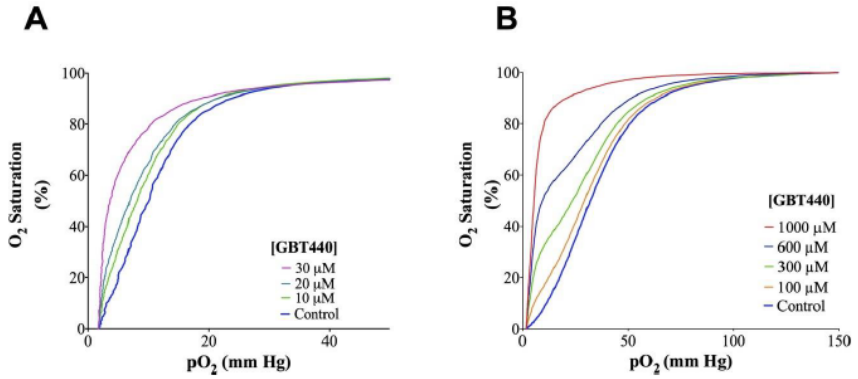
Voxelotor is a compound that is designed to bind the oxygen loaded haemoglobin (Hb) and stabilises this form. This is an important feature as oxygen loaded sickled Hb (HbS) is less prone to result in vaso-occlusive crises and the consequences of it. Haemoglobulin is a hetero-tetramer of 2 α-globulins and 2 β-globulins. Although sickle cell patients harbour a mutation in the β-globulin, which apparently influences the affinity for oxygen, voxelotor appears to bind to the α-globulin.

As support for the treatment of haemolytic anaemia by voxelotor in sickle cell patient from 12 years and older the applicant submitted an extensive number of *in vitro* and *in vivo* pharmacology studies, which will be summarised below.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Table 1 In vitro pharmacodynamics studies

N° Study / Title	Methods	Results and main findings
PRC-18-048 Crystal Structure of Hemoglobin S Bound to Voxelotor	X-ray crystallography	Voxelotor binds to the N-terminal valine residue of an alpha chain; a single voxelotor molecule binding per **HbS tetramer** in a 1:1 stoichiometry. The voxelotor binding site is distant from the heme pockets => does not sterically prevent dissociation of O_2 from HbS.
PRC-14-027-R Effect of GBT440 on Oxygen Equilibrium Curves in Purified Hemoglobin and Whole Blood	**Hemox Analyzer** Hb concentration of 1mM incubated 45 to 60 min with or without Voxelotor	**Figure 2: Effect of Voxelotor on Hemoglobin-Oxygen Affinity in Purified Hemoglobin and Whole Blood from Subjects with SCD (Study PRC-14-027-R)**  Abbreviations: O_2, oxygen; pO_2, partial pressure of O_2. Note: GBT440 is synonymous with voxelotor. **Panel A** shows results from hemoglobin. **Panel B** shows results from whole blood. OEC = Oxygen equilibria curve

<table>
<tr><th>N° Study / Title</th><th>Methods</th><th>Results and main findings</th></tr>
<tr><td></td><td></td><td>

Hb purified from SS blood (SS blood from transfused sickle cells donor): 30% HbS / 70%HbA and whole blood: 70/90% HbS.
Voxelotor dose dependently decreases the p50 in purified Hb and whole blood from subjects with SCD.

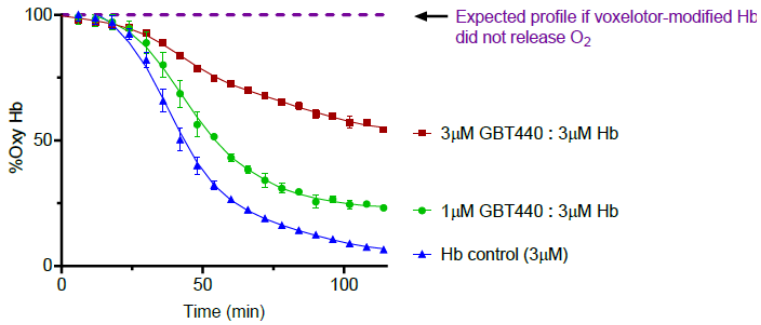
Table 3: Effect of Voxelotor on Blood p50 Values (Study PRC-14-027-R)
<table>
<tr><th>Species (Strain)</th><th>Control p50 (mm Hg)</th><th>Voxelotor p50 (mm Hg) [a]</th><th>N</th></tr>
<tr><td>Human AA</td><td>28.85</td><td>24.77</td><td>6</td></tr>
<tr><td>Human SS</td><td>32.95</td><td>25.88</td><td>5</td></tr>
<tr><td>Rat (Sprague Dawley)</td><td>35.47</td><td>31.59</td><td>2</td></tr>
<tr><td>Mouse (C57Bl/6)</td><td>45.73</td><td>35.15</td><td>3</td></tr>
<tr><td>Dog (Beagle)</td><td>29.78</td><td>23.21</td><td>1</td></tr>
<tr><td>Monkey (Cynomolgus)</td><td>22.98</td><td>16.34</td><td>1</td></tr>
</table>
Abbreviations: AA, homozygous for adult hemoglobin; p50, partial pressure of oxygen at which hemoglobin is 50% saturated with oxygen; N, number of different blood samples tested in duplicates; SS, homozygous for sickle hemoglobin.
Note: results shown are mean.
[a] Voxelotor concentration that is expected to modify 30% of Hb (ie, molar ratio of 1:3 voxelotor:Hb).

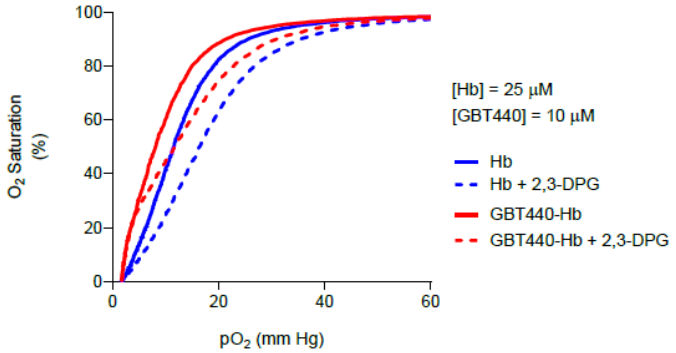
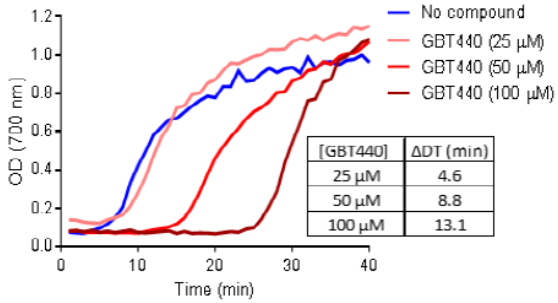
Because the N-terminal valine of the α chain of Hb is conserved across all mammals, voxelotor elicits an increase in Hb-O_2 affinity in all blood samples as evidenced by the reduction in p50 values.
Table 3 shows the p50 values for control and voxelotor-treated blood from healthy subjects (HbAA), subjects with SCD (HbSS), and various animal species: voxelotor-modified Hb has a higher O_2 affinity than unmodified Hb.

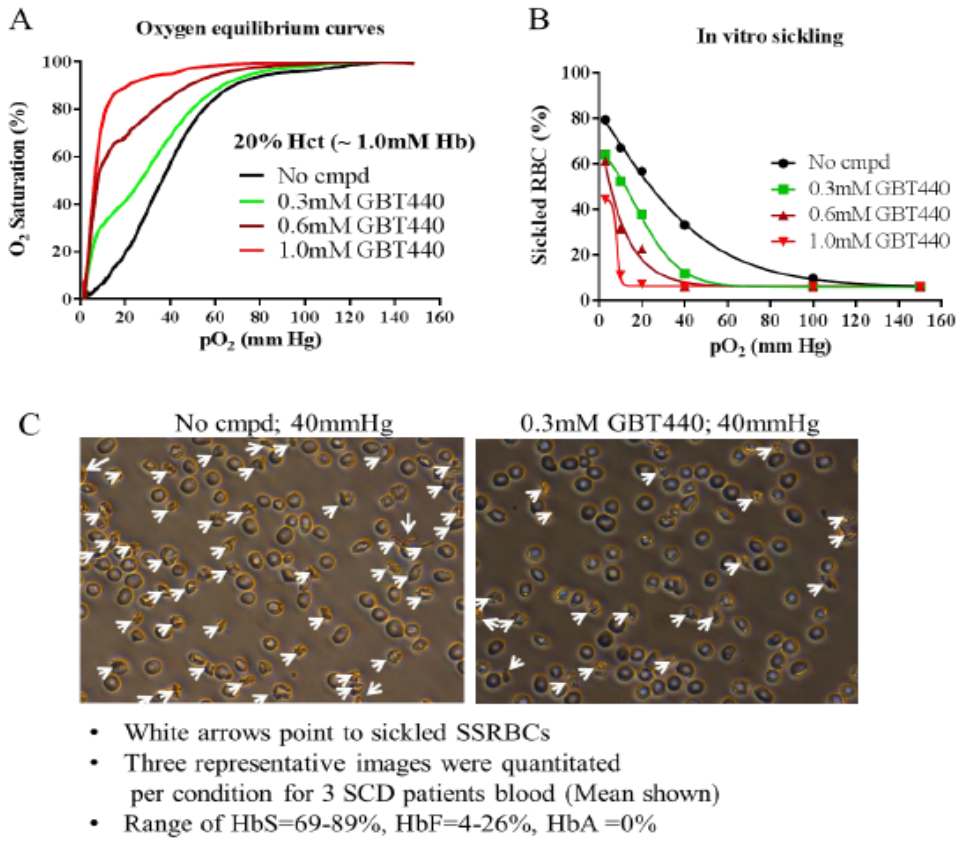
</td></tr>
<tr><td>PRC-14-0033-R
Effect of GBT440 on Dissociation of Oxygen from Oxygenated Hb</td><td>Oxygen dissociation assay
3 µM voxelotor during 2 hours</td><td>

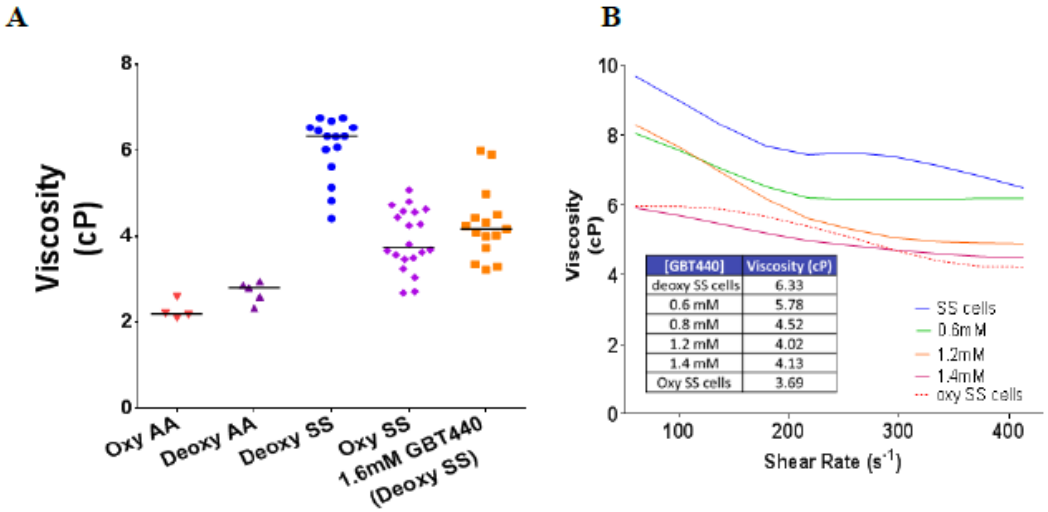
Voxelotor dose dependently maintains the OxyHb state with an EC_{50} of 1,6 µM. Voxelotor is capable of maintaining a fraction of Hb in the OxyHb state under hypoxic condition.

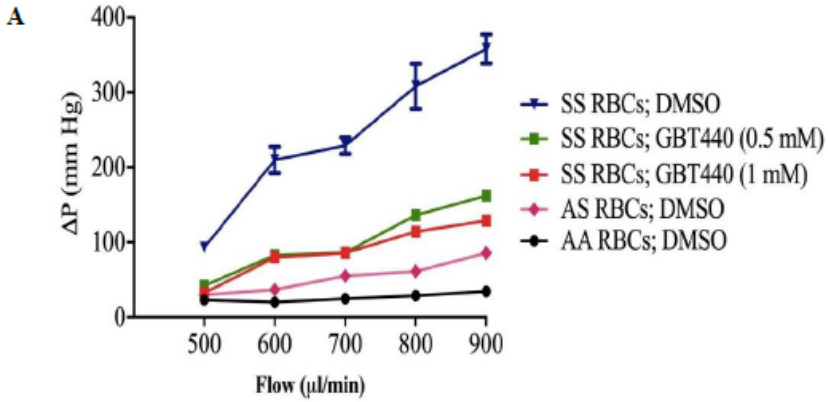
</td></tr>
</table>

N° Study / Title	Methods	Results and main findings
PRC-18-046 Mechanistic In Vitro Studies of Oxygen Offloading From Voxelotor Modified Hemoglobin and **PRC-14-029** Effect of GBT440 on the Oxygen Dissociation from Hemoglobin at Various pHs	Oxygen dissociation assay Purified Hb with Voxelotor at 1 and 3 µM at different pHs : 7,4 or 7,0 or 6,8) for 1 hour followed by deoxygenation for 2 hours Purified Hb (25 µM) was incubated with voxelotor (10 µM) and 2,3-DPG (500 µM) for 1 hour	**Figure 3: Voxelotor Delays the Transition from Oxygenated Hemoglobin to Deoxygenated Hemoglobin (Study PRC-18-046)**  Abbreviations: Hb, hemoglobin; O_2, oxygen; oxyHb, oxyhemoglobin. Note: GBT440 is synonymous with voxelotor. Voxelotor dose-dependently increased the proportion of OxyHb molecules: in the presence of Voxelotor at 1 µM, there is 23% oxyHb, at 3 µM there is 54% oxyHb versus 6,5% oxyHb for the Hb alone control. <u>Effect of pH on Hb</u> with voxelotor (1:1 voxelotor:Hb), the percentage of oxyHb decreased from 54% to 38% to 29% at pH 7.4, 7, and 6.8, respectively, after 2 hours of deoxygenation. At different pH, voxelotor caused a left-shift of the OEC (indicating an increase in the Hb-O_2 affinity) relative to control at each pH but the shift of the OEC is similar with or without Voxelotor at pH 6,8 and pH 7. **Table 4: p50 at Various pHs in Presence or Absence of Voxelotor (Study PRC-18-046)** | | p50 (mm Hg) | | | | | pH 7.4 | pH 7.0 | pH 6.8 | | Control | 25.7 | 40.4 | 48.9 | | Voxelotor | 22.3 | 34 | 40 | <u>Effect of 2,3-DiPhosphoGlycerate on Hb at pH 7,4</u>

N° Study / Title	Methods	Results and main findings
		Figure 5: Effect of 2,3-Diphosphoglycerate on Voxelotor-Modified Hemoglobin (Study PRC-18-046)  Abbreviations: DPG, diphosphoglycerate; Hb, hemoglobin; O_2, oxygen. Note: GBT440 is synonymous with voxelotor. 2,3-DPG, the major allosteric effector for Hb, provides another physiologic mechanism to augment O_2 offloading from Hb but in presence of Voxelotor, the right shift of the OEC is observed.
PRC-14-040-R Effect of GBT440 on In Vitro HbS Polymerization	Purified HbS was incubated with various concentrations of voxelotor prior to deoxygenation. [voxelotor] = 25,50 and 100µM	In this assay, inhibition of HbS polymerisation by voxelotor was assessed by its ability to increase the delay time (DT) prior to the onset of HbS polymers: At 25, 50, and 100 µM, voxelotor delayed polymerisation of deoxy-HbS (50 µM) with a ΔDT of 4.6, 8.8 and 13.1 minutes, respectively. **Figure 7: Voxelotor Delays Sickle Cell Hemoglobin Polymerization in a Concentration-Dependent Manner (Study PRC-14-040-R)**  Abbreviations: DT, delay time; OD, optical density. Note: GBT440 is synonymous voxelotor. No compound refers to no voxelotor.

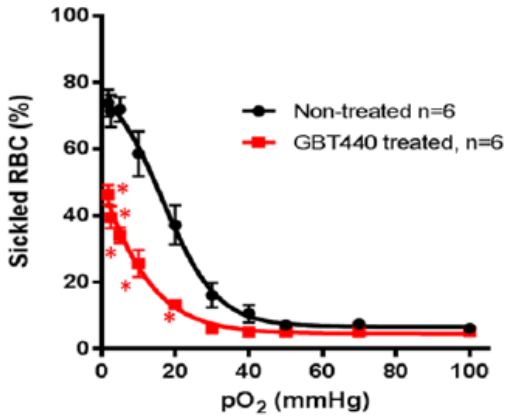
N° Study / Title	Methods	Results and main findings
		These data indicate that like HbF, voxelotor is a potent inhibitor of *in vitro* HbS polymerisation and suggests that by delaying HbS polymerisation, voxelotor may prevent RBC damage and sickling from subjects with SCD.
PRC-14-042-R Inhibits RBC sickling	**TCS Hemox Analyzer and morphometric measurements** Whole blood (20% Hct) from **patients with SCD (HbS > 70%)** [Voxelotor] = [GBT440] = 0; 0.3; 0.6 or 1 mM 1 hour	**Figure 8: Voxelotor Increases Hemoglobin-Oxygen Affinity and Prevents Red Blood Cell Sickling (Study PRC-14-042-R)**  • White arrows point to sickled SSRBCs • Three representative images were quantitated per condition for 3 SCD patients blood (Mean shown) • Range of HbS=69-89%, HbF=4-26%, HbA =0% Abbreviations: cmpd, compound; no cmpd, no GBT440; HbF, fetal hemoglobin; HbS, sickle hemoglobin; Hct, hematocrit; O_2, oxygen; pO_2, partial pressure of O_2; SCD, sickle cell disease; SS RBC, sickled red blood cell. Note: GBT440 is synonymous with voxelotor. • Concentration-dependent left shift in the OEC (=> increase of the Hb-O_2 affinity).

N° Study / Title	Methods	Results and main findings
		• Dose-dependently decrease in the number of SS RBCs under hypoxic conditions (1 mM) • In tissues capillaries, 0.3 mM was sufficient to prevent sickling of SS RBCc in whole blood *(Figure 8-C)*
PRC-14-044-R Reduction of viscosity of RBCs from subjects with SCD	Blood viscosity measurements Voxelotor at 1.6 mM Incubated for 30 min and reaction mixture was deoxygenated for 2 hours	**Figure 9: Voxelotor Reduces the Hyperviscosity Observed in SCD Blood (Study PRC-14-044-R)**  Abbreviations: AA, homozygous for adult hemoglobin; cP, centipoise; deoxy, deoxygenated; oxy, oxygenated; SS, homozygous for sickle hemoglobin. Note: GBT440 is synonymous with voxelotor. • At 1.6 mM, voxelotor reduced the viscosity of the deoxygenated SS blood. • The viscosity of deoxygenated SCD blood improves with increasing voxelotor concentrations and at higher concentrations of voxelotor, the viscosity profile is similar to that of oxygenated SCD blood.

N° Study / Title	Methods	Results and main findings
PRC-14-031-R Deformability of RBCs from subjects with SCD	Gel filtration deformability assay [Voxelotor] = 0.5 and 1 mM	**Figure 10: Voxelotor Improves Red Blood Cell Deformability Under Hypoxic Conditions (Study PRC-14-031-R)**  • Incubation with voxelotor at 0.5 or 1 mM reduced the pressure required to pass SS RBCs through a polycarbonate filter and lowered the tension required to aspirate SS RBCs into a micropipette under hypoxic conditions. • The deformability of SS RBCs in the presence of voxelotor was similar to that of RBCs heterozygous for the sickle trait (AS RBCs).

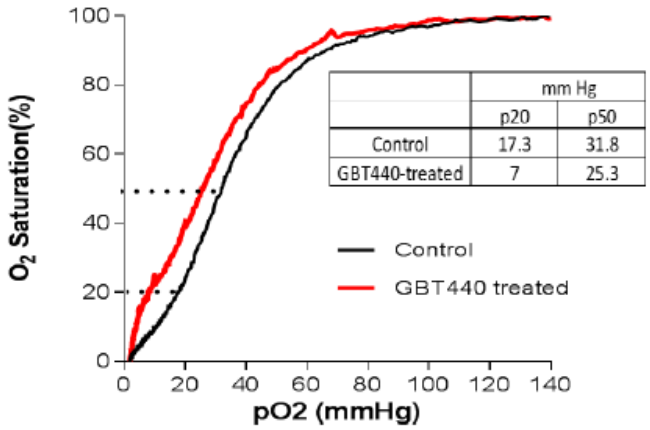
PK/PD model: In study PRC-18-043 the applicant used *in vivo* patient data as well as *ex vivo* data to find the best predictor for Hb-O2 affinity by means of PK/PD modelling. For the treatment, the applicant aims at a concentration voxelotor:Hb of 1:3. The maximal voxelotor bound Hb concentration in blood will is thus aimed at ~30 %. As this population has a higher affinity for O2 but also shows less efficient oxygen offloading or dissociation, the voxelotor-Hb population will be visible in lower left corner of an OEC. The p20 is regarded a relevant parameter to reflect the effect of voxelotor treatment on O2 affinity of the voxelotor-Hb population. This parameter is less likely to be contaminated with a Hb population not bound to voxelotor. The delta p20 is reflecting the change in p20 between control and sample. It is anticipated that control situation reflects untreated SS blood / SCD subjects and sample is reflecting voxelotor treated SS blood / SCD subjects. When considering both model development and model robustness, Δp20 appears the best parameter to relate to voxelotor mediated change in Hb-O2 binding.

Table 2 In vivo pharmacodynamics studies

N° Study / Title	Methods	Results and main findings
PRC-14-036-R **PRC-14-037-R1** **PRC-14-038-R** **PRC-14-039-R** PK/PD Studies in Normal Animals	Voxelotor blood concentrations and Hb-O_2 affinity in Sprague-Dawley rats and mice C57BL/6 (LC-MS/MS)	Studies in rats and mice showed a strong correlation (R2 = 0.8) between the voxelotor RBC concentrations and the Hb-O_2 affinity. • Voxelotor concentration-dependent increases in Hb-O_2 affinity. • Voxelotor presents linear, predictable, and highly correlated PK and PD properties.
PRC-14-025-R Efficacy of Voxelotor Following Single *In Vivo* Oral Dosing in a SCD Mouse Model	Mice *Ex vivo* exposure to low pO_2 (10mmHg) [voxelotor] = 100 mg/kg	**Figure 13: Oral Dosing of Voxelotor Reduces Ex Vivo Sickling in a Sickle Cell Mouse Model (Study PRC-14-025-R)**  Abbreviations: RBC, red blood cell; pO_2, partial pressure of oxygen. *Statistically significant differences (two-tailed paired t test). p = 0.0018. Notes: GBT440 is synonymous with voxelotor.

N° Study / Title	Methods	Results and main findings

Figure 14: Oral Dosing of Voxelotor Elicits an Ex Vivo Increase in Hemoglobin-Oxygen Affinity in a Sickle Cell Mouse Model (Study PRC-14-025-R)



Abbreviations: O_2, oxygen; p20, partial pressure of O_2 at which hemoglobin is 20% saturated with O_2; p50, partial pressure of O_2 at which hemoglobin is 50% saturated with O_2; pO_2, partial pressure of O_2.
Note: GBT440 is synonymous with voxelotor. Data presented as mean ± SEM.

- At 100 mg/kg PO, there is a significant reduction in the number of sickled RBCs 26% +/- 4 in treated mice vs 59%+/-7 in untreated mice, p=0.0018) following *ex vivo* exposure to low pO_2 (10 mmHg).
- Data for all 6 voxelotor-treated mice indicated mean Δp20 and Δp50 changes of **39 ± 7% and 15 ± 3%, respectively, compared to the pre-treatment**

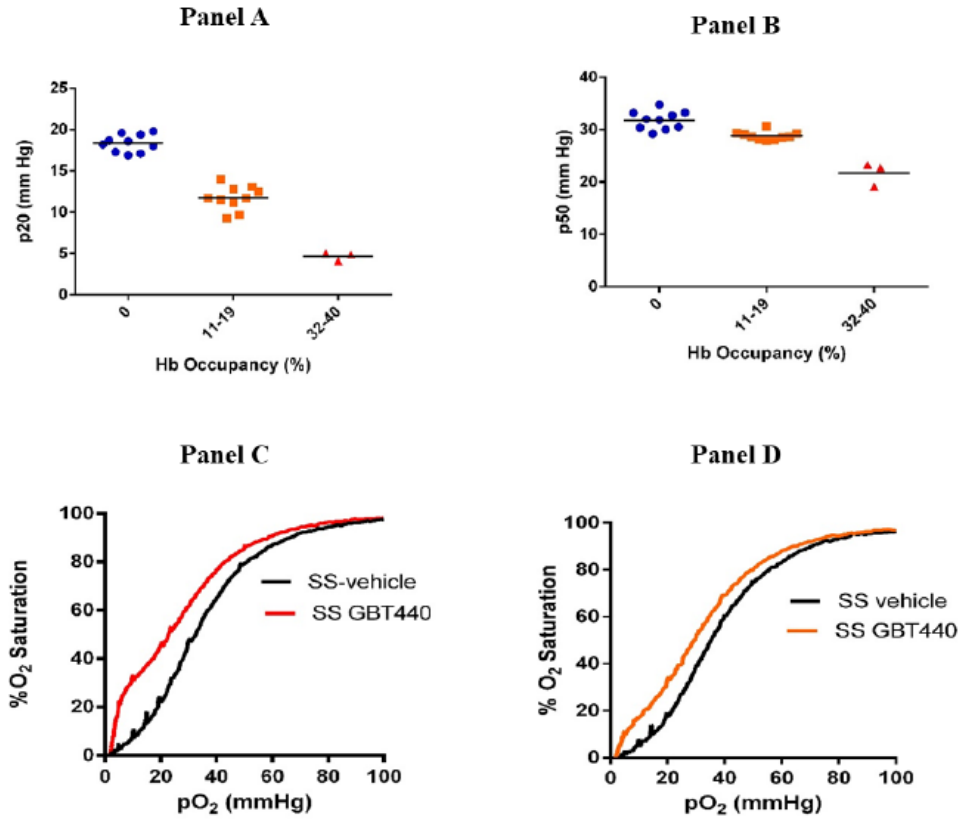
Table 9: Summary of Voxelotor Concentration in Blood and Plasma Following Acute Dosing in SS Mice (Study PRC-14-025-R)

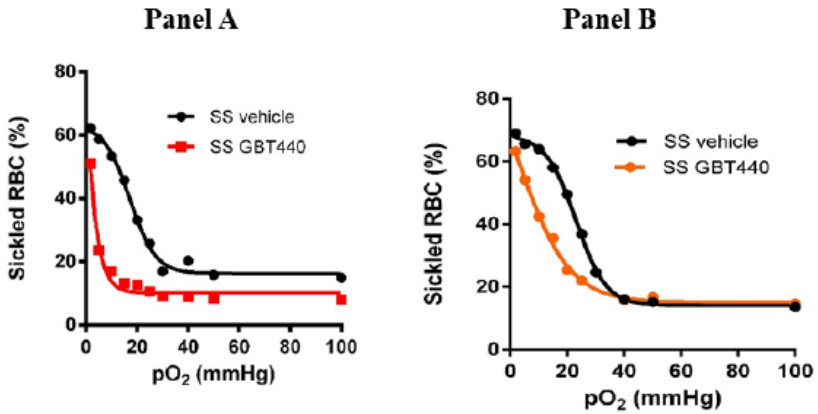
	Blood (µM)	Plasma (µM)	Blood/Plasma
Average	158	21	7.5
SEM	31	4.5	0.41

Abbreviation: SS, homozygous for sickle hemoglobin.

- single dose of voxelotor achieved average blood and plasma concentrations at 4 hours of 158 µM and 21 µM, respectively, indicating a blood:plasma partitioning of 7.5:1 (lower than the partition observed in C57BL/6 mice.

N° Study / Title	Methods	Results and main findings
		• a calculated occupancy of 12% **(obtained by dividing the voxelotor blood concentrations by the Hb concentration as determined by the % Hct).** This %Hb occupancy was sufficient to reduce the number of *ex vivo* sickled RBCs present at $pO_2 \leq 20$ mmHg.
PRC-14-030-R Efficacy of Voxelotor Following **repeated** *In Vivo* Oral Dosing in a SCD Mouse Model	SS Mice [voxelotor] = 100 or 150 mg/kg BID for 9 to 12 days	<u>Prolongation of Red Blood cell Half-life and Reduction in Sickled RBC</u> • From PK experiment in SS mice, the half-life was of 9 hours (and C_{max} at 4 hours of 284 +/- 57 µM) suggesting a repeated daily (BID) dosing would be required to achieve target steady state concentrations. • From a total of 14 mice (3F and 11M) only 4 mice M was achieved voxelotor blood concentrations of 484, 496, 557 and 558 µM corresponding to calculate Hb occupancies of 39.6; 32.3; 36 and 37.2% respectively. For the other 11 mice, voxelotor concentrations was of 100 to 272 µM corresponding to Hb occupancy of 11.5% to 19%. • The blood/plasma ratio varied from 4.8 to 16.7:1 indicating a preferential partition to the blood compartment. <u>Increase Hb-O_2 affinity at haemoglobin occupancy > 11%</u> • All voxelotor-treated SS mice exhibited an increase in Hb-O_2 affinity and a decrease in the *ex vivo* RBC sickling**, the effect was dose dependent** (mice with the highest levels of Hb occupancy (> 32%) exhibited the highest effects in %Δp20 (73 ± 1%), %Δp50 (29.7 ± 3.9%) and percent decrease (51 ± 9%) in *ex vivo* sickled cells. • The SS mice (n = 10) with Hb occupancy of 11.5 to 19% also elicited an increase in %Δp20 (38.2 ± 4.7%) and decrease in the percent of sickled cells (28.6 ± 1.7%) relative to vehicle-treated mice.

N° Study / Title	Methods	Results and main findings
		Figure 15: Repeat Dosing with Voxelotor Increases Hemoglobin-Oxygen Affinity at Hemoglobin Occupancy > 11% (Study PRC-14-030-R)  Abbreviations: Hb, hemoglobin; O_2, oxygen; p20, partial pressure of O_2 at which hemoglobin is 20% saturated with O_2; p50, partial pressure of O_2 at which hemoglobin is 50% saturated with O_2; pO_2, partial pressure of O_2; SS, homozygous for sickle hemoglobin. Notes: GBT440 is synonymous with voxelotor. • Increase in Hb-O_2 affinity following repeat dose in mice with different levels of Hb occupancy: ○ Panel A and B: the decrease of p20 and p50 (mmHg) is dependent of % Hb occupancy ○ Panel C: Hb occupancy of 36%, left shift curve (%Δp20 = 73%, %Δp50 = 30%)

N° Study / Title	Methods	Results and main findings
		○ Panel D: Hb occupancy of 12%, left shift curve more moderate p20 (%Δp20 = 38%) and on the p50 (%Δp50 = 9%) <u>Decreased RBC sickling at Hb occupancy > 11%</u> **Figure 16: Repeat Dosing with Voxelotor Decreases Ex Vivo Red Blood Cell Sickling at Hemoglobin Occupancy > 11% (Study PRC-14-030-R)**  Abbreviations: pO_2, partial pressure of oxygen; RBC, red blood cell; SS, homozygous for sickle hemoglobin. Note: GBT440 is synonymous with voxelotor. • At 36% Hb occupancy: notable effect on RBC sickling (60% decrease compared to vehicle-treated mice). • At 12.1%, moderate effect on RBC sickling (27% decrease compared to vehicle-treated SS mice). <u>Prolongation RBC half-life in SS mice that achieved ≥ 32 % Hb occupancy</u> • Mice that achieved 11-19% Hb occupancy, no significant increase in the RBC $T_{1/2}$ (2.5 +/- 0.1 days vs SS mice control 2.4 +/- 0.1 days). • Mice that achieved 32% Hb occupancy: increase in RBC $T_{1/2}$ (3.8 +/- 0.1 days) vs mice control (but not significant because of low number of animals–n=4 mice). <u>Decreased Reticulocytes count in mice that achieved ≥ 32 % Hb occupancy</u>

N° Study / Title	Methods	Results and main findings
		• No decrease for mice with a low % Hb occupancy. • Voxelotor-treated mice that achieved > 32% Hb occupancy versus the vehicle-treated SS mice **showed a decrease in % reticulocyte count** 36 ± 11% (n = 4) vs 52 ± 2% (n = 10).

In this study, occupancy was calculated as a molar ratio of the concentrations of voxelotor to Hb in blood as determined by the % Hct (obtained at Cmax (4 h post last oral dose), as MCHC data was not available. The applicant has provided additional information on the calculation of the Hb occupancy in the preclinical studies. The occupancy was calculated according to the equations (1) and (2) depicted below; however, instead of the estimated Hb concentration of 5000 µM included in the equation 2, the MCHC value, as estimated in the preclinical studies, was used. MCHC is a mean corpuscular haemoglobin concentration, which represents the average concentration of haemoglobin inside a single red blood cell. It is not measured directly in the studies, but is calculated from the haemoglobin concentration in the whole blood, divided by the haematocrit level, which in turn represents the volume percentage of the red blood cells in the whole blood. Thus the Hb occupancy was calculated as a ratio between the voxelotor concentration in the red blood cells, calculated from equation 4, to the haemoglobin concentration within a single blood cell (MCHC) expressed in µM.

The MCHC value was converted from g/dL, as reported in the studies, into µM by dividing it by the molecular weight of Hb (64458 g/mol). The average MCHC values of two sexes at a particular timepoint were used in the calculations.

The concentration of voxelotor in the red blood cells was determined from equation 2:

$$\%Hb\ occupancy = \frac{[Voxelotor]_{RBC}}{5000} \qquad (1)$$

$$[Voxelotor]_{RBC} = \frac{[Voxelotor]_{whole\ blood} - (1 - Hct)[Voxelotor]_{plasma}}{Hct} \qquad (2)$$

The results indicated that the increases in voxelotor blood exposure are accompanied by corresponding increases in % Hb occupancy (See section 2.5.4.2 Repeat doses toxicity).

Table 3 Secondary pharmacodynamic studies

Study	Methods	Results
PRC – 14-026-R HEK293 cell viability	Different [voxelotor] for 48h Measurement ATP	• Incubation of HEK293 cells with various concentrations of voxelotor shows a half maximal effect on inhibition of cell viability at 138 ± 24 µM.
PRC 14 – 043 – R1 Effect on T-Cell Activation	Measure by induction of CD69 expression in Ficoll-Paque (FP) isolated lymphocytes and in whole blood from healthy subjects + Measure of IL-2 release Different [voxelotor] for 16-24h	• At concentrations up to 500 µM, voxelotor does not activate T-cells in isolated lymphocytes or in whole blood. At 1 mM voxelotor activated T cells in FP lymphocytes (Panel A) but had no effect in whole blood. • Additional results (not shown) showed **no B cell activation**, as measured by CD69 expression, in either FP lymphocytes or in whole blood. • Voxelotor at concentrations up to 1 mM did not induce IL-2 production indicating no effect on T-cell activation.
PRC 15-021-R **PRC-18-044** Voxelotor Receptor, Enzyme, and Ion Channel Binding and Inhibition		• Voxelotor (15 µM) showed no activity against a broad panel of receptors, enzymes, and ion channels (binding assays and enzyme *in vitro* inhibition). • Inhibition (> 50%) was detected for the dopamine transporter, gamma-aminobutyric acid (GABA) receptor complex, angiotensin receptor 1, PDE 4A1A and insulin receptor. • Follow up studies on PDE subtypes showed an IC_{50} for voxelotor > 30 µM for PDE4A1A, PDE4B1 and PDE4D2. • There were no corresponding *in vivo* changes noted in the safety pharmacology and toxicology studies. In addition, tissue distribution studies showed minimal voxelotor levels in the CNS. No inhibition was detected in hERG binding in this panel.

Table 4 Safety pharmacology programme

Study reference	Organ Systems Evaluated / Species /Methods	Method of Admin. Doses (mg/kg) Gender and No. per Group	Major Findings
PRC-14-058-R GLP	hERG channel hERG inhibition *in vitro*	*In vitro* test 1 µM 10 µM	• Voxelotor inhibited hERG current by 4.7% ± 1.2% (mean ± SEM) at 1 µM (n = 4) and 15.3% ± 1.3% at 10 µM (n = 4) versus 1.6% ± 0.6% (n = 3) in control. hERG inhibition at 10 µM was statistically significant ($p < 0.05$) when compared to vehicle control values. • The IC_{50} for the inhibitory effect of voxelotor on hERG potassium current was not calculated but is **greater than 10 µM**. The IC_{50} for inhibition of hERG potassium channel currents, corrected for protein binding is greater **than 70-fold the maximum plasma concentration of voxelotor in patients receiving 1500 mg, once daily.**
PRC-14-052-R GLP	CNS Male Sprague Dawley® SD® rats Irwin test	8 rats /group Single dose on Day 1 [vox] = 100, 320 or 1000 mg/kg of free base Form II, milled drug substance Oral gavage at a dose volume 10 mL/kg	**No neurological effects** related to voxelotor were evident at any timepoint in the group home cage, hand held, open field, or elicited response components of the modified Irwin observational battery at any dose level. NOEL = 1000 mg/kg NOAEL > 1000 mg/kg
PRC-14-053-R GLP	Respirato-ry system Male	8 rats /group Single dose on Day 1	• No effect on mortality, clinical observations, or minute volume but mildly lowered tidal volume by 0.24 mL (-13%) at 1000 mg/kg.

Study reference	Organ Systems Evaluated / Species /Methods	Method of Admin. Doses (mg/kg) Gender and No. per Group	Major Findings
	Sprague Dawley ® SD® rats Plethys mo-graphy	[vox] = 100, 320 or 1000 mg/kg of free base Form II, milled drug substance Oral gavage at a dose volume 10 mL/kg	• **Increased respiration rate** by as much as 14 breaths/minute (19%) at 320 mg/kg => small in magnitude and generally considered to be mild with limited biological relevance. NOEL = 1000 mg/kg
PRC-14-054-R GLP	Cardio-vascular Dog (beagles)	16 male /group Single dose on Day 1 [vox] = 100, 300 or 1000 mg/kg of free base Form II, milled drug substance Oral gavage at a dose volume 5 mL/kg	• Three of 4 dogs given 1000 mg/kg had an incidence of vomitus following dosing. In addition, a few dogs given 1000 mg/kg had some combination of discolored, nonformed, or liquid faeces. • No voxelotor-related changes in body weight or body temperature. • No effect on any of the electrocardiogram (ECG) parameters, including PR interval, QRS duration, QT interval, and QTc interval. • No qualitative ECG abnormalities were attributed to administration of voxelotor. Voxelotor-related haemodynamic changes consisted of a small increase in systolic pressure at 1000 mg/kg. At 6 hours postdose, covariate-adjusted mean systolic pressure for dogs given 1000 mg/kg was +11 mm Hg (8%) higher than the time-matched control. No voxelotor-related changes in diastolic and mean arterial pressures, heart rate, or pulse pressure occurred.

2.5.2.2. Pharmacodynamic drug interactions

No pharmacokinetic drug interaction studies were conducted.

2.5.3. Pharmacokinetics

Voxelotor (GBT440) was investigated in a range of *in vitro* and *in vivo* pharmacokinetic (PK) and toxicokinetic (TK) studies in the C57BL/6J mouse, Sprague Dawley (SD) rats, New Zealand White rabbits and *Cynomolgus* monkeys (Macaca fascicularis). These studies were conducted to define the absorption, distribution, metabolism, and excretion (ADME) of voxelotor following oral (PO) and parenteral administration (IV). Data from these studies were used to characterise the PK and TK properties of voxelotor to support nonclinical toxicology evaluations and to support its intended clinical use. Voxelotor has a low water solubility (~51 µg/mL).

Methods of analysis: Liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods were employed to analyse blood and plasma samples from both GLP and non-GLP nonclinical studies in rat, mouse, rabbit, dog and monkey. In general, GBT440 and an internal standard, GBT1592 (GBT440-D_7), were extracted using liquid-liquid extraction and analysed by a Sciex API 4000 LC-MS-MS equipped with an HPLC column. The analytical range (LLOQ – ULOQ) for blood samples was 200 to 200,000 ng/mL, for plasma samples was 10 to 10,000 ng/mL and for rat milk was 10.0 to 10,000 ng/mL. For non-GLP, 50 to 100,000 ng/mL and 10 to 20,000 ng/mL for blood and plasma, respectively. The methods met all validation criteria with respect to accuracy, precision, sensitivity, linearity, reproducibility, and matrix stability. Incurred sample reproducibility for nonclinical sample analysis was conducted once per method per species.

Table 5 Mean pharmacokinetic parameters of voxelotor following a single dose in mouse, rat, dog, and monkey

Species	Matrix	Intravenous						Oral					
		Dose (mg/kg)	t½ (h)	AUC0-∞ (µg•h/mL)	Vss (L/kg)	CLs (mL/min/kg)	Blood: Plasma Ratio	Dose (mg/kg)	Tmax (h)	Cmax (µg/mL)	AUC0-∞ (µg•h/mL)	F (%)	Blood: Plasma Ratio
Mouse C57BL/6 J Male Study PRC-14-003-R.	Blood	71	11.7	10,409	0.104	0.113	28.6	30	4	81.9	3122	70.5 b	70.1
	Plasma		6.40	372	1.44	3.16	-		4	1.72	34.2	21.5	
Sprague Dawley Rat Male Study PRC-14-004-R.	Blood	1.6	19.1	874	0.049	0.031	70.7	7.2	5.00	71.2	2353	59.8	69.0
			(7.80)	(11.7)	(10.0)	(11.7)	(20.2)		(51.6)	(8.46)	(8.39)	(8.39)	(10.6)
	Plasma		21.8	14.8	2.78	1.80	—		1.25	2.41	39.6	59.3	—
			(9.73)	(5.94)	(16.0)	(5.64)			(46.2)	(8.35)	(11.0)	(11.0)	
Beagle Dog Male and Female Study PRC-14-007-R.	Blood	1	66.0	559	0.171	0.031	65.0	2.5	8.00	5.56	607	36.6	74.4
			(16.7)	(19.0)	(14.3)	(14.7)	(13.4)		(0.00)	(28.9)	(52.1)	(27.5)	(11.9)
	Plasma		93.5	13.3	8.45	1.29	--		0.643	1.04	8.32	36.0	—
			(38.3)	(19.3)	(25.0)	(18.6)			(38.0)	(28.3)	(26.2)	(24.7)	
Cynomolgus Monkey	Blood	1	28.8	1073	0.041	0.016	69.0	4.25	18.0	25.2	1604	36.1	70.9
			(13.9)	(17.5)	(22.4)	(17.9)	(21.1)		(57.7)	(21.6)	(19.3)	(27.4)	(11.2)

Study PRC-14-012-R.	Plasma		28.8	17.7	2.34	0.943	—		4.67	0.861	25.1	33.2	—
			(10.1)	(5.86)	(9.57)	(5.97)			(24.7)	(54.0)	(26.0)	(23.1)	

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-\infty}$, AUC from time 0 to infinity; CL_s, system clearance; C_{max}, maximum concentration; %CV, percent coefficient of variation; F, bioavailability; $t_{1/2}$, half-life; T_{max}, time to peak concentration; V_{ss}, volume of distribution at steady state.
Note: The blood: plasma ratio was calculated by comparing AUC of blood and plasma concentration-time profiles of voxelotor during the terminal phase (e.g., 24 to 144 hours) to ensure equilibrium between the 2 matrices was reached.

Absorption

In an *in-vitro* study, voxelotor showed a high permeability when using a polarised monolayer of Madin-Darby Canine Kidney (MDCK)-MDR1 cells or Caco-2 cells. The influence of the gut and the liver (first-pass effect) on the oral absorption process of voxelotor was studied in the rat by measuring the portal and femoral vein blood levels. The fraction of voxelotor that escaped the gut and liver were 0.64 and 0.74, respectively, suggesting that oral bioavailability was moderately restricted by gut absorption or by liver first-pass metabolism.

In fasted male Sprague Dawley rats, the single dose PK of voxelotor was studied following IV dosing at 1.6 mg/kg and oral gavage dosing at 7.2 mg/kg voxelotor hydrochloride (n = 4). Following IV and oral administration in rats, the plasma concentrations of voxelotor declined in a bidirectional fashion but blood concentration increased or was constant for hours before declining. Distribution volume (Vss) was low for blood (0.05 L/kg), indicating mainly distribution to blood volume, and high in plasma (2.8 L/kg), i.e. 4-fold more than body water. Clearance was low for blood and plasma (0.031 and 1.80 mL/min/kg). Terminal elimination half-life ($t_{1/2}$) values in blood and plasma were similar (19.1 and 21.8 hrs, respectively). Following oral administration, absorption was fast in plasma (Tmax 1.25 hrs) and moderate in blood (5 hrs). Exposure, based on AUC, in blood was ~70-fold higher than in plasma but oral bioavailability was similar for blood and plasma when using a solution formulation (~60%) or suspension (~46%).

Dose linearity of pharmacokinetics was evaluated in the rat. Upon oral dosing of voxelotor (HCl-salt), blood exposure ($C_{max,}$ $AUC_{0-\infty}$) increased about 10-fold less than dose-proportional over the dose range of 10 to 1000 mg/kg. No differences were found in exposure, when using the free base, hydrochloride salt, or sulphate salt (100 - 1000 mg/kg) in the 0.5% methylcellulose plus 0.5% sodium dodecyl sulphate (SDS) formulation or when using the voxelotor free base polymorphic Form II or Form N. API particle size did also not influence absorption as the free base form II, milled versus non-milled, gave similar exposure. A food effect study showed only a modest decline (30%) in bioavailability in the fed rat (10 mg/kg).

In fasted male and female Beagle dogs, the single dose PK was studied following IV dosing at 1.0 mg/kg and oral gavage dosing at 2.5 mg/kg voxelotor hydrochloride (n = 4/sex). Following IV and oral administration in dogs, the plasma concentration of voxelotor declined in a bidirectional fashion but blood concentration increased or was constant during the first 8 hrs before slowly declining. Distribution volume (Vss) was low for blood (Vss 0.17 L/kg), indicating slightly more than blood volume, and for plasma high (8.4 L/kg), i.e. 14-fold more than body water. Clearance was low for blood and plasma (0.031 and 1.29 mL/min/kg). Terminal elimination half-life ($t_{1/2}$) values in blood and plasma were very high (60 – 100 hrs but measured only up to 72 hrs). Following oral administration, absorption was fast in plasma (Tmax 0.65 hrs) and moderate in blood (Tmax 8 hrs). Exposure, based on AUC, in blood was 70 to 80-fold higher than in plasma. Oral bioavailability was similar for blood or plasma (32% - 42%).

In male Beagle dog (n=3), orally dosed with 100 mg/kg voxelotor, no differences were found in exposure, when using a capsule, filled with voxelotor Form II, milled drug substance, or a suspension (0.5% w/w Methocel E50 containing 0.01% w/w polysorbate 80 and 10 mM phosphate buffer, pH 7), nor was a food effect seen. The latter formulation was used in the majority of the nonclinical studies including the GLP toxicology and safety pharmacology studies. Upon oral dosing of voxelotor (free base), blood exposure ($C_{max,}$ $AUC_{0-\infty}$) increased less than dose-proportional over the dose range of 50 to 1000 mg/kg.

In fasted male *Cynomolgus* monkeys, the single dose PK of voxelotor was studied following IV dosing at 1.0 mg/kg and oral gavage dosing at 4.25 mg/kg voxelotor hydrochloride (n = 3). Following IV and oral administration, the plasma concentration of voxelotor declined in a multidirectional fashion but blood concentration increased or was constant during the first 18 hrs before declining. Distribution volume (Vss) was low for blood (Vss 0.041 L/kg), indicating less than blood volume, and for plasma high (2.3 L/kg), i.e. ~4-fold more than body water. Clearance was low for blood and plasma (0.016 and 0.94 mL/min/kg). Terminal elimination half-life ($t_{1/2}$) values in blood and plasma were similar (36 and 28 hrs). Following oral administration, absorption was moderate in plasma (Tmax 4.6 hrs) and slow in blood (Tmax 18 hrs). Exposure, based on AUC, in blood was ~70-fold higher than in plasma. Oral bioavailability was similar for blood or plasma (~35%).

In fasted male C57BL/6J mice, the single dose PK of voxelotor was studied following IV dosing at 71 mg/kg and PO dosing at 30 mg/kg voxelotor hydrochloride (n = 3 mice/time point). The blood sampling times, up to 24h, were too short to give an accurate value of the blood PK parameters, although it is clear that a similar PK profile as with the other studied species was found, i.e. that voxelotor resides more in blood than in plasma.

Upon multiple dosing of voxelotor in rat, dog or monkey, both blood and plasma exposure increased less than dose-proportional. In the dog, the accumulation of voxelotor over time was less than expected based on its long elimination half-life and did not follow linear PK profile in that only a 1.2-fold increase in exposure was seen with a 5-fold increase in dose. In the monkey, plasma voxelotor exposure seemed to have reached steady-state after eight days of dosing, while for voxelotor blood exposure this was not yet (52 – 74%) achieved. In the multiple dose safety studies in rat (4, 13 & 26 wk), dog (4 wk) and monkey (13 & 39 wk), the toxicokinetics (TK) of voxelotor was determined. The increase in exposure in blood was less than dose-proportional, while, generally, in plasma it was more dose-proportional. Accumulation over time was, dependent on the dose and duration of dosing, between 1.0 and 3.5.

Distribution

The *in vivo* tissue distribution of ^{14}C-voxelotor (^{14}C-GBT440) was investigated in the male albino SD rat and the partially-pigmented Long Evans rat after oral administration of 10 mg/kg (150 µCi/kg) using quantitative whole-body autoradiography (QWBA) at 0.5 h up to 72 h (SD) and up to 672 h (Long Evans) post dosing. Tissue distribution in non-pigmented rats was comparable to that in the pigmented male rats. Following oral administration, radioactivity was quickly distributed to all tissues studied but mainly confined to the blood (RBCs) compartment. The highest ^{14}C-related radioactivity was found at 4 – 8 hours post dose in bile, blood, lung, spleen (red pulp), liver, bone marrow, and kidney. Tissue to blood ratio (T/B) was generally found to be lower than 0.5 for all tissues during the first 24 hours post dose. At 336 hrs post single dose administration of ^{14}C-voxelotor, radioactivity was very low but still measurable in blood, liver, lung, eye uveal tract and kidney. Radioactivity was found to cross the blood brain barrier, but exposure was at least 30-fold lower than in the blood. As pigmented and non-pigmented skin were similarly labelled, it is concluded that there is no melanin binding. At 672 hrs post dose, no radioactivity was still measurable.

The partitioning of voxelotor into plasma and blood was determined after single-dose administration of voxelotor to mouse, rat, dog and monkey. The blood to plasma (B/P) ratio, based on exposure (AUC) was found to be about 70 (62 - 81), indicating a red blood cell (RBC) partitioning of >99%. In human, the B/P ratio, based on the exposure (AUC_{0-24}) upon daily oral dosing of 1500 mg voxelotor, corresponds to an RBC partitioning of about 96%.

Protein binding studies with voxelotor were performed *in vitro* with plasma (in the absence of Hb) from human, monkey, dog, rat, and mouse at 5 µM and 50 µM using an ultracentrifugation method. Plasma protein binding of voxelotor was 99.6% in dog or mouse plasma and 99.8% in human, monkey and rat plasma. Voxelotor had higher binding affinity to albumin than to alpha-1-acid glycoprotein.

Developmental and reproductive toxicity studies were performed in SD rats and New Zealand White rabbits. In the rat pre- and postnatal development study, voxelotor was found to be excreted in the milk and exposure in milk was about 26% – 41% of the maternal plasma exposure. On lactation day 10, plasma exposure of voxelotor was found in the pups, which amounted to ~3.6% of maternal plasma voxelotor concentration, indicating that voxelotor is readily excreted in the milk leading, subsequently, to plasma exposure in the pups.

Metabolism

Metabolism of voxelotor was evaluated in both *in vivo* and *in vitro* studies. *In vivo* metabolism with metabolite identification was evaluated in rats and dogs, providing information on possible metabolic pathways. Blood, plasma, bile, faecal homogenates, and urine were pooled and profiled for metabolites of ^{14}C-GBT440 (voxelotor, LoQ = 1%). Structures of the metabolites were identified by liquid chromatography-mass spectrometry (LC-MS and/or LC-MS/MS) and were verified against reference standards, when available.

Following a single oral administration of 10 mg/kg ^{14}C-voxelotor to male SD rats (n=3), radio-HPLC profiles showed that unchanged voxelotor was the major source of circulating radioactivity in blood (99%) and in plasma (~80%). In rats ^{14}C-voxelotor was metabolised by both phase I and phase II biotransformation. The largest of the five circulating radioactive metabolites in plasma were M24 (~8%) and M11 (~6%). It should be noted that the extraction recovery was low, ~50% for plasma and 63% for blood. In urine, containing about one tenth of the radioactive dose, unchanged voxelotor and 40 metabolites were found, of which M23 was excreted as the largest radioactive component (~1% of the radioactive dose), while the others were <0.6%. In faeces, containing three quarters of the radioactive dose, most of the excreted radioactivity was associated with unchanged voxelotor (15%) and 20 metabolites, of which GBT1659 (3.4%), GBT1226 (3.4%), GBT921 (1.5%) and M19 (1.2%) were each above 1% of the radioactive dose. In bile, obtained from bile duct cannulated (BDC) rats (n=2), given a single intravenous administration of 2 mg/kg ^{14}C-voxelotor, unchanged voxelotor (~7%) and 21 metabolites were found, of which the glucuronides M11 and M13C (both ~10%), M80 and M84 (both ~7%) were each above 4% of the radioactive dose.

Following a single oral administration of 20 mg/kg ^{14}C-voxelotor to male Beagle dogs (n=3), unchanged voxelotor was the major source of circulating radioactivity in blood (92-97%) and was the second most abundant species in plasma (22-32%). In dogs, ^{14}C-voxelotor was metabolised by both phase I and phase II biotransformation. The major circulating radioactive components in plasma were M24 (34%), unchanged voxelotor (22-32%), GBT1659/GBT921 (combined 12-15%) and M113C (8%). In urine, containing about a quarter of the radioactive dose, unchanged voxelotor with 15 metabolites were found and GBT1659 was excreted in urine as the major radioactive component (~4.5% of the radioactive dose). In faeces, containing two third of the radioactive dose, most of the excreted radioactivity was associated with unchanged voxelotor

(15%) and 14 metabolites, of which GBT1659/GBT921 (~10%) and GBT1226 (1%) were above 1% of the radioactive dose.

A comparison with rats and dogs was made of metabolites present in humans. In humans, an AME study indicates that M218/1 (named as M24 in rat and dog) was a major circulating metabolite in plasma accounting for 16.8% of the total radioactivity in the 0 to 48-hour pooled plasma samples. M218/1, named as M24, was also found in plasma of rats and dogs as 8.1% and 34%, respectively, of total radioactivity upon oral administration of ^{14}C-voxelotor. M24 (M218/1) was identified as a phase II sulphate-conjugated metabolite of *O*-dealkylated voxelotor, and it is likely to be pharmacologically inactive as evidenced by the non-partitioning into the whole blood (RBCs). None of the Phase I metabolites represented more than 10% of total drug related exposure in human plasma or blood. All metabolites, except two trace human phase II metabolites, M419/1 and M673/1 (< 1% of total radioactivity in human AME study), were detected in either rat or dog. Overall, the circulating plasma metabolite profiles of rats and dogs are considered similar to that of humans.

The *in vitro* metabolite profile of voxelotor was obtained following incubation with Sprague-Dawley rats, beagle dogs, *Cynomolgus* monkeys, and human liver microsomes and hepatocytes. Voxelotor, studied at 1 µM or 10 µM, was moderately (10% to 49% after 2 hrs) metabolised through both Phase I (*O*-dealkylation, mono-oxidations and reductions) and Phase II (glucuronidation and sulfation) metabolisms in both animal and human hepatocytes. Thirteen metabolites were identified, and no unique metabolite was observed from human liver microsomes or hepatocytes that was not also formed by rat, dog, or monkey microsomes or hepatocytes. The applicant provided a comparative table of voxelotor metabolites, specifying the percentage in all species, including human. There was no unique metabolite observed from human liver microsomes or hepatocytes that was not also formed by mouse, rat, dog, or monkey microsomes or hepatocytes.

In vitro metabolism studies using human liver microsomes and recombinant enzymes are consistent with voxelotor metabolism by CYP 1A1, 1B1, 2B6, 2C9, 2C19, 3A4, and 3A5 enzymes. With respect to Phase II metabolism pathway multiple sulfation (SULT 1A1, 1A3, 1B1, 1C4) or glucuronidation (UGT 1A1, 1A3, 1A4, 1A6, 1A9, 2B7, and 2B15) enzymes are possibly involved. Further study showed comparable contribution of the two main UGT enzymes, 1A1 and 1A9.

Excretion

After single oral administration of [^{14}C]voxelotor, the excretion of radioactivity was predominantly through the faecal (biliary) pathway, and, for the intact rat, and dog, this accounted for 79% and 66% of the radioactivity dose, while the urinary route contributed 9.7% and 26%. The total recovery of radioactivity, ten days after dosing, was high in the rat (92%), dog (96%) and human (>90%). In bile duct-cannulated rats, following intravenous administration, excretion into the bile, faeces, urine and expired air was 84.2%, 1.8%, 7.5% and 0.9% of the radioactivity dose, respectively, indicating a predominant biliary clearance. The main route of elimination of voxelotor is by metabolism. Following oral administration to rat or dog, 15% to 16% of the dose was excreted into faeces as unchanged voxelotor and this was <0.1% into urine. Most of the [^{14}C]voxelotor–related radioactivity, 66% and 51%, was excreted into faeces as 20 and 13 metabolites in rat and dog, respectively. Similarly, in humans, 63% of the administered radioactivity was found in the faeces (~34% as intact drug) while 35% was excreted in the urine after 22 days (97% of the administered dose).

In conclusion, following intravenous or oral administration, voxelotor was primarily cleared after metabolism via biliary excretion and faecal elimination in the tested preclinical species (rat and dog) and in human. Renal clearance plays a lesser role.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single dose toxicity studies were performed in rats and dogs using dose levels up to 1000 mg/kg. No mortalities occurred and the clinical signs were limited to vomiting and diarrhoea in dogs and piloerection in rats.

Table 6 Overview of single dose toxicity studies with voxelotor

Study ID	Species/ Sex/Number/ Group	Dose/Route	Approx. lethal dose / observed max non-lethal dose	Major findings
PRC-14-009-R, non-GLP	Beagle dog 1/sex/dose	500, 800 and 1000 mg/kg (milled product) Oral gavage	>1000 mg/kg	Emesis
PRC-14-010-R, non-GLP	Beagle dog 3 females/dose	100 and 500 mg/kg (milled and non-milled product) Oral gavage	>1000 mg/kg	Emesis, diarrhoea
PRC-14-011-R	Rat, Sprague-Dawley, 3/sex/dose	1000 mg/kg Oral gavage		

2.5.4.2. Repeat dose toxicity

Repeated dose toxicity of voxelotor was studied in rats, mice, dogs and monkeys. Studies are summarised in the tables below:

Table 7 Overview of repeat-dose toxicity studies with voxelotor

Study ID Species/Sex/ Number/Group	Dose/ Route/Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
Rat			

PCR-14-051-R, GLP 15/sex /dose (controls & high dose toxicity - 10/sex/dose sacrificed immediately post-dosing, 5/ sex/dose recovery group), 4/sex/dose (controls TK), 10 sex/dose (low, mid and high-mid dose toxicity + TK, high dose TK)	0, 15, 50, 250 and 1000 mg/kg/ day, oral gavage 28 days with 4 weeks recovery	250 mg/kg/ day	**≥250:** diuresis; ↑ RET, RBC, HCT, Hb, WBC (lymphocytes, neutrophils, monocytes, basophils, large unstained cells (F)) correlated with spleen extramedullary haematopoiesis and hypercellular bone marrow; ↑ PT (M); periportal hepatocyte hypertrophy (M) correlated with ↑ liver weight; thyroid follicular cell and pituitary basophil hypertrophy (secondary to liver enzyme induction); ↑ heart weight correlated with myocardial histiocytic infiltrate. No recovery was checked, but the reported effects were reversible at the next dose level. **1000:** mortality/euthanasia *in extremis* correlated with degenerative/regenerative changes in GIT (degeneration/necrosis, hyperplasia, erosion/ulcer, inflammation in stomach/gut); ↓ BW and food consumption; ↑ erythropoietin correlated with erythroid and myeloid hypercellularity in bone marrow, ↑ PT (F), APTT; ↑ ALT correlated with periportal hepatocyte hypertrophy and ↑ liver weight; ↓ total protein, albumin and globulin; ↓ Ca^{2+}; ↑ spleen weight correlated with extramedullary haematopoiesis; ↓ splenic marginal zone lymphocytes; ↓ thymus weight correlated with ↓ thymus lymphocytes. Most changes recovered post-treatment (except GIT effects, spleen weight and (mild) erythroid/myeloid hypercellularity in bone marrow).
PRC-15-019-R, GLP Rat, Sprague-Dawley, 15/sex/dose (toxicity controls + high-dose - 10/sex/dose sacrificed immediately post-dosing, 5/ sex/dose recovery group), 10/sex/dose (toxicity low- and mid-dose), 3/sex/dose (controls TK), 9/sex/dose (low-, mid- and high-dose TK)	0, 15, 100/50[a] and 700/250[a] mg/kg/day, oral gavage 13 weeks with 4 weeks recovery	250 mg/kg/day	**≥ 15:** bone marrow erythroid hypercellularity (minimal/moderate), CYP1A and CYP2B induction (F) **≥100/50:** ↓ platelets (M); ↑ RBC, Hb, HCT, ↑ WBC (F, primarily neutrophils, lymphocytes, monocytes) correlated with bone marrow hypercellularity and splenic extramedullary haematopoiesis with ↑ splenic germinal centre lymphocytes; ↑ ALT (M), CYP1A and CYP2B induction; thyroid follicular cell hypertrophy and pituitary basophil hypertrophy (M) (secondary to liver enzyme induction); ↓ mandibular salivary gland weight. No recovery was checked at this dose level, but the observed effects were reversible at the next dose level. **700/250:** ↓ BW and food consumption (M) → dose reduction to 250 mg/kg/day; ↓ platelets (F); ↑ RET, MCV, MCH; ↑ total lymphocytes, total T, CD4+, CD8+, B, with ↑ relative percent B, ↓NK cells, correlated with ↑ splenic germinal centre lymphocytes, ↓ marginal zone lymphocytes and ↑ spleen weight; ↓ anti-KLH IgG titres; ↑ ALT (F) correlated with periportal hepatocyte hypertrophy, CYP1A, CYP2B, CYP3A (F) and UDPGT induction and ↑ liver weight, ↑ kidney weight (F) correlated with chronic progressive nephropathy; ↑ severity of valvular myxomatous change (M) correlated with ↑ heart weight; forestomach hyperplasia/hyperkeratosis; sciatic nerve perivascular mineralisation (M). Complete recovery was seen for all effects except for periportal hepatocyte hypertrophy and sciatic nerve perivascular mineralisation (partial recovery).

PRC-16-008, GLP Rat, Sprague-Dawley, 20/sex/dose (controls and high-dose toxicity), 3/sex/dose (controls TK), 15/sex/dose (low- and mid-dose toxicity), 9/sex/dose (low, mid- and high-dose TK)	0, 15, 50 and 250 mg/kg/day, oral gavage 26 weeks with 4 weeks recovery	250 mg/kg/day	**≥15:** ↑RBC, RET (M), ↑MCH, (F); ↑ spleen germinal centre lymphocytes ; ↑ heart weight (M) **≥ 50:** ↓platelets; ↑HCT, RET; ↑ spleen germinal centre lymphocytes; ↑ heart weight (F), ↑ ALT, liver weight **250:** ↓ BW (F), ↑MCV, MCH, MCHC, WBC (lymphocytes, neutrophils, monocytes) correlated with hypercellular bone marrow, ↑ spleen weight and splenic haematopoiesis; ↑PT, APTT; ↑AST (M) correlated with hepatocyte hypertrophy, bile duct hyperplasia and ↑ liver weight; ↑ thyroid weight correlated with follicular cell hypertrophy and pituitary basophil hypertrophy (M) (secondary to liver enzyme induction); ↓spleen marginal zone lymphocytes; ↑kidney weight correlated with chronic progressive nephropathy and diuresis; ↑ lung weight; degenerative cardiomyopathy (M); forestomach hyperplasia/hyperkeratosis; perivascular sciatic nerve mineralisation. Recovery was seen, except partial recovery for liver, spleen and thyroid weights and liver, heart, forestomach and sciatic nerve microscopic findings.
Mouse			
PCR-16-014, GLP Mouse, wild type, 10/sex/dose (toxicity), 6/sex/dose (controls TK), 36/sex/dose (low, mid- and high dose TK)	0, 50, 150 and 500 mg/kg/day, oral gavage 28 days	Not established	**≥ 50:** ↓platelets; ↑RBC, Hb (M), ↑ HCT correlated with hypercellular bone marrow; ↑ heart weight (F), ↑ hepatic enzyme induction (↑ microsomal protein yield, CYP450 content (F), CYP2B, CYP3A, CYP2E (F) activities) **≥ 150:** ↑MCV, MCH; ↑WBC (lymphocytes) (M); splenic extramedullary haematopoiesis; ↑liver weight (F) correlated with ↑hepatocyte vacuolation, ↑CYP1A activity **500:** ↑RET, WBC (lymphocytes) (F), ↑ spleen weight; ↑ microsomal protein yield (M).
Dog			
PCR-14-050-R, GLP Dog, Beagle, 5/sex/dose (controls, high-dose); 3/sex/dose (low, mid and-mid-high dose)	0, 30, 100, 300 and 1000 mg/kg/day, oral gavage 28 days with 4 weeks recovery	300 mg/kg/day	**≥ 30:** discoloured faeces (M), liquid faeces **≥100:** discoloured faeces (F) **≥ 300:** vomitus/emesis; mucoid and non-formed faeces (F) **1000:** Euthanasia *in extremis* (2 F), mucoid and non-formed faeces (M), ↓ BW and food consumption (F, recovered post-treatment).
Monkey			
PRC-15-020-R, GLP Monkey, Cynomolgus, 6/sex/dose (controls + high-dose, 4/sex/dose terminated post-dosing, 2/sex/dose recovery group), 4/sex/dose (low- and mid-dose)	0, 30, 130/100 and 600/300[b] mg/kg/day, oral gavage 13 weeks with 8 weeks recovery (high-dose necropsied after 30 days)	30 mg/kg/day	**≥ 30:** vomitus/emesis, ↑ RBC, Hb, HTC (M) correlated with hypercellular bone marrow/ splenic red pulp and ↑ spleen weight; ↓ total protein (M) **≥ 100**: sacrifice *in extremis* (1 M): liquid faeces, ↓BW and food consumption; focal degeneration/necrosis of myocardium, erosion/ulceration in colon and inflammatory cell infiltrates in stomach/colon/heart. Survivors: liquid, mucoid and/or nonformed faeces; ↓ food consumption, swelling in different body parts (1 M); ↓ Ca^{2+}; ↓ thymus weight correlated with ↓ cortical lymphocytes **300:** swelling in different body parts, skin/subcutis abnormalities (discoloured/gelatinous/thickened), faecal abnormalities, hunched posture, hypoactivity, ataxia; ↓ BW, food consumption → early termination; ↑ RBC, Hb, HTC correlated with hypercellular bone marrow, splenic haematopoiesis and ↑ erythropoietin (individual animals); mucosal erosion/ulceration, epithelial cell degeneration/necrosis, inflammatory cell infiltrates in multiple tissues incl. GIT correlated with ↑ WBC (neutrophils), ↑ fibrinogen, ↓ total protein + albumin + albumin: globulin ratio and ↓ electrolytes (Na^+, Cl^-); ↑ QT and QTc interval; 1F with myocardial degeneration/necrosis. Observed changes resolved following the recovery. **600:** liquid faeces, ↓ food consumption → dose reduction to 300 mg/kg/day

PRC-16-007, GLP Monkey, Cynomolgus, 6/sex/dose (controls and high-dose – 4/sex/dose terminated immediately after dosing, 2/sex/dose recovery group), 4/sex/dose (low- and mid-dose)	0, 15, 30 and 60 mg/kg/day, oral or nasogastric gavage 39 weeks with 4 weeks recovery	15 mg/kg/day	**≥30:** sacrifice *in extremis* (2 M, 1 F, after 13+ weeks). In moribund animals: ↓ BW + food consumption, faeces abnormalities; M: abnormal clotting response (↑ APTT); ↓ platelets; ↓albumin + Ca^{2+}; ↑ fibrinogen; haemorrhage/haemolysis resulting in ↓RBC and/or HTC and/or WBC; associated microscopic findings: gingiva necrosis, bone marrow hypoplasia (1M); globular nephropathy (1M). F: ulcerative dermatitis (erythema, oedema, scabs, pruritis, erosions/ulcers), ↓albumin, ↑ monocytes. **60:** sacrifice *in extremis* (2M, 2F). In moribund animals: ↓ BW; 1M: abnormal clotting response (↑ APTT), ↓albumin + Ca^{2+}; ↑ fibrinogen; ↓RBC, HTC, Hb; ↑ RET; ↑ lymphocytes; associated microscopic findings: bone marrow hypercellularity, ↓ lymphocytes in thymus. 1M: periorbital oedema; ↓albumin + Ca^{2+}; microscopic findings: inflammatory cell infiltrates in both eyelids, ↓ lymphocytes in spleen, thymus and lymph nodes. Both F: GI erosions/ulcers, enterocolitis with neutrophil infiltrates. Survivors: faecal abnormalities (F); ↓ BW gain; ↓anti-KLH IgM and IgG titres, delayed peak IgG response; ↑ spleen weight.

[a] Beginning on Day 9 of the dosing phase, dose levels were lowered to 50 mg/kg/day and 250 mg/kg/day for Groups 3 and 4, respectively.

[b] In Phase 1 of the study, animals were dosed at 0, 15, 65 and 300 mg/kg/dose BID (0, 30, 130 and 600 mg/kg/day) for 1 week. Dosing was stopped for the high-dose group on day 3 due to adverse effects. Days 4 and 5 were washout days for this group, and the dosing resumed on day 6 with the 2 days dosing BID followed 1 day washout. However, the dosing was stopped for all groups on day 7 and resumed after one week washout with 0, 30, 100 and 300 mg/kg/day. The high-dose group was terminated after 30 days due to adverse effects; animals designated for recovery group (2/sex/dose) underwent 63 days recovery.

Table 8 Overview of supportive repeat-dose toxicity studies with voxelotor

Study ID Species/Sex/ Number/Group	Dose/Route Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
Rat			
PRC-14-011-R, non-GLP Rat, Sprague-Dawley, 3/sex/dose	400, 600 and 1000 mg/kg/day, oral gavage 7 days	Not determined	**≥400:** Dehydration, decreased activity; ↑ WBC (lymphocytes, monocytes), ↓ RBC, ↑ MCV, ↑ % RDW; ↑ LDH; ↑ phosphorus, ↑ cholesterol, ↑ triglycerides; ↓ albumin **≥600:** ↓ BW, ↓ haematocrit (M), ↑ MPV, ↑ ALT **1000:** ↑ PT, ↑ MCHC
PRC-14-047-R, non-GLP Rat, Sprague-Dawley, 3/sex/dose	400, 600 and 1000 mg/kg/day, oral gavage 4 days	Not determined	**≥400:** decreased activity; fluffy fur; ↑ ALT, ↑ AST, ↑ CPK, ↑ GGT, ↑ cholesterol, ↑ triglycerides, ↑ total bilirubin; ↑ erythropoietin; ↓ ALP, ↓ albumin, ↓ K^+, ↓ Cl^-; ↑ PT, ↑ platelets; ↑ MPV; ↑ reticulocytes; ↑ RDW **1000:** ↓ RBC, ↓ HgB, ↓ haematocrit (F)
PRC-14-048-R, non-GLP Rat, Sprague-Dawley, 2 groups of 6/sex/dose	0, 25 and 200 mg/kg/day, oral gavage 11 days	Not determined	**≥ 25:** ↑ ALT (M), ↑ Mg^{2+}(M), ↑ extramedullary haematopoiesis in spleen, ↑ bone marrow erythroid hyperplasia, decreased M:E ratio (F) **200:** ↑ haematocrit; ↑ MCV; ↑ MCHC; ↑ RDW; ↑ reticulocytes; ↑ CH-reticulocytes; ↑ MCV-reticulocytes; ↑ neutrophils (M); ↑ RBC (F), ↑ haemoglobin (nss), ↑ APTT (M), ↑ ALT (F), ↑ bilirubin, ↑ CPK (M), ↑ GGT, ↓ glucose, ↓ amylase
RPC-14-049-R, non-GLP Rat, Sprague-Dawley, 5/sex/dose	25, 50 and 100 mg/kg/day, oral gavage 4 days	100 mg/kg/day	**100:** No clinical signs or effects on body weights. No other parameters examined.
Dog			

PRC-14-057-R, non-GLP Dog, Beagle, 2/sex/dose	200, 700 and 1000 mg/kg/day, oral gavage 7 days	**≥200:** vomitus/emesis, excessive salivation, liquid/mucoid/non-formed faeces, ↓ BW

Major findings associated with repeat-dose administration of voxelotor in mice, rats and *Cynomolgus* monkeys were changes in hematopoietic parameters and gastrointestinal (GI) intolerance that was attributed to local irritation.

Hematologic changes included increased RBCs, reticulocytes, and haematocrit, with increased cellularity of bone marrow and extramedullary haematopoiesis in spleen consistent with exaggerated pharmacology of voxelotor in normal animals. The exposure in dogs in the 4-week study at the highest tolerated dose was not sufficiently high to cause decreased tissue O2 extraction and dogs did not have erythroid or bone marrow changes, therefore dogs were not further considered as test species. The GI effects were accompanied by decreased food consumption, decreased body weights and/or body weight gain and early terminations (early sacrifice and or early death). Other findings attributed to voxelotor include induction of CYP enzymes in the liver of rats, altered T cell-dependent antigen response in rats and monkeys, and prolongation of QTc intervals in monkeys.

The pharmacological effects observed in rats, mice and monkeys were largely comparable. Voxelotor induced a dose-dependent increase in the red blood mass (RBC, HCT, Hb) which correlated microscopically with the increased hypercellularity of the bone marrow and extramedullary haematopoiesis in the spleen.

The calculated Hb occupancies by voxelotor and the observed haematological effects in the studies with different species are presented below:

Table 9 Voxelotor: Calculated occupancy in repeated dose pharmacology studies in SCD mice

	Dose (mg/kg) Route	Blood Concentration (C_{max}) (mM)	Plasma Concentration (C_{max}) (mM)	Hct (%)	Concentration in RBC (mM)[a]	% Hb Occupancy[b]
9-12 days	100 /150, PO BID					
		484	NA	24.4	NA	39.6
		558	64	30.1	1710	37.2
		557	35	30.5	1746	36
		496	38	30.7	1530	32.3
		272	21	28.6	897.5	19
		250	36	26.8	834.7	18.5
		207	20	23.9	802.4	17
		218	18	29.5	696	15
		205	13	29.3	668.3	14
		189	21	27.4	633.6	13.8
		174	20	27.6	578	12.6
		175	14	28.9	571	12.1
		101	21	16.6	503	12
		184	11	31.9	553.3	11.5
	Average	290.7	25.5	27.6	986.2	20.8

Abbreviations: Hb, hemoglobin; Hct, hematocrit; MCHC, mean corpuscular hemoglobin concentration; MAA, Marketing Authorisation Application; RBC, red blood cell.

[a] Voxelotor concentration in RBCs based on whole blood concentration, corrected for plasma concentration and hematocrit as described in Equation 4 from Section 2.6.2.2.1.11 of the MAA

[b] Occupancy (%) calculated by dividing the concentration of voxelotor in blood expressed in µM by the concentration of hemoglobin in blood as determined by Hct (for example 20% Hct estimated to be 1mM Hb), expressed in µM. The ratio was expressed as %.

Source: Report PRC-14-030-R

Table 10 Voxelotor: Calculated occupancy in repeated-dose toxicity studies in Cynomolgus monkeys

Evaluation Time	Dose (mg/kg/day)	Blood Concentration (C_{max}) (ng/ml)	Plasma Concentration (C_{max}) (ng/ml)	Hct (%)	Concentration in RBC (ng/ml)[a]	Concentration in RBC (µM)[b]	MCHC (g/dL)	MCHC (µM)[c]	% Occupancy Red Cell Mass[d]
13-Week Monkey (Phase 2) (PRC-15-020-R)									
Day 1[e]	30	115000	4000	41.9	268916	797	31.9	4941	16
	100	242000	11550	41.8	553296	1640	31.3	4856	34
	300	457500	44400	42.9	1007337	2986	31.4	4871	61
Week 5	300	444000	33000	47.4	901004	2670	32.3	5011	53
Week 13	30	214000	7825	44.4	472183	1399	30.9	4794	29
	100	384000	22400	47.2	789314	2339	30.9	4794	49
39-Week Monkey (PRC-16-007)									
Day 1	15	62300	2470	46.3	131692	390	30.8	4771	8
	30	98500	4460	44.6	215312	638	30.1	4662	14
	60	175000	8460	46.0	370503	1098	29.9	4631	24
Week 13	15	180000	6800	48.5	364282	1080	30.3	4693	23
	30	227000	12800	42.0	522800	1549	30.5	4732	33
	60	330000	17700	46.1	695876	2062	29.9	4639	44
Week 39	15	195000	8010	43.9	433955	1286	33.3	5158	25
	30	239000	13200	40.4	572803	1698	33.2	5151	33
	60	375000	20500	42.4	856585	2539	34.3	5314	48

Abbreviations: Hb, hemoglobin; Hct, hematocrit; MCHC, mean corpuscular hemoglobin concentration; MAA, Marketing Authorisation Application; RBC, red blood cell.

[a] Voxelotor concentration in RBCs based on whole blood concentration, corrected for plasma concentration and hematocrit as described in Equation 4 from Section 2.6.2.2.1.11 of the MAA.

[b] Conversion of concentration in RBC from ng/ml to µM based on molecular weight of voxelotor (337.4 g/mol).

[c] Conversion of MCHC from g/dL to µM based on molecular weight of Hb of 64458 g/mol.

[d] Occupancy (%) calculated by dividing concentration of voxelotor in the red cells (µM) by the concentration of hemoglobin in red cells (MCHC) expressed as µM and converting quotient to %.

[e] Hct and MCHC values are from samples collected on Pretest Day 15.

Table 11 Voxelotor: Calculated occupancy in repeated-dose toxicity studies in rodents

Evaluation Time	Dose (mg/kg/day)	Blood Concentration (C_{max}) (ng/ml)	Plasma Concentration (C_{max}) (ng/ml)	Hct (%)	Concentration in RBC (ng/ml)[a]	Concentration in RBC (µM)[b]	MCHC (g/dL)	MCHC (µM)[c]	% Occupancy Red Cell Mass[d]
4-Week Mouse (PRC-16-014)									
Week 4	50	329000	19100	58.7	547489	1623	27.5	4259	38
	150	611000	49800	64.8	915849	2714	27.5	4266	64
	500	842000	84900	74.9	1096390	3250	27.3	4228	77
4-Week Rat (PRC-14-051-R)									
Week 4	15	170000	5090	52.5	319504	947	32.7	5073	19
	50	440000	14300	53.6	809258	2399	32.8	5089	47
	250	1055000	43900	61.3	1694676	5023	33.4	5182	97
	1000	986500	62450	64.1	1505151	4461	31.7	4918	91
13-Week Rat (PRC-15-019-R)									
Week 13	15	284500	5930	51.3	548951	1627	32.6	5058	32
	100/50	615500	18700	54.7	1109742	3289	32.7	5065	65
	700/250	743500	56050	62.3	1160387	3439	32.5	5042	68
26-Week Rat (PRC-16-008)									
Week 26	15	302000	6850	54.2	551407	1634	29.9	4639	35
	50	621000	22600	56.3	1086422	3220	31.1	4825	67
	250	1040000	56200	63.4	1609160	4769	31.7	4918	97

Abbreviations: Hb, hemoglobin; Hct, hematocrit; MCHC, mean corpuscular hemoglobin concentration; MAA, Marketing Authorisation Application; RBC, red blood cell.

[a] Voxelotor concentration in RBCs based on whole blood concentration, corrected for plasma concentration and hematocrit as described in Equation 4 from Section 2.6.2.2.1.11 of the MAA.

[b] Conversion of concentration in RBC from ng/ml to µM based on molecular weight of voxelotor (337.4 g/mol).

[c] Conversion of MCHC from g/dL to µM based on molecular weight of Hb of 64458 g/mol.

[d] Occupancy (%) calculated by dividing concentration of voxelotor in the red cells (µM) by the concentration of hemoglobin in red cells (MCHC) expressed as µM and converting quotient to %.

2.5.4.3. Genotoxicity

Table 12 Overview of pivotal repeat-dose toxicity studies with voxelotor

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative /equivocal
Gene mutations in bacteria, PRC—14-060-R, GLP	*S. typhimurium* TA98, TA100, TA1535 and TA1537 *E. coli* WP2 *uvr*A	15, 50, 150, 500, 1500 and 5000 µg/plate, +/- S9 (Arochlor-induced rats)	Negative
Combined *in vivo* micronucleus and Comet assay, PRC-14-059-R, GLP	Rat, Sprague-Dawley, 5/sex/dose (controls, positive controls, low and mid-dose), 8/sex/dose (high-dose group)	0, 500, 1000 and 2000 mg/kg/day, 3 consecutive days	Negative

In vitro bacterial reverse mutation assays and *in vivo* evaluations (micronucleus and comet assays) from rats dosed up to 2000 mg/kg/day did not demonstrate evidence of mutagenicity or clastogenicity (studies PRC-14-060-R and PRC-14-059-R). Therefore, there is a low risk of voxelotor being genotoxic in man.

2.5.4.4. Carcinogenicity

Carcinogenicity of voxelotor was studied in the 2-year study with rats study (PRC-16-009) and the 26-week study with transgenic mice (study PRC-17-006). In rats, increased incidence of hepatocellular adenoma and adrenal pheochromocytoma was seen in high-dose females (100 mg/kg/day). Voxelotor was demonstrated to induce liver enzymes in repeated dose toxicity studies, leading to hepatocellular hypertrophy and increased liver weight in subchronic studies. Induction of CYP450 enzymes is a well-known non-genotoxic mode of action for rodent hepatocarcinogenesis, resulting in the CAR nuclear receptor activation and subsequent increased hepatocellular proliferation; however, the latter response is not observed in humans. Therefore, the observed increased incidence of hepatocellular adenomas is not considered to represent carcinogenic risk for humans.

Benign pheochromocytoma is a commonly occurring tumour in rats and up to date there are no indications that the substances inducing pheochromocytomas in animal experiments also induce corresponding tumours in humans. Therefore, the increased incidence of pheochromocytomas in high-dose females observed in the rat study is also not considered to represent carcinogenic risk to humans. No increased tumour incidence was seen in the 26-week study with transgenic mice administered voxelotor up to the dose level of 500 mg/kg/day.

The applicant has provided a justification that an increased incidence and severity oval cell hyperplasia seen in female rats administered ≥ 30 mg/kg/day is a rare spontaneous lesion which is possibly related to the CYP induction. In the literature it has been demonstrated that dose-related increases in hepatocellular adenomas are a common finding in rats administered compounds that cause induction of CYP enzyme activity (Maronpot, 2010; Hall, 2012) and that rodent liver is more sensitive in response to CAR/PXR/PPAR activation than human liver.

The sciatic nerve mineralisation and axonal degeneration seen in rats was considered to be an exacerbated background change which occurred at incidences comparable with historical control data. Thus this effect was not considered adverse.

2.5.4.5. Reproductive and developmental toxicity

Reproductive and developmental toxicity of voxelotor was studied in the fertility and early embryonic development (FEED) study in rats, embryo-foetal developmental (EFD) toxicity studies in rats and rabbits, pre- and postnatal developmental toxicity study in rats and a dose-range finding study in juvenile rats. In the FEED study, statistically significantly reduced sperm motility, reduced percentage of normal sperm and the increased percentage of abnormal sperm in cauda epididymis, increased testicular and prostate weight and decreased seminal vesicles weight were observed in the high-dose animals (250 mg/kg/day). The reproductive function was not affected. In the absence of testicular changes in the available long-term studies and the adverse effects on the male fertility these findings are considered non-adverse. Voxelotor did not have an effect on the embryo-foetal development in either rats or rabbits at dose levels causing maternal toxicity.

In the pre- and post-natal developmental toxicity study reduced pup viability index and reduced F1 generation body weight (in males until post-pairing day 55, in females until maturation day 7) was seen at the dose level of 250 mg/kg/day. The applicant hypothesised that decreased pup survival (PND 0-4) and persisting effects on body weight noted in rat pups at this dose level were related to maternal toxicity. However, voxelotor is also readily excreted in milk of lactating rats. Milk exposure was up to 0.4-fold plasma exposure of the dams, leading, subsequently, to plasma exposure in the pups.

Mating of F1 animals from the treated F0 dams resulted in slightly (not statistically significantly) decreased male and female fertility indices, with an apparent dose-response trend (M: 86, 83, 74 and 71%, F: 95, 91, 83 and 82% in controls, low-, mid- and high-dose groups, respectively). In order to check whether male fertility was adversely affected by treatment, the F1 males from treated females were additionally mated with naïve females. In this case no adverse effects on fertility were noted. In the F1 dams from the treated females, statistically significantly reduced number of corpora lutea, number of implantation sites and number of live pups were observed compared to control animals. However, the observed values were still within the historical control ranges provided by the applicant and therefore appear to be caused by the unusually high (outside the historical control ranges) values in the concurrent controls.

In the dose-range finding juvenile toxicity study, decreased body weight gain and dehydration were observed in high-dose (250 mg/kg/day) pups. Furthermore, increased red cell mass and spleen weight in high-dose animals were observed, consistent with pharmacological action of voxelotor. As the observed effects in juvenile animals were consistent with the effects seen in adult animals, no full study was conducted.

2.5.4.6. Toxicokinetic data

2.5.4.7. Local tolerance

Local tolerance of voxelotor was evaluated in two *in vitro* eye irritation assays and an *in vivo* skin irritation study. Based on the results of the study, voxelotor was not irritating to either skin or eyes. However, these studies are considered irrelevant for the envisaged administration route (oral). In the conducted repeated dose toxicity studies with rats, dogs and monkeys voxelotor caused gastrointestinal tract irritation. This effect is considered clinically relevant.

2.5.4.8. Other toxicity studies

Phototoxicity of voxelotor was evaluated in an *in vitro* and an *in vivo* assays. While positive results were obtained *in vitro*, *in vivo* voxelotor gave no indication of phototoxicity.

No ***dependence studies*** have been conducted; however, the secondary pharmacology studies provide evidence of inhibition of DOPA and GABA receptors by voxelotor *in vitro*. However, the voxelotor exposures in plasma were factor 90- to 180-fold lower than the IC50 values derived in the DOPA and GABA receptor assays *in vitro*. Furthermore, no evidence of CNS toxicity was seen in the available safety pharmacology study with rats and in the overall repeated dose toxicity studies. Thus voxelotor is not expected to induce dependence based on available data.

With regard to **impurities** the specified impurity GBT441 has been qualified through toxicological studies according to ICH Q3A(R2). The applicant has provided an adequate Ames test with GBT441 which was negative.

2.5.5. Ecotoxicity/environmental risk assessment

In the ERA of the applicant, the Fpen was refined based on the prevalence of sickle cell disease (1.5 per 10,000), which gives an Fpen of 0.00015 (resulting in a refined PECsw of 0.1125 µg/L. However, EMA's public summary on opinion on orphan designation EU/3/16/1769 for voxelotor (as adopted by the Committee for Orphan Medicinal Product (COMP) provides a different prevalence number: 3.2 in 10,000, which gives a new Fpen of 0.00032. The Environmental Risk Assessment (Report VY23FR) has been adapted to reflect this recalculated value. There is no impact on the safety assessment based on this 2-fold increase in the Fpen value, given that both values generate the Phase I estimate of the PECsw > 0.01 µg/L. The applicant was also requested to append study report FT36BR (Griffiths, 2019) with the measured pH values during the study, which was needed to finalise the risk assessment for the surface water compartment. The amended report has been evaluated and is considered acceptable.

Voxelotor is not Persistent, bioaccumulative and toxic substance (PBT), nor very Persistent very Bioaccumulative (vPvB).

Table 13 Summary of main study results

Substance (INN/Invented Name): Voxelotor			
CAS-number (if available): 1446321-46-5			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD 107	3.16	Potential PBT: N
PBT assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	3.16	
	BCF_{KL}	161	not B
Persistence	ready biodegradability	Not readily biodegradable	

	DegT50	$DT_{50, water(l)}$ = 14 d/13 d $DT_{50, sediment(l)}$ = >1000 d (both systems; l/l) $DT_{50, system(l)}$ = 16 d/17 d (l/l)	l=lake DT_{50} values corrected to 12°C. Conclusion: vP
Toxicity	NOEC algae NOEC crustacea NOEC fish	80 µg/L 210 µg/L 40 µg/L	not T
	CMR	Not carcinogenic, mutagenic or reprotoxic	not T
PBT statement:	Voxelotor is considered not PBT, nor vPvB		
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
$PEC_{surface\ water}$, refined	0.240	µg/L	> 0.01 µg/L threshold: Y
Other concerns (e.g. chemical class)			N
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc\ sludge}$ = 1330, 1190 L/kg $K_{oc\ soil}$ = 433, 1170, 386 L/kg	
Ready Biodegradability Test	OECD 301B	not readily biodegradable	
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water(l)}$ = 6.1 d/5.8 d $DT_{50, sediment(l)}$ = >1000d (both systems; l/l) $DT_{50, system(l)}$ = 6.8 d/7.1 d (l/l) % shifting to sediment = 34 - 44% Transformation products > 10%: GBT001226 = 55.3 %, $DT_{50, sediment}$ (12°C) = 120 d/250.5 d GBT000921 = 37.7 %, $DT_{50, sediment}$ (12°C) = 2356 d/ -	l=lake Reported DT_{50} values at 21 °C. Significant shifting to sediment (and NER) observed. TPs seem to be very persistent GBT000921 continuously increasing in sediment of system 2

Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*R. subcapitata*	OECD 201	NOEC	80	µg/L	Growth rate
Daphnia magna. Reproduction Test	OECD 211	NOEC	210	µg/L	Reproduction
Fish, Early Life Stage Toxicity Test/*P. promelas*	OECD 210	NOEC	40	µg/L	Body length

Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥32000	µg/L	respiration
Phase IIb Studies					
Bioaccumulation/*O. mykiss*	OECD 305	BCF_{kL}	161	L/kg	%lipids: 3.51
Sediment dwelling organism/ *C. riparius*	OECD 218	NOEC	≥677 ≥3077	mg/kg_{dw} mg/kg_{dw}	2.2% o.c. normalised to 10% o.c.

2.5.6. Discussion on non-clinical aspects

Assessment of pharmacology data submitted and further analysis requested allowed to conclude the following:

- Affinity and dissociation constants for voxelotor to Hb for human HbS, HbA and HbF and for the animal equivalents and it is not expected that the voxelotor-Hb binding is different or not-reversible in animals.
- Partitioning / binding data for voxelotor to whole blood, plasma, RBC, Hb and HSA as well as information on the free voxelotor fraction in blood and data on accumulation in one of those fractions for human AA, AS, SC and SS subjects show that plasma ratio for healthy AA subjects is lower than for SS subjects, mainly due to the slightly higher Hb levels in plasma in SS subjects.
- The effect of voxelotor on the curve blood with low versus high level of HbF (~2 and ~30 %) looks different. The meaning of this difference is not clear. In the clinical part the relation between efficacy and percentage of HbF in blood is also discussed.
- Regarding the PK/PD model, from the pool of blood included in the model development and model testing, the range of % haemoglobin (Hb)F included was 0% to 45%, with a median of 12% HbF. This means that HbF was at forehand not considered a factor to be of influence on the level of voxelotor Hb occupancy. It is questioned whether this is a fair decision however in the clinical part the relation between HbF percentage and efficacy from treatment with voxelotor is further discussed. In the model, a distinction was made for AA or SS blood by means of use of different equations for both types of blood. Apparently the MCHC values are even a bit underestimated, and consequently the Hb occupancies are slightly overestimated.

Overall, the primary pharmacodynamic studies provided adequate evidence that voxelotor binds to and stabilises oxygen loaded Hb, but also affects the dissociation of O2 from voxelotor bound Hb. Voxelotor preferentially partition to the RBC, which however differs between healthy and diseased blood / RBCs, which may be caused by a higher plasma Hb level in blood from SCD subjects. Voxelotor improves the sickling of blood, the blood viscosity and the deformability of RBCs, which is most effective at Hb-occupancies higher than the intended 30% in *in vitro* experiments due to experimental limitations. The effective dose *in vivo* is based on clinical data. From animal experiments a target level of voxelotor Hb occupancy ≥11% was sufficient to increase Hb O2 affinity and reduce *ex vivo* sickling, however, prolongation of RBC half-life and decrease in reticulocyte count were only observed at higher Hb occupancy of ≥32 %. First signs of compensatory erythropoiesis is observed in *Cynomolgus* monkey at voxelotor-Hb occupancy of 35%.

Further signs of hypoxia and the immunosuppressive action of voxelotor were observed in animals in which a voxelotor-Hb occupancy of ~50% was reached. In animals there seems to be only a narrow window for

voxelotor-Hb occupancy that appears safe and effective. It is also not very clear whether increase in reticulocytes (due to compensatory erythropoiesis and/or haematopoiesis) is taken into account in the calculation of the voxelotor-Hb occupancies. It is considered that the support for an effective and safe dose should be based on clinical data and that accompanying voxelotor-Hb occupancies are controlled in patients. This is considered important as the increase O2 affinity of voxelotor-Hb also compromises the O2 off-loading capacity. It can be considered that the body needs to find a new balance, involving the generation of new reticulocytes.

The results of the calculations of the Hb occupancy at different timepoints in the toxicological studies are further discussed in the toxicology section and can be accepted. It is considered that the support for an effective and safe dose in patients should be based on clinical data only. In that respect this issue is regarded solved from non-clinical of view.

From the pharmacokinetic point of view, the preclinical species rat, dog and monkey can be used for non-clinical safety assessment. It should be considered, however, that due to the strong binding to Hb the whole blood PK behaviour is disturbed, and plasma PK seems more appropriate to assess peripheral voxelotor effects.

Voxelotor was found to be excreted in the milk and exposure in milk was about 26% – 41% of the maternal plasma exposure. On lactation day 10, plasma exposure of voxelotor was found in the pups, which amounted to ~3.6% of maternal plasma voxelotor concentration. In conclusion, voxelotor is readily excreted in the milk leading, subsequently, to plasma exposure in the pups. This has been reflected in sections 4.6 and 5.3 of the SmPC .

Overall, the toxicology programme revealed that the exaggerated pharmacological action of voxelotor leads to lower offloading of oxygen to tissues and compensatory erythropoiesis in the bone marrow and spleen in different species (rat, mouse, monkeys). The applicant stated that this occurs only above the Hb occupancy by voxelotor above 50% and will not occur in patients for whom 30% Hb occupancy by voxelotor is envisaged. Based on the additionally provided calculations of the Hb occupancy at the different timepoints in the preclinical studies, it can be agreed that the Hb occupancy appears to be relatively stable after reaching the steady state, which occurs after 13 weeks of dosing in rats and monkeys, and that no appreciable degree of compensatory erythropoiesis occurs in case Hb occupancy < 50%. However, as the safety margins between the preclinical studies and the anticipated clinical exposure are very low, the applicant has agreed to include compensatory erythropoiesis as an identified risk to be evaluated in the PSUR.

Voxelotor caused gastro-intestinal tract effects in rats and monkeys, which were particularly severe in monkeys. These effects are also considered clinically relevant. However, as in the pivotal clinical studies the majority of adverse events of diarrhoea was Grade 1 or Grade 2, self-limiting, and manageable without the need for dose interruption, dose reduction, or treatment discontinuation. Therefore, diarrhoea an identified risk is not considered important for inclusion in the list of safety concerns in the RMP; nevertheless, the applicant will monitor these findings in the PSUR.

A number of adverse effects were observed in the test animals at dose levels comparable or even lower than the anticipated clinical exposure. These include in particular overall low tolerability of voxelotor in monkeys (mortality at EM ~0.9 based on plasma C_{max}); the immunosuppressive action of voxelotor, manifested as significantly reduced IgG (rats, monkeys) and IgM (monkeys) titres, delayed antibody response (monkeys) and changes in the relative lymphocyte distribution (rats) at EM of ~0.5 in monkeys and ~4.5 in rats (based on plasma C_{max}); prolonged QT and QTc intervals in monkeys at EM of ~2.5 (based on plasma C_{max}) and gastro-intestinal tract lesions in rats and monkeys (EM ~ 1.5 in monkeys based on plasma C_{max}). While poor tolerability

in monkeys was explained by the applicant by adverse gastro-intestinal tract effects, it is considered more likely that it was caused by opportunistic infections due to immunosuppressive action of voxelotor. In view of these findings the applicant has agreed to include the immunosuppression as an identified risk in Part II module SII of the Risk Management Plan. The prolonged QT and QTc intervals could have been related to the poor condition of the animals, as they were not seen in the 39-week study at comparable (slightly lower) exposure levels. Furthermore, based on the calculated free voxelotor concentrations in plasma and IC50 values for the hERG channel inhibition *in vitro* the "true" QT interval prolongation due to hERG channel inhibition by voxelotor is considered not likely.

Implications of the assessment of non-clinical data for the Safety Specification of the Risk Management Plan (RMP): The following non-clinical safety observations were considered relevant for the clinical safety to the extent that it will be included by the applicant in the Part II module SII of the Risk Management Plan:

1) Compensatory erythropoiesis observed in rats, monkeys and mice (early stages observed at EM ~0.5 of the anticipated clinical exposure in rats and ~0.6 in monkeys based on plasma C_{max}). In addition, the applicant will monitor these findings in the PSUR.
2) The immunosuppressive action of voxelotor, manifested as increased mortality due to opportunistic infections in monkeys, significantly reduced IgG (rats, monkeys) and IgM (monkeys) titres, delayed antibody response (monkeys) and changes in the relative lymphocyte distribution (rats) at EM of ~0.5 in monkeys and ~4.5 in rats (based on plasma C_{max}).

Environmental Risk Assessment: The applicant concludes that voxelotor is unlikely to represent a risk to the aquatic or terrestrial environments and is not bio-accumulative but is very persistent in sediment which is reflected in Sections 5.3 and 6.6 of the SmPC.

2.5.7. Conclusion on the non-clinical aspects

From a non-clinical point of view, although uncertainties remain about the degree to which Hb occupancy can be controlled and its correlation with the induction of compensatory erythropoiesis, these issues are not further pursued in view of the obtained clinical safety data in healthy subjects and SCD patients. The applicant has agreed to include the compensatory erythropoiesis, immunosuppression and adverse gastro-intestinal tract effects action as important non-clinical safety findings in Part II module SII and as identified risks in Part II module SVII of the Risk Management Plan) which provides sufficient reassurance.

Therefore, from a non-clinical point of view, a voxelotor is considered approvable.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the EU were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- ## Tabular overview of clinical studies

Table 14 Tabular listing of clinical studies

Study No./Phase **No. of Sites/ Location** **Study Start/End Da tes**	**Study Design & Objectives (Primary Endpoint)**	**Study Population**	**Treatment & Duration**	**No. of Subjects Enrolled/Completed** **Sex M/F** **Mean Age (range)**
GBT440-001 Phase 1 2 sites/ United Kingdom 09-Dec-14 to 27-Mar-17	Randomised, PBO-controlled, double-blind, single & multiple ascending dose Safety, tolerability, PK, PD, & efficacy (AEs, clinical laboratory evaluations, vital signs, ECGs, PEs, exercise testing)	Healthy subjects	Part A (Cohorts 1–5): Voxelotor 100, 400, 1000, 2000, or 2800 mg or PBO Single dose	Part A (Cohorts 1–5): 40/40 (30/30 voxelotor; 10/10 PBO) 39 M/1 F 34 y (19–51 y)
			Part B (Cohorts 8–10): Voxelotor 300, 600, or 900 mg or PBO QD 15 days	Part B (Cohorts 8–10): 24/21 (18/16 voxelotor; 6/5 PBO) 24 M/0 F 36 y (22–54 y)
		Subjects with SCD	Part A (Cohort 7): Voxelotor 1000 mg or PBO (Cohort 7) Single dose	Part A (Cohort 7): 8/7 (6/6 voxelotor; 2/1 PBO) 4 M/4 F 31 y (20–47 y)
			Part B (Cohorts 11, 12, & 14): Voxelotor 500 or 700 mg or PBO QD Voxelotor 1000 mg (500 mg BID) or PBO 28 days	Part B (Cohorts 11, 12, & 14): 38/37 (28/27 voxelotor; 10/10 PBO) 20 M/18 F 33 y (20–56 y)

Study No./Phase **No. of Sites/ Location** **Study Start/End Da tes**	**Study Design & Objectives (Primary Endpoint)**	**Study Population**	**Treatment & Duration**	**No. of Subjects Enrolled/Completed** **Sex M/F** **Mean Age (range)**
			Part B (Cohort 15): Voxelotor 600 mg or PBO QD HbSC genotype (Cohort 15) 28 days	Part B (Cohort 15): 7/7 (6/6 voxelotor; 1/1 PBO) 1 M/6 F 38 y (21–46 y)
			Part C (Cohorts 16 & 17): Voxelotor 700 or 900 mg or PBO QD 90 days (700 mg) 90-118 days (900 mg)	Part C (Cohorts 16 & 17): 16/16 (12/12 voxelotor; 4/4 PBO) 10 M/6 F 36 y (18–53 y)
GBT440-024 **Phase 2a** (OLE)[e] 1 sites/ United Kingdom 03-Aug-16 to 02-Jun-17	Open-label, multiple-dose (for subjects in Study GBT440-00 1) Long-term safety, tolerability, & efficacy (AEs, clinical laboratory tests, vital signs, ECGs, PEs, exercise testing)	Adult subjects with SCD	Voxelotor 900 mg QD 6 months (including Study GBT440-001)	5/5 (1/1 from Part B Cohort 15 (HbSC); 4/4 from Part C Cohort 17) 4 M/1 F NA (21–42 y)
GBT440-031 Phase 3 58 sites/ International 13-Dec-16 to 08-Oct-19	Randomised, PBO-controlled, double-blind Efficacy, safety, & PK (Hb response at Week 24)	Adults & paediatric subjects 12 years & older with SCD	Voxelotor 900 or 1500 mg or PBO QD Up to 72 weeks	Groups 1 & 2: 274 enrolled 115 M/159 F 28 y (12–64 y): 46 (12 to<18y), 228 (>18y) Group 3: No subjects enrolled
GBT440-034 Phase 3 (OLE) 58 sites/ International	Open label extension study for subjects in Study GBT440-031	Adults & paediatric subjects 12 years &	Voxelotor 1500 mg QD	178 enrolled 78 M/100 F 28.7 y (13–61 y): 28 (12 to<18y),

Study No./Phase **No. of Sites/ Location** **Study Start/End Dates**	**Study Design & Objectives (Primary Endpoint)**	**Study Population**	**Treatment & Duration**	**No. of Subjects Enrolled/Completed** **Sex M/F** **Mean Age (range)**
Ongoing Data cutoff: 31 December 2019	Long-term safety and treatment effect of voxelotor (SCD related complications and heamolitic anaemia parameters)	older with SCD		150 (>18y)
GBT440-007/Phase 2a Part A & Part B: 11 sites/ United States & Lebanon Part A & Part B: 21-Jul-16 to 04-Jan-19 Part C: 01-Oct-18 to Ongoing Part D: No subjects enrolled as of 03-Nov-2020	Open-label, single- & multiple-dose PK, safety, tolerability, & efficacy (Part A: Voxelotor PK) (Part B: Change from baseline to Wk 24 in Hb) (Part C: Change from baseline to Wk 48 in cerebral blood flow as measured by TCD ultrasonography)	Part A: Paediatric subjects with SCD aged 12 to < 18 y & 6-11 y	Part A: 600 mg Single dose	Part A: Cohort 1 (12 to < 18 y): 7/7 Cohort 2 (6 to < 12 y): 6/6 6 M/7 F 14.0 y (6–16 y)
		Part B: Paediatric subjects with SCD aged 12 to < 18 y	Part B: 900 or 1500 mg QD 24 weeks	Part B: 25/22 (900 mg) & 15/12 (1500 mg) 14 M/11 F (900 mg) 5 M/10 F (1500 mg) 14.0 y (12–17 y) (900 mg) 14.0 y (12–17 y) (1500 mg)
		Part C: Paediatric subjects with SCD aged 4 to < 18 y	Part C: Voxelotor 1500 mg QD (subjects aged 12 to < 18 y) Weight-based dosing (subjects aged <12 y) 48 weeks	Part C: 56[b]

Study No./Phase No. of Sites/ Location Study Start/End Da tes	Study Design & Objectives (Primary Endpoint)	Study Population	Treatment & Duration	No. of Subjects Enrolled/Completed Sex M/F Mean Age (range)
		Part D: Paediatric subjects with SCD aged 6 months to < 4 y	Part D: Weight-based dosing 48 weeks	Part D: 30 subjects planned 0 patients enrolled[c]

Abbreviations: AE, adverse event; BID, twice daily; ECG, electrocardiogram; F, female; Hb, haemoglobin; HbSC, haemoglobin sickle cell disease with 1 HbS sickle cell gene and 1 haemoglobin C (HbC) gene; LDH, lactate dehydrogenase; M, male; NA, not available; ND, not determined; OLE, open-label extension; PBO, placebo; PD, pharmacodynamic; PE, physical examination; PK, pharmacokinetics; QD, once daily; SCD, sickle cell disease; TBD, to be determined; TCD, transcranial Doppler; Wk, week.

[a] Efficacy was not assessed.

[b] Enrollment as of 30 September 2020.

[c] Enrollment as of 03 November 2020.

[d] Efficacy data not available.

[e] Extension study for subjects in Study GBT440-001.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetics of voxelotor have been investigated in 18 clinical studies (16 studies in healthy volunteers and 3 studies in patients) in whole blood, plasma and red blood cells. Only the PK of voxelotor in whole blood and plasma is reported. The PK of voxelotor in red blood cells is a calculated value based on the concentration in whole blood and plasma and the haematocrit value. Therefore, the PK of voxelotor in red blood cells is an indirect derived value.

Table 15 Clinical PK studies with voxelotor

study	population	dose and objective
GBT440-001	Healthy volunteers (N=64)	Single dose of 100, 400, 1000, 2000 and 2800 mg Repeated dose of 300, 600, 900 once daily To assess the PK in plasma, whole blood and red blood cells
GBT440-002	Healthy volunteers (N=7)	Repeated dose with 2000 mg on day 1 followed by 400 mg for 4 days Mass balance study to assess the absorption, metabolism and excretion

study	population	dose and objective
GBT440-003	Healthy volunteers (N=24)	Repeated dose with a loading dose of 900 mg for 2 days followed by 600 mg for 5 days Cocktail DDI study (voxelotor as perpetrator) with caffeine (CYP1A2), warfarin (CYP2C9), omeprazole (CYP2C19), and midazolam (CYP3A) in plasma and whole blood
GBT440-004	Healthy volunteers (N=26)	Single dose of 1×300 mg capsule or 3×100 mg capsule Relative bioavailability in whole blood
GBT440-005	Healthy volunteers (N=16)	Single dose of 900 mg Food effect study in plasma and whole blood
GBT440-008	Healthy volunteers (N=18)	Repeated dose with a loading dose of 900 mg for 2 days followed by 600 mg for 2 days DDI study (voxelotor as perpetrator) with rosiglitazone (CYP2C8) in plasma and whole blood
GBT440-017	Healthy volunteers (N=24)	Repeated dose with a loading dose of 900 mg for 2 days followed by 600 mg for 3 days DDI study (voxelotor as perpetrator) with metoprolol (CYP2D6) in plasma and whole blood
GBT440-018	Healthy volunteers (N=26)	Single dose of 300 mg capsule or 300 mg tablet Relative bioavailability in whole blood
GBT440-019	Healthy volunteers (N=16)	Single dose of 900 mg DDI study (voxelotor as victim) with omeprazole (proton pump inhibitor) in whole blood
GBT440-0110	Healthy volunteers (N=16)	Single dose of 900 mg Renal impairment study (8 subjects with renal impairment) in plasma and whole blood
GBT440-0112	Healthy volunteers (N=16)	Single dose of 600 mg (hepatic impaired subjects) or 1500 mg (normal hepatic function) Hepatic impairment study (21 subjects with hepatic impairment) in plasma and whole blood
GBT440-0113	Healthy volunteers (N=20)	Single dose of 900 mg dispersible tablet or 3×300 mg tablet Relative bioavailability in whole blood
GBT440-0114	Healthy volunteers (N=20)	Single dose of 900 mg tablet or 3×300 mg tablet Relative bioavailability in whole blood
GBT440-0115	Healthy volunteers (N=54)	Repeated dose of 1200, 1500, or 1800 mg once daily for 14 days TQT study with PK in plasma and whole blood
GBT440-0116	Healthy volunteers (N=22)	Repeated dose with 1500 mg for 5 days DDI study (voxelotor as perpetrator) with digoxin (P-glycoprotein) in plasma and whole blood
GBT440-0118	Healthy volunteers (N=25)	Single dose of 1500 mg DDI study (voxelotor as victim) with itraconazole (strong CYP3A4 inhibitor) in plasma and whole blood
GBT440-001	Patients with SCD (N=70)	Single dose of 1000 mg

study	population	dose and objective
		Repeated dose of 500, 600 and 700 mg once daily for 28 days, 700 and 900 mg once daily for 90 days and 500 mg twice daily for 28 days. To assess the PK in adults in plasma, blood and red blood cells
GBT440-007	Patients with SCD (N=53)	Single dose of 600 mg to subjects of 6-18 years Repeated dose of 900 or 1500 mg for 24 weeks to subjects of 12-18 years To assess the PK in plasma and whole blood
GBT440-031	Patients with SCD (N=274)	Repeated dose of 900 or 1500 mg for 72 weeks To assess the PK in patients 12 years and older in plasma and whole blood

Single dose studies were performed over a dose range of 100 to 2800 mg voxelotor. Multiple dose studies were performed over a dose range of 600 to 1800 mg voxelotor. In addition, several *in vitro* studies were performed to investigate the permeability, metabolism, transporter substrate potential and the inhibition and induction potential towards CYPs, UGTs, SULTs and transporters.

Physical-chemical properties

Voxelotor has a molecular weight of 337.38 g/mol. Voxelotor is a weak base and has better solubility in low pH buffers than in higher pH buffers. Voxelotor does not have any stereocentres.

Analytical methods

Voxelotor was analysed in K_2-EDTA whole blood or plasma using LC-MS/MS. The analytical methods used to determine voxelotor in whole blood and plasma appear to be sufficiently validated. The LLOQ ranged from 10 to 120 ng/mL in whole blood and from 0.10 to 6.0 ng/mL in plasma between the different analytical methods.

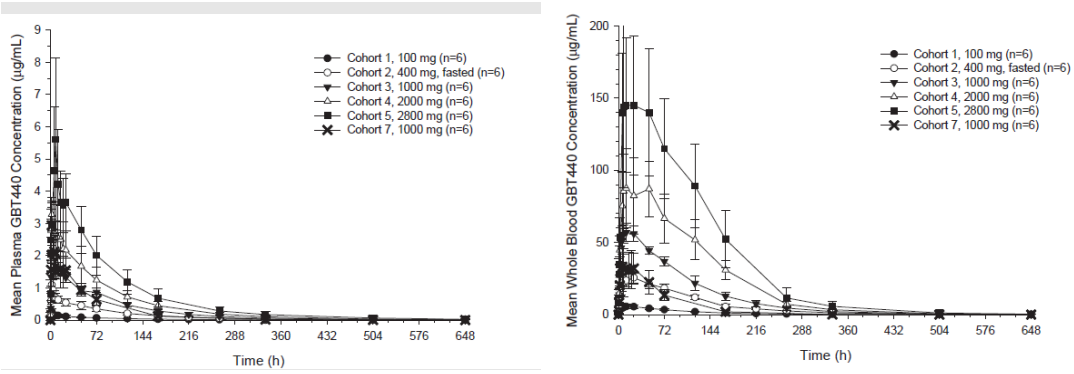
Population PK (PopPK) modelling: A PopPK model was developed to describe the PK of voxelotor in plasma and whole blood in patients with sickle cell disease. The joint model structure is quite empirical with an effect compartment describing the whole blood and plasma concentrations. A limitation to this approach is that differences between plasma and whole blood pharmacokinetics can only be detected in the blood to plasma ratio and the rate constant representing the delay between plasma and whole blood pharmacokinetics. Blood volume was included in the model as covariate, which is derived using body weight, height and gender. The final model adequately describes both plasma and whole blood pharmacokinetics reasonably well in patients aged 12 years and older. Parameter estimates are reasonable and no clear structural deviations can be observed in the goodness-of-fit plots.

Physiologically based pharmacokinetic (PBPK) modelling: The PBPK model was developed to investigate the PK in paediatric patients with sickle cell disease and to extrapolate the DDI results in healthy volunteers to patients with sickle cell disease. The final PBPK model was able to predict the PK in plasma and whole blood within 1.3-fold of observed exposures for patients aged 12 years and older.

Absorption

The PK of voxelotor in plasma and whole blood were investigated in 9 single dose (100-2800 mg voxelotor) clinical studies and 3 repeated dose (300-1800 mg voxelotor once daily) clinical studies in healthy subjects

under fasted conditions. Following a single dose, voxelotor is rapidly absorbed in plasma in healthy subjects and slower in whole blood. Median plasma t_{max} was around 2 hours (2-8 h) in plasma and ~18 hours (10-24 h) in whole blood. The t_{max} in whole blood decreased to ~8 hours following repeated dosing. Voxelotor is dose-proportional over the 100 to 2800 mg dose range in both plasma and whole blood. Steady-state is reached around 12 days in healthy subjects. In plasma, the observed accumulation ratio ranged from 2.1-fold to 5.8-fold for the C_{max} and from 2.8 fold to 6.7-fold for the AUC_{0-24} following repeated once daily dosing. In whole blood, the accumulation ratio ranged from 2.9-fold to 5.6 fold for the C_{max} and from 2.8-fold to 6.0-fold for the AUC_{0-24} following repeated once daily dosing. No time-dependency was observed; the elimination half-life observed after a single dose was comparable to the elimination half-life after repeated dosing in healthy volunteers.



A ***B***

Figure 2 Mean voxelotor plasma concentration - time curve (A) or mean voxelotor whole blood concentration - time curve (B) after a single dose (study GBT440-001)

No information was provided on the intra-individual variability in healthy volunteers. In plasma, the inter-individual variability was ~30% for the C_{max} and ~25% for the AUC. In whole blood, the inter-individual variability was ~25% for the C_{max} and ~20% for the AUC.

The absolute oral bioavailability was not investigated. The absorption of voxelotor following oral administration is ~35% (24.8-41.4%) based on the elimination of radioactivity in urine, but up to ~60% if it is assumed that only the first 48-hour radioactivity in faeces is unabsorbed voxelotor. The effect of first pass metabolism on the systemic exposure is unknown. Based on the mass balance study, two hours after dosing (t_{max}) voxelotor accounted for 35% of the radioactivity in plasma and 65% was metabolite. These data indicate that extensive first pass metabolism may occur following absorption after oral administration. Thus, the oral bioavailability of voxelotor is most likely moderate to low (~12% to 30%).

Concomitant administration with a moderate-fat breakfast had a small effect on voxelotor plasma PK (C_{max} 20% higher and AUC_{inf} 32% higher) and no effect on the whole blood PK. Concomitant administration with a high-fat meal had a more pronounced effect on the voxelotor plasma PK (C_{max} 95% higher and AUC_{inf} 43% higher) and whole blood PK (C_{max} 45% higher and AUC_{inf} 42% higher). Overall, food resulted in higher exposure to voxelotor compared to fasted conditions, with increasing exposure with higher fat content.

Different formulations were used during development. The different clinical formulation appear not to lead to significantly different exposure based on the PK data from the 3 bioequivalence studies.

Distribution

The *in vitro* plasma protein binding of voxelotor is >99%.

The *in vivo* blood-to-plasma ratio of voxelotor was ~33:1 (ranging from 15:1 to 45:1) after a single dose and ~23:1 (ranging from 15:1 to 38:1) after repeated dosing. At the clinical dose of 1500 mg following repeated dosing, the blood-to-plasma ratio was ~19:1.

Voxelotor is able to permeate Caco-2 cells via passive diffusion and is a high permeable compound.

The apparent volume of distribution (V/F) was ~800 L in healthy volunteers based on plasma data. If the oral bioavailability ranges from ~12 to 30%, the volume of distribution is 96 L to 240 L, indicating extensive distribution.

Elimination

In vivo human studies indicate that voxelotor is extensively metabolised through Phase I, Phase II, and combinations of Phase I and II metabolism. The major human metabolites are M218 (O-dealkylation-sulfation; 10-17%), M515 (reduction-glucuronidation), and M513 (glucuronidation) (combined 7.9-17%). Voxelotor is oxidised to many minor metabolites and directly glucuronidated to M513. The major human metabolite M218 is formed by oxidation and subsequent sulphate conjugation. The second most abundant plasma metabolite, M515, is formed by reduction and subsequent glucuronidation. The major metabolite M218 was not observed in one of the excreta (most likely the sulphate is deconjugated in faeces by the microflora or in urine due to the pH). The glucuronide metabolites M513 and 515 have been observed in urine and not in faeces, this may be because the glucuronide metabolites are only excreted via urine or are deconjugated by the intestinal microflora when excreted via faeces.

In vitro studies indicate that voxelotor is metabolised by multiple CYP, UGT and SULT isozymes. Voxelotor is metabolised by CYP3A4, 2C19, 1A1, 2B6, 3A5 and 2C9. In addition, voxelotor is glucuronidated mainly by UGT1A1 and 1A9 and to a lower extent also by UGT1A3, 1A4, 1A6, 1A9, 2B7, and 2B15. Furthermore, SULT1B1 and 1C4 are the main SULT isozymes involved in the sulphate metabolite of voxelotor M218 and SULT1A1 and 1A3 are involved to a lower extent.

Transporters

In vitro experiments were performed to investigate if voxelotor was a substrate of P-glycoprotein, BCRP, OATP1A2 OATP1B1, OATP1B3 and BSEP. Voxelotor was not a substrate of these transporters at the tested concentrations (up to 30 µM for OATP1A1, OATP1B1, OATP1B3 and BSEP and up to 300 µM for P-glycoprotein and BCRP).

Excretion

In the mass balance study, voxelotor radioactivity is eliminated via urine (35%) and faeces (63%). Data from the first 48 hour following dosing indicates that up to 60% of the dose may be absorbed. Thus, around half of the absorbed radioactivity dose is eliminated via urine and half via faeces.

Voxelotor is slowly cleared from plasma and whole blood. The $t_{½}$ is 108 h in plasma and 77 h in whole blood.

The apparent clearance from plasma is ~5.5 L/h and from whole blood 0.16 L/h. If the oral bioavailability ranges from ~12 to 30%, the clearance is 0.66 L/h to 1.65 L/h for plasma and 0.019 L/h to 0.048 L/h for whole blood, indicating low clearance from the body.

PK in patients with sickle cell disease

Following repeated dosing with 1500 mg once daily to patients with sickle cell disease, the C_{max} is ~14 µg/mL (CV% = 25) in plasma and 180 µg/mL (CV% = 31) in whole blood. The AUC is 278 µg × h/mL (CV% = 29) in plasma and 3830 µg × h/mL (CV% = 34) in whole blood. The PK is similar in paediatric patients aged 12-17 years compared to adults. The population pharmacokinetic model estimates a half-life in plasma of ~39 h following a 1500 mg dose. The estimated apparent clearance is 6 L/h.

Voxelotor was administered under fasted conditions in study GBT440-001, but independent of food in studies GBT440-007 and GBT440-031. The overall impact of the food effect is considered limited in patients with sickle cell disease (based on the PopPK model).

The PK of voxelotor in subjects with sickle cell disease is different from that in healthy subjects. In plasma, the exposure after repeated dosing with 1500 mg voxelotor once daily is ~1.6-fold higher in healthy volunteers compared to patients with sickle cell disease. In whole blood, the exposure after repeated dosing with 1500 mg voxelotor once daily is ~2.0-fold higher of healthy volunteers compared to patients with sickle cell disease.

The PopPK estimates an intra-individual variability of 24% in plasma and of 17% in whole blood. The inter-individual variability was higher in patients with sickle cell disease compared to healthy volunteers, but this is most likely due to different sickle cell genotypes which appear to have an effect on the PK.

Furthermore, the blood-to-plasma ratio of voxelotor following repeated dosing was ~16.6:1 in patients with sickle cell disease which is slightly lower than in healthy volunteers (~19:1).

The accumulation ratio in patients with sickle cell disease was ~2.5-fold for the C_{max} and ~3-fold for the AUC in plasma following repeated dosing and ~3-fold for the C_{max} and AUC for whole blood. The accumulation following repeated dosing is less than in healthy volunteers. Steady-state is reached around 8 days in patients with sickle cell disease which is 4 days less than in healthy volunteers.

Dose proportionality and time dependencies

Special populations

The effect of renal function and hepatic function were investigated in dedicated clinical studies. In addition, the effect of haematocrit, renal function, gender, race, weight and age was investigated using the developed final PopPK model.

Haematocrit

Time-varying haematocrit concentration was a significant covariate in the population pharmacokinetic model that influenced the blood to plasma ratio.

Genetic polymorphisms

Voxelotor is metabolised by many CYP and UGT isozymes. It is therefore unlikely that genetic polymorphisms in one of these isozymes will significantly affect the pharmacokinetics of voxelotor.

Renal impairment

Renal function had minor effects on voxelotor exposures in plasma in healthy volunteers (a 20% higher exposure in subjects with severe renal impairment). Furthermore, a 17 to 35% higher exposure was observed in patients with sickle cell disease with baseline Cystatin C levels of 0.52-0.71 mg/mL). Overall, renal function had minor effects on voxelotor exposures in healthy volunteers and patients with sickle cell disease. No dose adjustment is needed in patients with impaired renal function.

Hepatic impairment

In plasma, the C_{max} was 1.2-fold higher in subjects with mild hepatic impairment, 1.5-fold higher in subjects with moderate hepatic impairment and 1.4-fold higher in subjects with severe hepatic impairment and the AUC_{inf} was 1.1-fold higher in subjects with mild hepatic impairment, 1.2-fold higher in subjects with moderate hepatic impairment and 1.9-fold higher in subjects with severe hepatic impairment. In whole blood, increase in exposure was similar to that in plasma. No dose adjustment is warranted in subjects with mild to moderate hepatic impairment, but it is recommended to reduce the daily dose of voxelotor to 1000 mg in subjects with severe hepatic impairment. The C_{max} values in patients with severe hepatic impairment dosed at 1000 mg once daily are expected to be similar to those in patients with normal hepatic function treated at the recommended dose of 1500 mg daily. The AUC is expected to be ~25% higher in subjects with severe hepatic impairment compared to those in patients with normal hepatic function treated at the recommended dose of 1500 mg daily. This is not considered to be of clinical relevance.

Race

Voxelotor PK is similar in white and black patients. In Arab or middle-eastern subjects, whole blood observed trough exposures were statistically higher than exposures in other subjects (31% higher than black subjects). The difference in exposure will not lead to any difference in clinical practice.

Gender

Gender was not a significant covariate in the final PopPK model, but blood volume (derived by bodyweight, height and gender) was a significant covariate. Therefore, gender was indirectly a significant covariate. The applicant estimated that female subjects had an approximately 10% higher exposure compared to male subjects. This difference is not considered to be clinically relevant.

Age

The effect of age on the pharmacokinetics of voxelotor was based on simulations with a 1500 mg once daily dose using the final PopPK model. Age was not a significant covariate in the PopPK model. However, blood volume was a significant covariate in the model, which was estimated using body weight, height and gender. The addition of blood volume to the PopPK model, on the parameter representing the volume of distribution of the central compartment, resulted in the loss of an age effect. Age and blood volume were found to be correlated. Therefore, potential age affects are accounted for using the addition of blood volume. The difference between adolescents and adults in blood volume did not lead to statistically significant increases in voxelotor exposure.

Weight

Body weight was not a significant covariate in the final PopPk model. However, blood volume was included in the model, which is derived using body weight, height and gender. Therefore, body weight is influencing the pharmacokinetics of voxelotor through the estimated blood volume covariate.

Pharmacokinetic interaction studies

Voxelotor as victim

In vitro data indicate that voxelotor is metabolised via multiple routes (CYP3A4, 2C19, 1A1, 2B6, 3A5 and 2C9; UGT1A1 and 1A9 and SULT1B1 and 1C4). A clinical DDI study with a strong CYP3A4 inhibitor (itraconazole) showed no effect on the PK of voxelotor, indicating that the other enzymes are able to take over if CYP3A4 is inhibited. PBPK modelling indicated that strong CYP3A inhibitors had no effect on the PK of voxelotor, confirming the clinical DDI study in healthy volunteers.

The effect of a strong inducer on the PK of voxelotor was not investigated.

In a clinical DDI study, the proton pump inhibitor omeprazole did not affect the PK of voxelotor indicating that an increase in gastric pH does not affect the absorption of voxelotor. Furthermore, the PopPK model indicated that hydroxycarbamide (hydroxyurea) did not have an effect on the PK of voxelotor.

Voxelotor as perpetrator

In vitro data indicate that voxelotor is an inhibitor of CYP3A4 at maximal intestinal concentrations and at maximal systemic concentrations. In addition, voxelotor is a time dependent inhibitor of CYP3A4 at maximal systemic concentration. In addition, voxelotor is an *in vitro* inhibitor of CYP2B6, 2C8, 2C9, and 2C19 at maximal systemic concentration. Clinical DDI studies were performed with voxelotor as inhibitor towards CYP1A2 (caffeine), 2C8 (rosiglitazone), 2C9 (S-warfarin), 2C19 (omeprazole), 2D6 (metoprolol) and 3A4 (midazolam). No interaction of voxelotor was observed of substrates of CYP1A2, 2C8, 2C9, 2C19, and 2D6. A slight effect was observed towards the CYP3A4 substrate (~1.6-fold increase in AUC), indicating that voxelotor is a mild CYP3A4 inhibitor at this dosing. The clinical DDI studies were performed with a dose of 900 mg voxelotor for 2 days followed by 600 mg for 2 days. The C_{max} and AUC were much lower than observed in patients at steady state.

In vitro data indicate that voxelotor was not an inhibitor of UG1A1, 1A9 and 2B7 at maximal systemic concentration. Due to solubility issues, no concentrations up to maximal intestinal concentrations could be investigated for UGT1A1. No inhibition was observed towards UGT1A1 up to 100 µM (the highest concentration investigated).

In vitro data indicate that voxelotor is an inhibitor of P-glycoprotein at maximal intestinal concentrations and at maximal systemic concentrations. Voxelotor is an inhibitor of OATP1B1, OAT3, MATE1 and BSEP at maximal systemic concentration and also for OATP1B1 at maximal portal vein concentrations. A clinical DDI study was performed with voxelotor as inhibitor towards P-glycoprotein (digoxin). The study indicated that voxelotor is not an inhibitor of P-glycoprotein at clinically relevant concentrations.

No clinical DDI studies were performed towards OATP1B1, OAT3 and MATE1.

In vitro data indicates that voxelotor may be an inducer of CYP2B6 via CAR at maximal systemic concentrations.

2.6.2.2. Pharmacodynamics

Mechanism of action

Voxelotor is an orally bioavailable small-molecule haemoglobin S polymerisation inhibitor that allosterically modifies haemoglobin (Hb)-O2 affinity. A single voxelotor molecule binds per Hb tetramer in a 1:1 stoichiometry (one molecule per Hb tetramer), with high partitioning into the RBC. Voxelotor causes a dose dependent decrease in p20 and p50 (the partial pressure of oxygen resulting respectively in 20% and 50% saturation of haemoglobin with oxygen), indicating an increase in Hb-O2 affinity. Mechanistically, voxelotor delays the transition from oxyHb to deoxygenated Hb in hypoxic conditions, indicating the stabilisation of the oxyHb state.

It is hypothesised that increasing Hb oxygen affinity in at least 20-30% of HbS, inhibits HbS polymerisation and, as a result, RBC sickling. This target is based on the experience In patients with sickle hereditary persistence of foetal haemoglobin (s/HPFH), where it was shown that the dilution of HbS by 20% to 30% foetal haemoglobin (HbF) in all RBCs suffices to inhibit HbS polymerisation. Similar to HbF, oxyhaemoglobin is a potent inhibitor of HbS polymerisation. Therefore, the therapeutic target of 20% to 30% Hb modification by voxelotor was used as a target in the clinical studies.

Primary and Secondary pharmacology

Pharmacodynamics of voxelotor is based on (1) *in vitro* studies in human blood and (2) clinical studies in healthy volunteers and SCD patients.

Study GBT440-001 is the key clinical study for the investigation of the clinical pharmacology profiling of voxelotor. This was a Phase 1, first-in-human, multiple-centre, randomised, placebo-controlled, double blind, single and multiple ascending dose (MAD) study to evaluate safety and tolerability of voxelotor in healthy subjects and in subjects with SCD.

Based on the *in vitro* data, a model was established to determine the percentage haemoglobin modification (%HbMOD) and occupancy by voxelotor. The model is based on the oxygen equilibrium curves (OECs), which are modulated by the change in haemoglobin oxygen (Hb-O2) affinity by voxelotor. For this model, Δp20 was chosen as the best parameter to predict the voxelotor/Hb ratio (% Hb modification) at or below 40%.

Therefore, Δp20 values from blood samples of subjects dosed with voxelotor in Clinical Study GBT440-001 were used to calculate the % Hb modification, based on the equations below:

AA Blood $$\%Hb\ Mod = \frac{\Delta p20 - 0.07}{24.58}$$

SS Blood $$\%Hb\ Mod = \frac{\Delta p20 + 0.16}{27.33}$$

Note: The numerators (0.07 and 0.16) are the Y intercepts for AA and SS blood, respectively. The denominators (24.58 and 27.33) respectively are the slopes obtained from the linear fit of the model.

The %HbMOD mean values, which are based on Δp20, increased with increasing dose in both healthy subjects and subjects with SCD after single and multiple dosing and p20 values generally decreased with increasing dose, indicating an increase in Hb-O2 affinity. In healthy subjects there was also a decrease in p50 values with increasing dose but less than seen in p20 and in SCD patients no difference in p50 was observed with increasing dose. As an example, the data after multiple dosing is presented below.

Table 16 Mean (SD) pharmacodynamic endpoints for healthy subjects and subjects with SCD

Dosing Duration (Days)	Healthy Subjects[a]				Subjects with SCD[a]			
	15	15	15	15	28	28	28	28
Cohort	All	Cohort 8	Cohort 9	Cohort 10	All	Cohort 12	Cohort 11	Cohort 14
Dose (mg)	Placebo	300 mg	600 mg	900 mg	Placebo	500 mg	700 mg	1000 mg[b]
No. of Subjects	n = 6	n = 6	n = 5	n = 5	n = 9	n = 10	n = 12	n = 5
p50 (mm Hg)	30.7 (2.2)	29.9 (1.7)	24.3 (1.5)	24.6 ± 2.5	34.3 (3.3)	30.9 (2.1)	29.6 (2.6)	28.0 (3.2)
p20 (mm Hg)	16.2 (1.3)	14.1 (1.0)	9.4 (1.1)	6.3 (0.8)	18.4 (1.6)	15.1 (1.8)	13.9 (3.1)	10.0 (3.2)
%HbMOD (%)	-1.0 (4.8)	10.9 (3.6)	24.1 (2.4)	38.3 (8.6)	-1.4 (4.4)	10.6 (7.2)	14.7 (9.6)	27.0 (11.6)

Abbreviations: BID, twice daily; p20, partial pressure of oxygen resulting in 20% saturated of haemoglobin with oxygen; p50, partial pressure of oxygen resulting in 50% saturation of haemoglobin with oxygen; SCD, sickle cell disease; SD, standard deviation; %HbMOD, percent haemoglobin modification, the proportion of haemoglobin converted to a high affinity form by voxelotor.

[a] Data from 24 hours post-final dose; minimum blood or plasma concentration.

[b] 1000 mg administered as 500 mg BID. Source: CSR GBT440-001, Table 14.2.4.2.1 and Table 14.2.4.2.2.

This estimate of % Hb modification was correlated to the % Hb occupancy which is defined as the molar ratio of the voxelotor concentration in RBCs to the estimated Hb concentration (5000 µM) in RBCs (equation below) from voxelotor-dosed subjects.

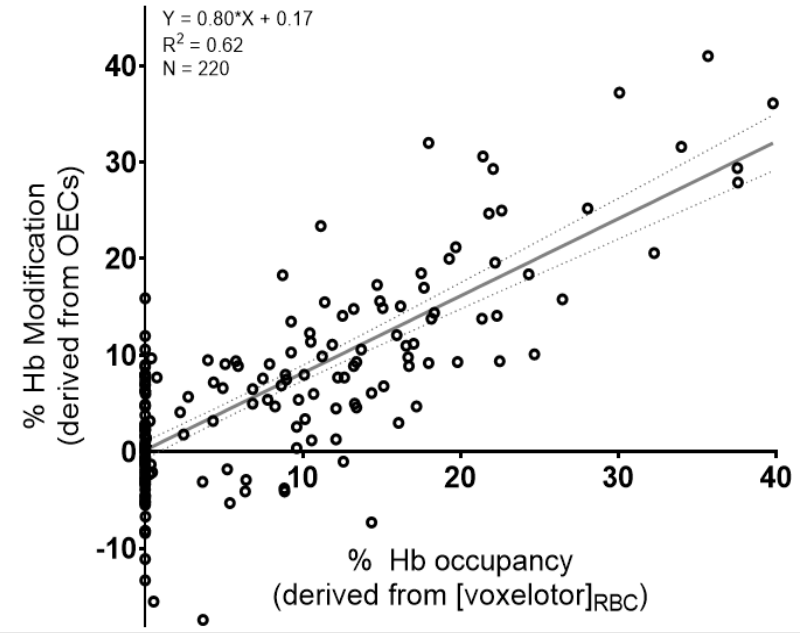
$$\%Hb\ occupancy = \frac{[voxelotor]_{RBC}}{5000}$$

The voxelotor concentration in RBCs was determined using the voxelotor concentration (µM) in whole blood and plasma (obtained from pharmacokinetic data) and the haematocrit (Hct) (obtained from haematology labs) as described in the equation below.

$$[voxelotor]_{RBC} = \frac{[voxelotor]_{whole\ blood} - (1 - Hct)[voxelotor]_{plasma}}{Hct}$$

It was observed that %Hb occupancy calculated from calculated voxelotor RBC concentration was a good predictor of the pharmacodynamic effect of increasing Hb-O2 affinity based on oxygen equilibrium curve (OECs) measurements (Δ p20). Therefore, %Hb occupancy was used in clinical studies assessing voxelotor to predict the PD effect of increasing Hb-O2 affinity. (see figure below)

Figure 3 Individual percent haemoglobin modification values versus individual percent haemoglobin occupancy for subjects with SCD



Abbreviations: Hb, haemoglobin; OEC, oxygen equilibrium curve; RBC, red blood cell; SCD, sickle cell disease. Source: (GBT440-001 CSR, Haemoximetry variables:16.2.6.7.1a (Part A), 16.2.6.7.2a (Part B); %Hb cooupancy:16.2.6.8.1 (part A), and 16.2.6.8.2 (Part B).

In study GBT440-001, the calculated %Hb occupancy mean values increased with increasing dose in subjects with SCD (see table below).

Table 17 The % Hb occupancy for Part C

Parameter	Dosing duration 90 days	
Dose	600 mg	900 mg
N	6	6
% Hb occupancy[a] (mean ± SD)	12.7 ± 4.4	19.8 ± 4.5

a % Haemoglobin Occupancy = RBC concentration (µM) / Haemoglobin concentration (5000 µM) × 100
Source: Table 11.39 from GBT440-001 CSR Data derived from Listing 16.2.6.3.3 and Listing 16.2.8.1.2.3

Haematological Response in SCD Subjects

Treatment response was evaluated by improvement in measures of haemolysis including evidence of increase in Hb and reduction from baseline in indirect bilirubin, reticulocytes, and LDH. The change from baseline in percent of sickled red cells was also evaluated.

In subjects (n = 13) receiving treatment with voxelotor for ≥90 days, a clinically meaningful increase in Hb (≥1 g/dL) was observed in 46% (6/13) versus 0% (0/14) of placebo subjects with concordant improvements in bilirubin and reticulocyte count demonstrating rapid and sustained reduction in haemolysis and a greater than 70% median decline in sickled red cells (see table below)

Table 18 Haemoglobin increase maintained with treatment for 90 days (Study GBT440-001: Part C)

	Voxelotor 700 mg × 90 Days Cohort 16 (n = 6)	Voxelotor 900 mg × ≥ 90 days Cohort 17 (n = 7) [a]	Placebo (Pooled - All) (N = 4)
Median hemoglobin change to end of treatment (25th and 75th percentile)[a]	1.1 g/dL (0.6, 1.3)	0.8 g/dL (0.5, 1.3)	-0.1 g/dL (-0.2, 0.1)
Proportion of subjects with ≥ 1 g/dL hemoglobin increase[b]	50%	43%	0%

[a] One placebo subject transitioned to voxelotor in the extension study (GBT440-024) and is included in Cohort 17 and pooled placebo. Data included was provided by the Sponsor.

[b] Values provided, based on the data presented in Figure 11.31.

Source: Cohort 16: Table 14.3.5.1.4. Cohort 17: Listings16.2.8.1.2.3 and Listing 16.2.8.1.2.1 for GBT440-024.

Table 19 Reduction in haemolysis, reticulocytes, and sickled red cells with treatment for ≥ 90 days

Percent Change from Baseline to End of Treatment (Median, 25th and 75th Percentile)	Voxelotor 700 mg 90 Days Cohort 16 (n = 6)	Voxelotor 900 mg ≥90 days Cohort 17 (n = 7)[a]	Placebo (Pooled All) 90 days (N = 4)
Indirect bilirubin (%)	-37.2 (-43.4, -23.7)	--42.9 (-58.9, -30.5)	14.8 (1.8, 18.5)
Lactate dehydrogenase (%)	0.8 (-14.7, 1.1)	-47.7 (-63.4, -12.5)	0.5 (-0.7, 7.2)
% Reticulocytes (%)	-21.0 (-32.9, -18.1)	-18.9 (-35.4, -6.2)	8.9 (2.5, 25.5)
Dense RBCs (%)	-35.5 [b] (-56.6, -1.4)	-21.0 [c] (-60.5, 11.3)	1.9 (-5.3, 4.0)
Sickled red cell (%)	-72.6 (-79.0, -60.6)	-79.2[c] (-91.3, -57.7)	6.9 (3.9, 10.3)

[a] One placebo subject transitioned to voxelotor in the extension study (GBT440-024) and is included in Cohort 17 and pooled placebo.

[b] n=4

[c] n=6; data only presented from study GBT440-001.

Source: Cohort 16: Table 14.3.5.1.4. Cohort 17: Listings 16.2.8.1.2.3, 16.2.8.1.5.3, and 16.2.8.1.2.1 (data from GBT440-024) and Listing 16.2.8.1.5.1 (data from GBT440-024).
Dense RBCs calculated internally at GBT based on data contained in Listing 16.2.6.9.3
Sickled red cells calculated internally at GBT based on data contained in Appendix 16.15

Secondary pharmacology

Study GBT440-0115, a thorough QT (TQT) was conducted in healthy subjects to investigate the effect of voxelotor on the QT interval/QT interval corrected for heart rate (QTc) and also evaluated the relationship of plasma voxelotor concentration and electrophysiologic effects. Moxifloxacin was included as a positive control to establish that the study was sufficiently sensitive to detect a small QT effect, thus demonstrating assay sensitivity (ICH, 2015; Shah, 2005).

Effect on Heart Rate

Mean ΔHR on voxelotor was larger than with placebo on Days 4 and 14, the days when plasma concentrations of voxelotor reached meaningful levels. Mean placebo-corrected ΔHR (ΔΔHR) ranged from 4.9 to 8.7 bpm on Day 4 and from 6.0 to 10.2 bpm on Day 14, thereby demonstrating a small drug effect on HR.

Effect on Cardiac Repolarisation: the QT Interval

A mild, but not apparently dose- or concentration-dependent effect of voxelotor was seen on ΔΔQTcF on Days 4 and 14. On Day 4, mean ΔΔQTcF exceeded 5 msec at several time points, with a largest mean value of 8.0 msec (90% CI: 4.60, 11.42 msec) at 24 hours post-dose. On Day 14, with higher plasma concentrations than on Day 4, the difference was smaller, with mean ΔΔQTcF ranging from 0.8 msec at 12 hours post-dose to 5.4 msec at 1 hour post dose.

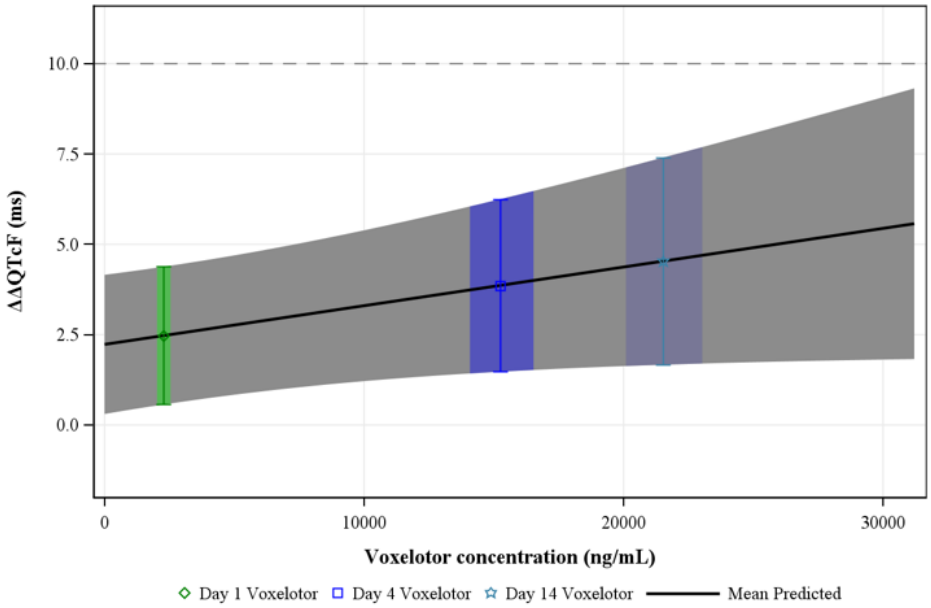
The predicted ΔΔQTcF at the GM peak voxelotor concentration overall and within each day is shown in table 20. Based on this concentration-QTc analysis, a QT effect (ΔΔQTcF) above 10 msec can be excluded in voxelotor plasma concentration of up to approximately 30 µg/mL.

Table 20 Predicted ΔΔQTcF interval at geometric mean peak voxelotor concentration (cardiodynamic population)

Treatment	Geometric Mean (µg/mL) (90% CI)	ΔΔQTcF Estimate (msec) (90% CI)
Voxelotor	20.1 (17.5, 23.0)	4.38 (1.58, 7.18)
Day 1 Voxelotor	2.27 (2.02, 2.55)	2.47 (0.55, 4.40)
Day 4 Voxelotor	15.3 (14.1, 16.5)	3.86 (1.43, 6.29)
Day 14 Voxelotor	21.5 (20.1, 23.0)	4.53 (1.61, 7.45)

Abbreviations: CI, confidence interval; C_{max}, maximum blood or plasma concentration; ECG, electrocardiogram; QTcF, QT interval corrected for heart rate using Fridericia's method.
Note: The C_{max} was calculated for each subject within each visit (treatment = day × voxelotor), as well as across all visits (treatment = voxelotor). Only plasma concentration values with time-matched ECGs were included in the calculation of C_{max}.
Note: ΔΔQTcF = placebo-corrected change from baseline for QTcF.

Figure 4 Predicted ΔΔQTcF interval at geometric mean peak voxelotor concentrations (cardiodynamic population)

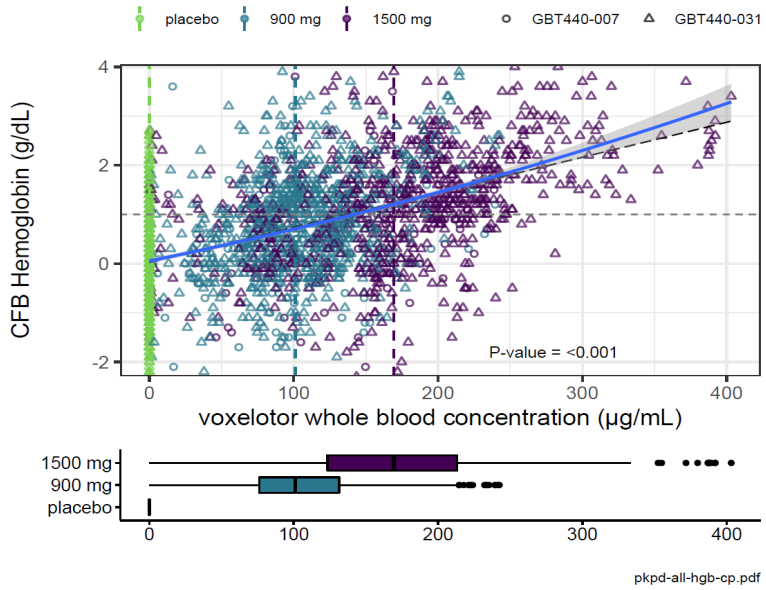


Abbreviations: CI, confidence interval; Cmax, maximum blood or plasma concentration; QTcF, QT interval corrected for heart rate using Fridericia's method.
Note: The solid black line with gray shaded area denotes the model-predicted mean (90% CI) ΔΔQTcF. The green, blue, and steel areas denote the estimated mean (90% CI) ΔΔQTcF at the geometric mean (90% CI) Cmax of voxelotor on Day 1, Day 4, and Day 14, respectively.
Source: CSR GBT440-0115, Figure 14.2.1.7.1.

Exposure-response analyses

Exposure-response (ER) and pharmacokinetic-pharmacodynamic (PKPD) analyses of voxelotor efficacy in adult and adolescent subjects up to at least week 72 were performed in study GBT-CP-014, for a pooled dataset including data from adolescent subjects in GBT440-007 and all subjects in GBT440-031. The changes from baseline in Hb and other measures of haemolysis were evaluated as a function of time-matched model-predicted whole blood voxelotor concentrations. Figure 5 shows CFB Hb increasing with whole-blood concentration, consistent with the mechanism of action of the drug.

Figure 5 CFB haemoglobin versus voxelotor whole-blood concentration (GBT-CP-014)



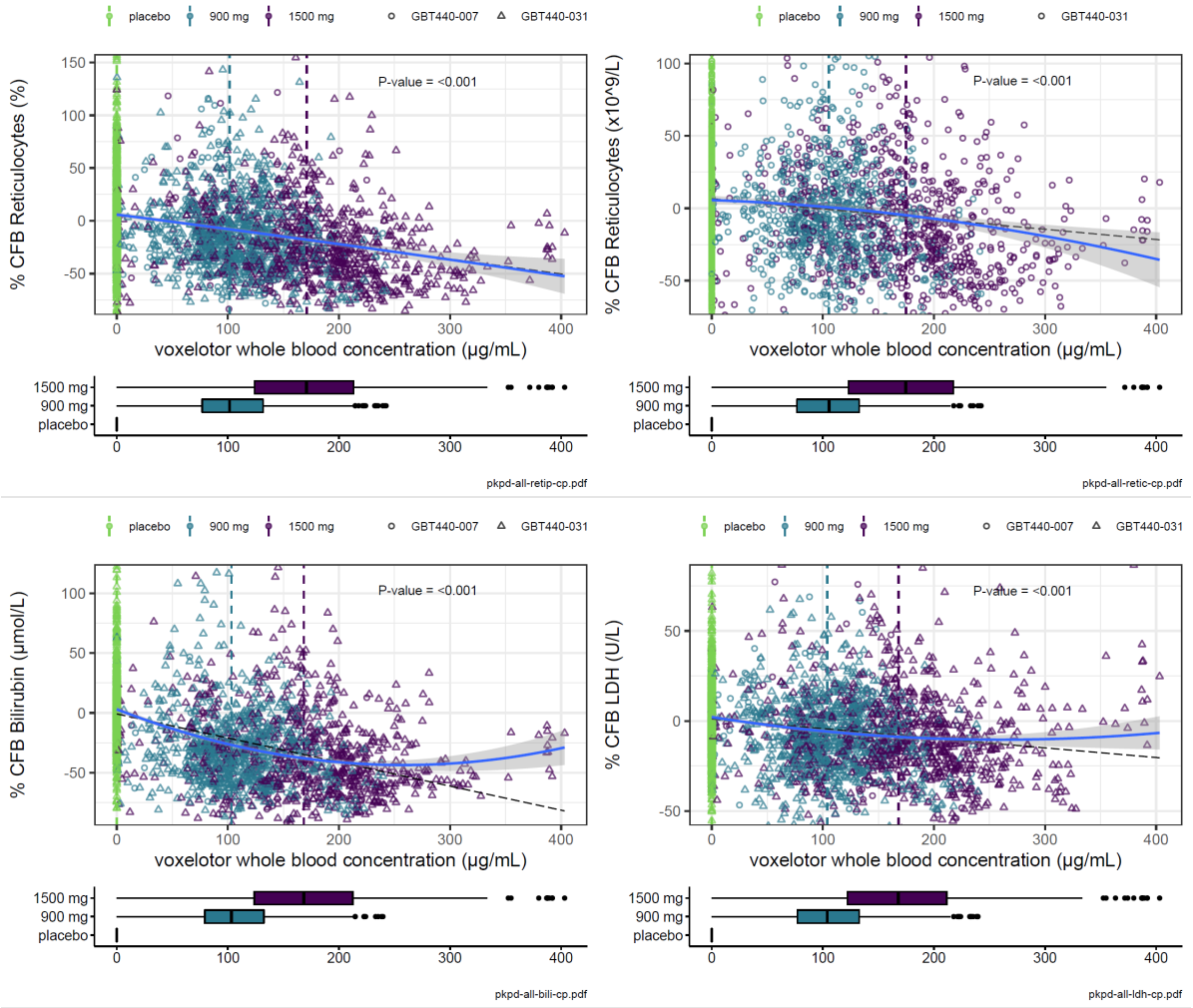
Abbreviations: CFB, change from baseline.
Note: The vertical dashed lines indicate the median of the concentrations for each dose group. The boxplots describe the distribution of exposures in each dose group. The left and right edges of the box correspond to the 25th and 75th percentiles, and the vertical line inside the box indicates the median. The horizontal gray dashed line indicates the target 1 g/dL increase in haemoglobin. The solid blue line and gray shaded area represent a 2nd degree polynomial regression and 95% confidence interval through the data. The p-value for the polynomial relationship compared with the null model (no relationship) is shown on the plot. The black dashed line is a linear regression line through the data.
Source: GBT-CP-014,

The data was also analysed by subject age (adolescent versus adult), and by nominal time of visit (≤ 12 weeks, 12 to 24 weeks, and 24 to 72 weeks). The same trends were observed as observed for the data including all subjects and all visits indicating that the ER relationship is similar for adults and adolescents and does not change over time. Relationships with other covariates were consistent. The slope in subjects with HU use was marginally shallower than in subjects without HU use; however, both cohorts surpass the targeted 1 g/dL increase at the median 1500 mg exposure. No differences were observed by sex, SCD genotype, weight, or race. No clinically impactful differences in the relationship between CFB Hb and covariates were observed.

The Figure below shows the relationship between % CFB % reticulocytes, absolute reticulocytes indirect bilirubin, and LDH and time-matched whole-blood concentrations. For percent and absolute reticulocytes,

indirect bilirubin, and LDH, the % CFB was larger at higher whole blood concentrations, and all relationships were statistically significant ($p < 0.001$). The magnitude of the % CFB for percent reticulocytes and for indirect bilirubin was noticeably larger than the magnitude of the % CFB for LDH and for absolute reticulocytes. While some patients did achieve substantial reductions in LDH and absolute reticulocytes, the mean responses for the 900 mg and 1500 mg dose groups were similar.

Figure 6 Relationships between change from baseline in clinical measures of haemolysis and model-predicted voxelotor whole-blood concentrations



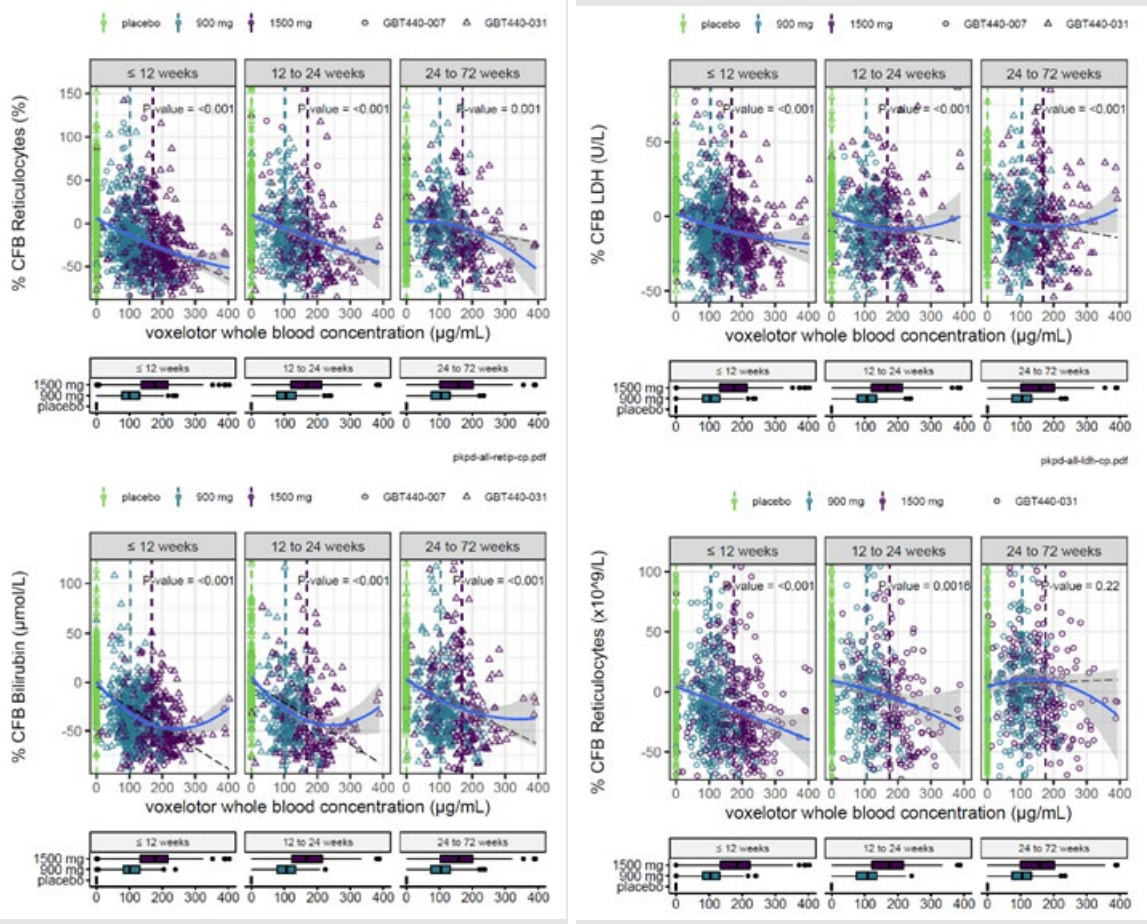
Abbreviations: CFB, change from baseline; LDH, lactate dehydrogenase.
Note: The vertical dashed lines indicate the median of the voxelotor blood concentrations for each dose group. The box plots describe the distribution of voxelotor blood concentrations in each dose group. The left and right edges of the box correspond to the 25th and 75th percentiles, and the vertical line inside the box indicates the median. The solid blue line and gray shaded area represent a 2nd degree polynomial regression and 95% confidence interval through the data. The black dashed line is a linear regression line through the data.
Source: GBT-CP-014, Figure 3.

When facetted by age group, the relationships for percent reticulocytes and bilirubin were similar in adolescents and adults. For absolute reticulocytes, the adult relationship was linear, but the % CFB absolute reticulocytes

in adolescents was mostly flat below the median exposure for the 1500 mg dose group (~170 µg/mL). The relationship for % CFB LDH showed similar distinctions between adult and adolescent subjects, however, the relationship in adults was mostly flat.

The analyses were also evaluated facetted by bins of nominal time. For all four measures of haemolysis, the relationship with whole blood concentration flattened over time to some degree, the relationship being non-significant for % CFB absolute reticulocytes between 24 to 72 weeks (Figure below).

Figure 7 % CFB versus time-matched whole blood concentration, facetted by nominal time of visit



2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of voxelotor have been investigated in 19 clinical studies (16 studies in healthy volunteers and 3 studies in patients) in whole blood, plasma and red blood cells. The PK was sufficiently investigated in patients with sickle cell disease aged 12 years and older. The PK of voxelotor in subjects with sickle cell disease is different from that in healthy subjects (exposure and blood-to-plasma ratio is higher in healthy volunteers compared to patients). Some uncertainties remain regarding drug-drug interactions (voxelotor as victim and as perpetrator).

Population PK (PopPK) modelling: A PopPK model was developed to describe the PK of voxelotor in plasma and whole blood in patients with sickle cell disease. The joint model structure is quite empirical with an effect compartment describing the whole blood and plasma concentrations. A limitation to this approach is that differences between plasma and whole blood pharmacokinetics can only be detected in the blood to plasma ratio and the rate constant representing the delay between plasma and whole blood pharmacokinetics. Blood volume was included in the model as covariate, which is derived using body weight, height and gender. The final model adequately describes both plasma and whole blood pharmacokinetics reasonably well in patients aged 12 years and older. Parameter estimates are reasonable and no clear structural deviations can be observed in the goodness-of-fit plots.

Physiologically based pharmacokinetic (PBPK) modelling: The PBPK model cannot be used to waive PK studies in subjects <12 years of age. Furthermore the PBPK model to extrapolate the DDI studies in healthy volunteers to patients with Sickle cell disease, to predict the inhibition potential of voxelotor towards transporter inhibition and to predict the effect of induction on the PK of voxelotor was not acceptable. The PBPK model was not sufficiently qualified to predict the effect of voxelotor as inhibitor towards CYP2C8, 2C9, 2C19 and 3A4 and OAT3. In addition, also the PBPK model to predict the effect of induction on the PK of voxelotor instead of performing a clinical DDI study is currently not acceptable. The model cannot be verified with clinical induction data.

Pharmacokinetic Interaction studies

The effect of a strong inducer on the PK of voxelotor was not investigated. A strong PXR inducer may lead to a significant decrease in voxelotor exposure and to decreased efficacy. Therefore, concomitant use of strong CYP3A4 inducers with voxelotor should be avoided due to the risk of decreased efficacy of voxelotor. This has been reflected in section 4.5 and 5.2 of the SmPC. Since PXR inducers are not commonly used concomitantly in patients with sickle cell disease, no clinical DDI study is currently warranted and a warning is sufficient.

It is currently unknown if voxelotor is a substrate of P-glycoprotein, BCRP, OATP1A2, OATP1B1 and OATP1B3 at clinically relevant concentrations. Therefore, currently no clinical transporter DDI studies are warranted.

The suitability of the DDI studies to predict clinical DDIs with voxelotor as perpetrator towards CYP2C8, 2C9, 2C19 and 3A4 is questioned (*in vitro* data already indicated that voxelotor is not an inhibitor of CYP1A2 and 2D6 at clinically relevant concentrations). The clinical DDI studies were performed with a dose of 900 mg voxelotor for 2 days followed by 600 mg for 2 days which is much lower than the 1500 mg dose of voxelotor administered to patients. Furthermore, the C_{max} and AUC were much lower than observed in patients at steady state. It is currently unknown if voxelotor is a clinically relevant inhibitor of CYP2B6, 2C8, 2C9, and 2C19 at maximal systemic concentration in patients with Sickle cell disease. Based on the available data that voxelotor is at least a moderate inhibitor of CYP3A4 and should not be co-administered with CYP3A4 substrates with narrow therapeutic index. However, it cannot be excluded that voxelotor is more than a moderate CYP3A4

inhibitor. The inhibition potential towards CYP2C8, 2C9, 2C19 and 3A4 will be investigated as part of the Post-Authorisation Measure (PAM) proposed by the applicant towards CYP2B6 inhibition in one cocktail DDI study.

A clinical DDI study with voxelotor as inhibitor towards OATP1B1, OAT3 and MATE1 will be performed as PAM. It is unknown if voxelotor may inhibit BCRP at maximal intestinal concentrations. However, no *in vitro* studies can be performed to investigate this due to cytotoxicity problems at such high concentrations. The applicant reviewed the safety data for subjects who used BCRP substrates concomitantly with voxelotor. Only three subjects received concomitant BCRP substrates. None of these three subjects showed an increase in adverse events compared with subjects who did not receive concomitant BCRP substrates. This may indicate that voxelotor is not a clinically relevant inhibitor of BCRP. However, three subjects is too limited to draw firm conclusions. A DDI study will be performed with rosuvastatin as substrate for OATP1B1 to investigate the inhibition potential of voxelotor towards OATP1B1. The applicant is advised to include measurement of Coproporphyrins I as biomarker for OATP1B1 to distinguish between potential OATP1B1 and BCRP inhibition, since rosuvastatin is a substrate of OATP1B1 and BCRP and Coproporphyrin I is a functional marker of OATP1B1 activity.

The clinical DDI studies were performed with voxelotor given for 3 days, this is too short to investigate the effect of induction. A clinical DDI study with voxelotor as inducer towards CYP2B6 will be performed as PAM. The inhibition potential of voxelotor towards UGT1A1, 1A9 and 2B7 is also currently unknown, but will be investigated at clinically relevant concentrations as a PAM.

Effect of voxelotor on other medicinal products such as CYP3A4 substrates, CYP2B6 substrates, CYP2C8, CYP2C9, and CYP2C19 substrates have been reflected in section 4.5 of the SmPC. In addition, recommendations have also been included with regards to transporter-mediated drug interactions and concomitant use of voxelotor with digoxin in section 4.5 of the SmPC. *In vitro* drug interactions and transporter-mediated interactions have also been reflected in section 5.2 of the SmPC.Drug-drug interaction potential with voxelotor and OATP1B1, OAT3 and MATE1 substrates, and the drug-drug interaction potential with voxelotor on CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 substrates has been added as missing information in the RMP and the applicant will provide the results of the following studies post-marketing:

- GBT440-0120: A Phase 1, Open-Label, Fixed-Sequence, Two-Period, Drug-Drug Interaction Study to Evaluate Effect of Voxelotor on the Pharmacokinetics of Probe Substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in Healthy Subjects;

- GBT440-0121: A Phase 1, Open-Label Study to Evaluate the Effect of Multiple Doses of Voxelotor on the Pharmacokinetics of Probe Substrates for MATE1, OAT3, and OATP1B1 in Healthy Subjects;

Pharmacodynamics

Pharmacodynamic data of voxelotor is based on *in vitro* studies in human blood and clinical studies in healthy volunteers and SCD patients.

Based on the ***in vitro* study** PRC-18-043, with donor blood from healthy or SCD subjects, a model to determine haemoglobin modification (%HbMOD) and occupancy by voxelotor was established using oxygen equilibrium curves (OEC) and four parameters (p20, Δp20, p50, Δp50) describing the change in Hb O2 affinity resulting from the binding of voxelotor to Hb. Changes in p20 (Δp20) was identified as the most optimal parameter to

serve as predictor of voxelotor/Hb ratio (% Hb modification- the proportion of Hb molecules modified to a high Hb-O2 affinity form by voxelotor) in blood from healthy subjects or from subjects with SCD.

Based on the clinical pharmacology Study GBT440-001, it was also shown that %HbMOD is directly correlated to voxelotor RBC concentration, which is calculated from and correlated to the concentration of voxelotor in blood. Also, %HbMOD was found to be directly correlated to percent Hb occupancy, which is calculated as the molar ratio of the voxelotor concentration in RBCs to the estimated Hb concentration (MCHC, 5000 μM) in RBCs. It is not clear if using the individual patient values for Hb concentration in RBCs, and not estimated values to calculate Hb occupancy, would have resulted in a different proportion of patients reaching the target 20% Hb occupancy. However, as the primary endpoint was haemoglobin response, this was not further pursued.

Due to this direct correlation between %HbMOD (that is reflective of Hb-O2 affinity) and Hb occupancy, the latter was used to approximate the PD effect of increase in oxygen affinity in the further clinical studies.

The main clinical pharmacology **Study GBT440-001** showed a decrease in p50 and p20 (pO2 at which there is 50% or 20% saturation of Hb with O2, accordingly) following a single or multiple dose of voxelotor treatment, compared to the placebo values. A smaller decrease was observed in p50 compared to p20, which is in line with a greater effect of voxelotor (left shift) at lower pO2. The targeted %HbMOD or % Hb occupancy were not achieved in this study, where only multiple doses up to 1000 mg were used. Increase in blood O2 saturation and a decrease in measured p50 values after voxelotor 1500 mg use following 14 days were also observed in another Study GBT440-0111. However, only 3 subjects were assessed in the voxelotor 1500 mg group that decrease the reliability of any conclusion.

In addition to PD parameters that reflect oxyHb stabilisation by voxelotor, several parameters related to haemolytic anaemia were measured in the Study GBT440-001, such as total Hb levels, indirect bilirubin, % reticulocytes and LDH. Overall, the data presented support the potential of voxelotor to reduce haemolysis by decreasing RBC sickling. The increase in haemoglobin values observed in the voxelotor-treated subjects compared to placebo, was accompanied by a decrease in the markers of haemolysis. Also, a decrease in RBC sickling was observed in almost all voxelotor groups.

Since targeted %HbMOD or % Hb occupancy were not achieved in the Study GBT440-001 and no plateau was reached with respect to the effect on haemolysis markers, a PK/PD model was developed to estimate the dose of voxelotor by which 30% Hb occupancy can be reached. This dose was estimated to be 1500 mg and was further tested in the pivotal Study GBT440-031 (see section 3.3.5 for details).

As voxelotor is for the most part present in RBCs and its PD effect is located inside the RBCs, whole blood concentration was chosen as a measure of exposure in the **Exposure-Response** (ER) analysis from the Phase 2 (GBT440-007) and Phase 3 study (GBT440-031) where the registration dose of 1500 mg was tested. ER analysis showed an exposure-dependent effect of voxelotor on Hb and haemolysis markers, such as indirect bilirubin, LDH, %reticulocyte and absolute reticulocyte count: change from baseline (CFB) or % CFB was larger at higher whole blood concentrations. The relationships were consistent when adults and adolescent were analysed separately. When analysis was split according to time (≤12 weeks, 12 to 24 weeks and 24 to 72 weeks), the correlation between blood concentration and Hb effect remained unchanged over time. However, for four measures of haemolysis, the relationship with whole blood concentration flattened over time to some degree, with the relationship being non-significant for % CFB Absolute Reticulocytes between 24 to 72 weeks. The dose of 1500 mg was shown to be more effective compared to the 900 mg, which supports the choice for the registration dose of 1500 mg.

A **dedicated TQT study** in healthy volunteers has been performed to evaluate any possible treatment induced QT effect of voxelotor. Although some time points in the Day 4 data may suggest for some QT effect, though not formally powered for such an analysis, these observations were not repeated at the Day 14 point results at higher concentration levels. Therefore, based on such lack of consistency in the by time analyses and the provided powered concentration-QT response analyses, which show no clear relationship, it is reasonable to conclude that no relevant QT prolongation effect is to be expected with voxelotor within the therapeutic dose range.

Even though **pharmacodynamic interactions** were not specifically discussed, the effect of voxelotor on Hb levels was shown to be independent on the concomitant HU use.

2.6.4. Conclusions on clinical pharmacology

The pharmacodynamics of voxelotor is complex. As expected from the mechanism of action, voxelotor leads to the increase in Hb affinity for O2, stabilising Hb in the oxygenated state. However, uncertainties remain about the consequences this Hb modification has on the ability of voxelotor-bound Hb to release O2 and contribute to the tissue oxygenation. This is discussed in the clinical sections (please see discussion in sections 3.2, 3.3.6, 3.3.9, 5). The pharmacokinetics of voxelotor were sufficiently investigated in healthy volunteers and patients with Sickle cell disease. There are some remaining uncertainties regarding drug-drug interactions (voxelotor as victim and as perpetrator) which will be investigated in studies submitted as PAMs (see also RMP cat 3 studies).

2.6.5. Clinical efficacy

This application is based on efficacy data obtained from the following studies:

- Pivotal phase 3 study GBT440-031
- Ongoing open label extension study GBT440-034 of study GBT440-031
- Phase 2 study GBT440- 007 Part B in paediatric patients

Please see below for more information.

2.6.5.1. Dose response study(ies)

No formal dose-response study has been performed. The data from phase 1 study GBT440-001 and its open-label extension (OLE) (GBT440-024) were used for dose determination for the Phase 3 study, supported with results from safety, PK, and PK/pharmacodynamic (PD) analyses.

In the GBT440-001 study, voxelotor treatment resulted in a dose dependent increase in Hb O2 affinity; the pharmacodynamic (PD) effect is reflected by a decrease in change in partial pressure of oxygen at which Hb

oxygen saturation of 20% and 50% is achieved (p20 and p50, respectively). Likewise, the related percent Hb modification in subjects with SCD increased with increasing voxelotor dose. Exposure response analysis and PK/PD modelling of GBT440-001 data demonstrate a highly significant and liner relationship between exposure and improvement in haemolysis measures (i.e. at the doses tested, a plateau on improvement in haemolysis measures has not been reached). The greatest Hb increase was seen in cohorts (Part C of study GBT440-001) dosed for 90 days with 700 mg and 900 mg dose.

The therapeutic target of 20% to 30% of % Hb occupancy was used to select the doses evaluated in the pivotal Phase 3 Study GBT440 031 (please see rationale for this target in the Pharmacodynamics section). In the GBT440-001 study, the targeted %Hb occupancy was not achieved with maximum dose tested for >90 days being 900 mg. Therefore, modelling and simulation of PK data was used to predict that voxelotor 900 mg and 1500 mg doses would achieve voxelotor blood concentrations at minimum observed concentration (Cmin) in the median subject equivalent to Hb modification of 16% (2.5th–97.5th percentile, 7%–31%) and 26% (2.5th–97.5th percentile, 12%–52%), respectively. Based on this prediction, 25% of subjects at the 900 mg dose and 76% of subjects at the 1500 mg dose were predicted to achieve the therapeutic target of > 20% Hb occupancy. Also, the effects of 900 mg and 1500 mg dose were predicted by the model (see table 21**Error! Reference source not found.**), where 1500 mg dose of voxelotor was predicted to have a higher efficacy compared to the lower 900 mg dose. Based on this modelling, two doses were chosen to be tested in the Phase 3 study – 900mg and 1500 mg.

Table 21 Simulated haemolysis measures outcomes (% change from baseline) for voxelotor 900 mg and 1500 mg (based on study GBT440-001)

Hemolysis Measure	Dose of Voxelotor	
	900 mg	1500 mg
Bilirubin (%)	-47 (27–84)	-66 (51–78) [a]
Reticulocytes (%)	-53 (30–93)	-84 (61–94) [a]
LDH (%)	-30 (17–54)	-64 (37–84) [a]
Hemoglobin (%)	11.9 (6.7–21.1)	—[c]
Hemoglobin (change from Baseline)[b,c]	1.06 (0.60–1.9)	—[c]

Values represent median (2.5th to 97.5th percentiles)

[a] Based on E_{max} model

[b] Based on a Baseline Hb of 9 g/dL

[c] The E_{max} model underestimated the change in Hb and cannot be used and the linear model may overestimate.

2.6.5.2. Main study(ies)

Title of study

Study GBT440-031 was a double-blind, randomised, placebo-controlled, multicentre 72-week study of subjects aged 12 to 65 years with sickle cell disease (SCD), including haemoglobin (Hb) sickle cell disease with 2 sickle

cell genes (HbSS), haemoglobin sickle cell disease with 1 HbS sickle cell gene and 1 haemoglobin C gene(HbSC), HbSβ thalassemia, or other sickle cell syndrome variants.

Methods

Study Participants

Key study eligibility criteria (selection):

- Male or female, aged 12 to 65 years, inclusive, with documented SCD (HbSS, sickle haemoglobin (S) and 1 beta zero thalassemia gene [HbSβ0thalassemia], sickle haemoglobin (S) and 1 beta plus thalassemia gene [HbSβ+thalassemia], haemoglobin sickle cell disease with 1 HbS sickle cell gene and 1 haemoglobin C [HbC] gene [HbSC], or other sickle cell syndrome variants).
- Subjects had had at least 1 episode of VOC in the previous 12 months. For study eligibility, VOC was defined as a previously documented episode of acute chest syndrome (ACS) or acute painful crisis (for which there was no explanation other than VOC) that required prescription or health-care professional–instructed use of analgesics for moderate to severe pain (documentation required to exist in the subject medical record prior to screening).
- Hb ≥ 5.5 and ≤ 10.5 g/dL at screening
- For subjects taking HU, the dose of HU was required to be stable for at least 90 days before the subject signed the informed consent form, with no anticipated need for dose adjustments or initiation during the study, in the opinion of the investigator.

Key exclusion criteria (selection):

- More than 10 VOCs within the past 12 months that required a hospital or emergency room or clinic visit
- Subjects who received regularly scheduled blood (RBC) transfusion therapy (also termed chronic, prophylactic, or preventive transfusion) or had received an RBC transfusion for any reason within 60 days of signing the ICF or at any time during the Screening period
- Subjects who were hospitalised for sickle cell crisis or other vaso-occlusive event within 14 days prior to signing the ICF (ie, a vaso-occlusive event could not take place within 14 days prior to signing of the ICF)
- Hepatic dysfunction characterised by alanine aminotransferase (ALT) > 4 × upper limit of normal (ULN)
- Subjects with clinically significant bacterial, fungal, parasitic, or viral infection that required therapy:
- Subjects with acute bacterial infection requiring antibiotic use were to delay Screening/enrollment until the course of antibiotic therapy had been completed.
- Subjects with known active hepatitis A, B, or C or who were known to be human immunodeficiency virus (HIV)–positive
- Severe renal dysfunction (estimated glomerular filtration rate at the Screening Visit, as calculated by the central laboratory, < 30mL/min/1.732 or on chronic dialysis)

- History of unstable or deteriorating cardiac or pulmonary disease within 6 months prior to consent
- Receipt of erythropoietin or other hematopoietic growth factors within 28 days of signing ICF or anticipated need for such agents during the study

Treatments

The study comprised 3 periods:

- Screening (28–35 days),
- Treatment Period (2–72 weeks), and
- End-of-Study Follow-Up Visit at 4 weeks (± 7 days) after the last dose of study drug.

In the double-blind treatment period the subjects in Groups 1 and 2 were randomised in a 1:1:1 ratio to receive daily doses of voxelotor 900 mg, voxelotor 1500 mg, or matching placebo OD. The 300 mg capsule was used at the time the study was initiated; however, the 300 mg tablet formulation became available shortly thereafter. Thus, the majority of subjects received only the tablet formulation. Subjects in voxelotor 1500 mg received 5 × 300-mg voxelotor capsule or tablet; subjects in voxelotor 900 mg group received 3 × 300-mg voxelotor capsule or tablet and 2 × placebo capsule or tablet; and subjects in the placebo group received 5 × placebo capsule or tablet orally.

Dose could be reduced by 1 tablet in case of study drug-related Grade 2 or higher AEs.

All approved therapies for SCD were allowed under the protocol; none were withheld. This included pain control, HU, L-glutamine, and blood transfusions. HU dose was to be stable for at least 90 days before the subject signed the ICF to avoid confounding the interpretation of the safety and efficacy endpoint in this study.

Objectives/ endpoints

The objectives/endpoint of the study are presented below.

Table 22 Objectives and endpoints of Study GBT440-031

Primary Objective	**Primary Endpoint**
The primary objective was to assess the effect of voxelotor compared with placebo on improvement in Hb in adults and adolescents with SCD.	The primary efficacy endpoint is Hb response at Week 24. Hb response was based on the difference between the average value of haemoglobin levels at Week 20 (Hb20) and Week 24 (Hb24) compared to baseline haemoglobin level (HbB). A subject was considered to be an 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. Subjects were classified as non-responders if any of the non-responder criteria were

	met: Hb assessment was missed at both Week 20 and Week 24; HU treatment was initiated post-randomisation and prior to Week 24; RBC transfusion due to anaemia was received within 8 weeks of the Week 24 Hb assessment
Secondary Objectives The secondary objectives were to evaluate the effects of voxelotor compared with placebo on: • Clinical measures of haemolysis • Long-term VOC incidence	**Secondary Endpoints** • Change from Baseline in Hb at Week 24 • Change and percentage change from Baseline in haemolysis measures, including unconjugated bilirubin, reticulocyte percentage, absolute reticulocytes, and LDH at Week 24 • Incidence of severe anaemic episodes (Hb < 5.5 g/dL) • Annualised IR of VOC
Exploratory Objectives The exploratory objectives were to evaluate the effects of voxelotor compared with placebo on: • Sickle Cell Disease Severity Measure (SCDSM) (Burke, 2016) • EuroQol health questionnaire (EQ-5D-5L™) (EuroQol, 1990; Herdman, 2011) • Clinical Global Impression of Change (CGIC)—Groups 1 and 2 only (Guy, 1976) • Incidence and time to first RBC transfusion and postbaseline onset of VOC • School and/or work attendance and the use of opioids during the treatment period as recorded via eDiary • Measures related to SCD pathophysiology and their utility as PD markers, including inflammatory biomarkers (Group 1 only), kidney function, and RBC rheology	**Exploratory Endpoints** • Change from Baseline in Hb at Week 48 and Week 72 • Change and percentage change from Baseline in haemolysis measures, including unconjugated bilirubin, reticulocyte percentage, absolute reticulocytes, and LDH, at Week 48 and Week 72 • Time to first VOC • Time to first ACS or pneumonia • Time to first RBC transfusion • Rate of opioid use as recorded in the eDiary • SCDSM • EQ-5D-5L • CGIC • School and/or work attendance as recorded in the eDiary

• Measures predictive of response to voxelotor	

Note: A VOC was defined in the protocol as a composite of acute painful crisis or ACS including the following:

- moderate to severe pain lasting at least 2 hours;
- no explanation other than VOC;
- required oral or parenteral opioids, ketorolac, or other analgesics prescribed or directed by a healthcare professional;
- required documentation in the subject medical record that the subject was seen or contacted the physician within 1 business day of the event.

The event may have taken place in a medical setting (hospital, clinic or emergency room). Priapism and acute chest syndrome (ACS) events that met the protocol definition of a VOC event were also counted in the analysis of the VOC secondary endpoint.

Randomisation and blinding (masking)

Subjects in Groups 1 and 2 were randomised in a 1:1:1 ratio to receive daily doses of voxelotor 900 mg, voxelotor 1500 mg, or matching placebo. Group 2 subjects were randomised after enrollment of the 62nd subject in Group 1. The randomisation was carried out centrally through an IXRSAt the time of randomisation. Subjects were stratified for HU use (yes/no), geographic region (North America, Europe, Other), and age (adolescent, 12 to <18 years, and adults, 18 to 65 years).

This was a double-blind study. The voxelotor and placebo capsules or tablets were matched for shape, size, and colour. All individuals involved in the conduct of the study (ie, site staff and subjects, investigator, contract research organisation [CRO] personnel, sponsor personnel) were blinded to randomised treatment assignment. Other sponsor and CRO personnel could be unblinded as required per regulatory reporting requirements of suspected unexpected serious adverse reactions (SUSARs). Also, to facilitate the 2 IAs and the primary analysis (based on 24-week data from Groups 1 and 2), certain sponsor representatives and sponsor designees were unblinded to treatment assignments prior to and during the data analysis (including the biostatistics CRO, sponsor biostatistics and programming staff, and external groups for bioanalytical PK/PD).

Statistical methods

The **sample size** for the entire study, including Groups 1, 2 and 3, was estimated to be approximately 370 participants (up to a maximum of approximately 435 participants, depending on the dose[s] selected for the Group 3).

The primary efficacy measure, Hb, will be evaluated as 2 endpoints in Group 1: as change from Week 12 to Baseline; and as a responder endpoint (change from Week 12 to Baseline >1 g/dL).

For the endpoint of change from Baseline in Hb, power calculations assume a mean treatment effect of 0.8 g/dL (voxelotor at either dose, minus placebo), the placebo change from Baseline is equal to 0, a per-group SD of 0.6 g/dL. With N = 20 participants per arm, the power exceeds 95% of detecting a treatment difference between either voxelotor dose versus placebo using a t-test. The assumptions are based on data at Day 90 from Cohorts 16 and 17 from the GBT440-001 study. For the responder endpoint at Week 12, the voxelotor doses will be pooled. Assuming responder proportions of 35% and 5% for pooled voxelotor data (N = 40) and placebo (N = 20), the power with Fisher's exact test at a two-sided alpha = 0.05 is 80%.

Group 2 is designed to allow continued enrolment between Group 1 and Group 3 while the Group 1 data are analysed and until decision is made on voxelotor dose selection for Group 3. Group 2 sample size was estimated based on these considerations and no formal statistical assessment was performed.

Based on the results from Group 1 analysis (62 participants), and a second analysis which included 94 subjects from Group 2 (total of 156 participants) with a minimum of 24 weeks of follow up, it was decided that the combination of Group 1 and all Group 2 participants, for a total of 274 randomised subjects, would constitute the basis for the primary analysis of the study. For the primary analysis of Hb response rate comparing voxelotor 1500 mg to placebo, assuming a 10% Hb response rate in placebo, the study with approximately 90 subjects per treatment group will have >95% power to detect a targeted difference of 30%, using Fisher's exact test with a two-sided alpha of 0.0481.

Group 3 sample size was to be determined when the voxelotor dose(s) is selected. Eventually, following the results of the primary analysis, it was decided that Group 3 would not be recruited.

Statistical analysis plan (SAP) version 5 specifies the statistical methods used for analysis of data from Groups 1 and 2. SAP version 5 was finalised prior to the unblinding of Group 2b data (data from the patients in Group 2 that were not analysed in the second interim analysis).

All subjects who were randomised into the study were included in the Intent-to-Treat (ITT) Population and were analysed based upon their randomised treatment group. This was the primary population for efficacy analyses. All subjects who were randomised to a treatment group and received at least 1 dose of study medication were included in the modified Intent-to-Treat (mITT) Population, used as supportive analyses. All subjects who received at least 1 dose of study medication were included in the Safety Population and were analysed based upon the study drug received.

Unless otherwise specified, analyses of data from subjects in Groups 1 and 2 combined were adjusted for the randomisation stratification factors. For Group 2b analysis, due to the small sample size, adjustment was made for HU use at Baseline only.

The primary endpoint of Hb response at Week 24 was analysed using an exact Cochran-Mantel-Haenszel (CMH) general association test. The primary analysis of Hb response rate was to compare voxelotor 1500 mg with placebo. Hb response was based on the difference between the average value of Hb levels at Week 20 and Week 24 compared to baseline Hb level, if one time point was missing, the other was used. If both Hb assessment were missed, HU treatment was initiated or RBC transfusion due to anaemia was received within 8 weeks of the Week 24 Hb assessment subjects were classified as a non-responders. Hb assessments after RBC transfusion for reasons other than anaemia were imputed using last observation carried forward (LOCF).

Change from Baseline in Hb or haemolysis measurements over time was analysed using a mixed-effects model for repeated measures (MMRM). A single model was fit using all available data through Week 72, including fixed-effects terms treatment, visit, treatment by visit interaction, and stratification factors. Baseline Hb was a

covariate. Within-subject variability was modelled using an unstructured covariance matrix. Missing data due to early dropout or missed visit were not imputed for this analysis. Data after HU initiation or VOC were set to missing and assumed to be missing at random, data after RBC transfusion were imputed using LOCF.

The number of VOC events was modelled using a negative binomial model with the independent variable of treatment group and adjusted for the stratification factors used for randomisation. The mean cumulative function of VOC events was presented using recurrent-events analysis methods. For the rate of VOC, the analyses did not make any adjustments due to missing data.

Kaplan Meier methods were used to summarize time-to-event endpoints, including time to first VOC, time to first ACS or pneumonia and time to first RBC transfusion.

A Lan-DeMets α spending function with the O'Brien-Fleming boundary was used to determine the significance level for each interim a primary analysis (significance levels 0.000005, 0.0059 and 0.0481), to maintain an overall 2-sided Type I error rate of 5%. A fixed-sequence hierarchical test procedure was used to formally evaluate the voxelotor 1500-mg and 900-mg dose groups in comparison with placebo. The first hypothesis testing was to compare Hb response rate at Week 24 in voxelotor 1500 mg vs placebo. If the null hypothesis in the primary efficacy analysis was rejected at a 2-sided significance level of 0.0481, secondary endpoints were tested for voxelotor 1500 mg vs placebo, followed by primary and secondary endpoints for voxelotor 900 mg vs placebo, until the first nonrejection.

Subgroups defined by subject age group, sex, race, geographic region, baseline HU use, baseline VOC history, and baseline Hb level were analysed to evaluate the internal consistency of the study outcomes. In addition, comparability of study cohorts (e.g. Group 1, Group 2a, Groups 1 and 2a, and Group 2b) were assessed.

Results

- **Participant flow**

Table 23 Subject disposition and reasons for discontinuation—ITT Population

Subject Status	Placebo QD	Voxelotor 900 mg QD	Voxelotor 1500 mg QD	All Subjects
Randomised (ITT Population), N	92	92	90	274
Subjects Treated (mITT Population), n(%)	91 (98.9)	92 (100.0)	88 (97.8)	271 (98.9)
Completed Study[a], n (%)	66 (71.7)	70 (76.1)	63 (70.0)	199 (72.6)
Early Discontinuation from Study, n(%)	26 (28.3)	22 (23.9)	27 (30.0)	75 (27.4)
Primary Reason for Study Discontinuation, (n, %)				
Adverse Event	6 (6.5)	6 (6.5)	11 (12.2)	23 (8.4)
Withdrawal of Consent	10 (10.9)	12 (13.0)	6 (6.7)	28 (10.2)
Discretion of the Investigator	1 (1.1)	2 (2.2)	1 (1.1)	4 (1.5)
Subject is Lost to Follow-Up	0	1 (1.1)	1 (1.1)	2 (0.7)
Subject is Noncompliant	3 (3.3)	1 (1.1)	5 (5.6)	9 (3.3)
Pregnancy	1 (1.1)	0	0	1 (0.4)

Subject Status	Placebo QD	Voxelotor 900 mg QD	Voxelotor 1500 mg QD	All Subjects
Other	5 (5.4)	0	3 (3.3)	8 (2.9)
Completed Assigned Treatment (72 weeks)[a, n] (%)	66 (71.7)	68 (73.9)	63 (70.0)	197 (71.9)
Early Treatment Discontinuation, n (%)	26 (28.3)	24 (26.1)	27 (30.0)	77 (28.1)
Primary Reason for Treatment Discontinuation, n (%)				
Adverse Event	7 (7.6)	8 (8.7)	11 (12.2)	26 (9.5)
Withdrawal of Consent	9 (9.8)	10 (10.9)	6 (6.7)	25 (9.1)
Discretion of the Investigator	1 (1.1)	2 (2.2)	1 (1.1)	4 (1.5)
Subject is Lost to Follow-Up	0	1 (1.1)	0	1 (0.4)
Subject is Noncompliant	3 (3.3)	1 (1.1)	6 (6.7)	10 (3.6)
Pregnancy	1 (1.1)	0	0	1 (0.4)
Other	5 (5.4)	2 (2.2)	3 (3.3)	10 (3.6)
Duration of Follow-Up (weeks)				
N	92	92	90	274
Mean (SD)	61.1 (21.60)	63.2 (22.34)	59.5 (22.55)	61.3 (22.14)
Median	72.1	72.5	72.1	72.1
Min, Max	0.1, 87.1	4.9, 86.0	0.1, 88.6	0.1, 88.6

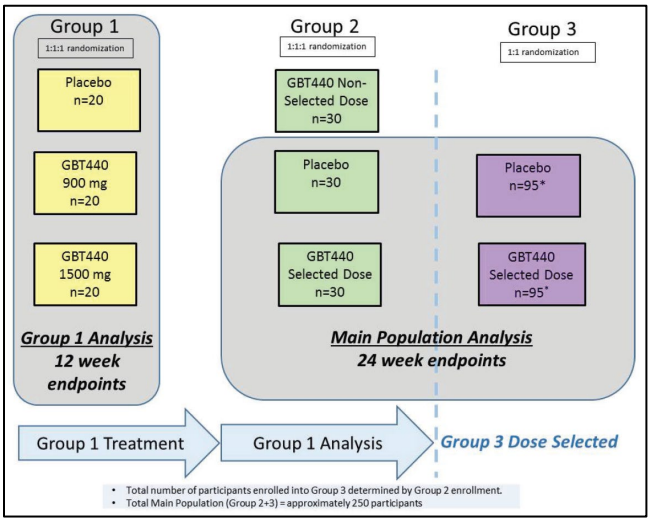
- ## Recruitment

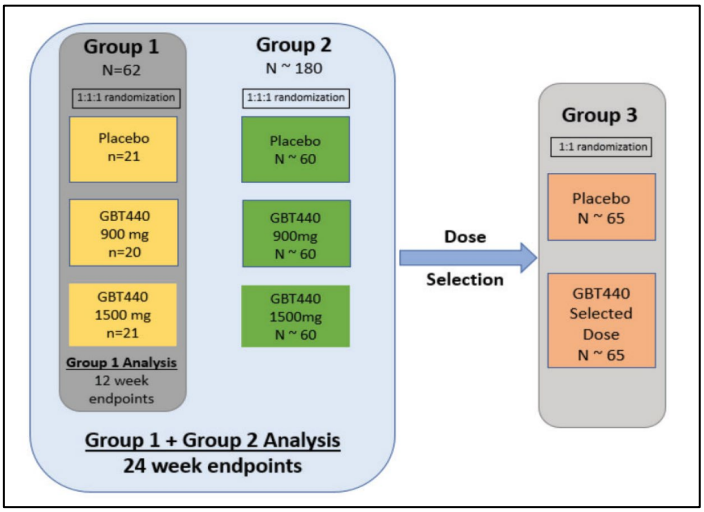
First Subject First Visit was on 13 December 2016, and between January 2017 and May 2018, a total of 274 subjects were randomised at 58 study sites across 12 countries (United States, Kenya, Egypt, Great Britain, Turkey, Oman, Netherlands, Lebanon, Canada, Jamaica, France, and Italy). Last Subject Last Visit was on 08 October 2019.

- ## Conduct of the study

The Study GBT440-031 was to be conducted in 3 groups (see figure below) . Initially, Group 1 was to be used to select the dose for Group 3 – confirmatory group, while Group 2 was designed to allow continued enrollment between Group 1 and Group 3. The Group 3 and the patients on the selected dose in the Group 2 were to be used for the Primary Analysis (, left). Two interim analysis took place: first one to analyse the data from Group 1 and second to analyse the data from Groups 1+ part of the patients from Group 2 (Group 2a). Following the second interim analysis, the latest protocol amendment#4 was implemented that brought substantial changes to the study design and primary analysis (, right). The primary analysis was now to be performed on the participants from Group 1 and Group 2 (274 subjects in total, including 156 subjects that were used in the second interim analysis – Group 2a), with Group 3 not being used in the primary analysis. Also, a number of secondary endpoints were changed following protocol amendment #4, including the addition of the CGCI scale endpoint.

Figure 8 Study schematic





Baseline data

- In general, demographic and other baseline characteristics, including age, sex, race, genotype, HU use, and Hb and haemolysis measures, were similar across treatment groups (Table 24 and Table 25)
- The history of SCD-related complications, including overall VOCs, was also generally balanced across treatment groups. The number of acute chest syndrome episodes during the 12 months prior to screening was somewhat greater in the voxelotor groups than in the placebo group.

Table 24 Study GBT440-031: Demographic and other baseline characteristics in adults and paediatric subjects 12 years and older with SCD (ITT Population)

Characteristic	Placebo QD N = 92	Voxelotor 900 mg QD N = 92	Voxelotor 1500 mg QD N = 90	All Subjects N = 274
Age (Years), n				
Mean (SD)	28 (11.5)	28 (11.8)	27 (11.7)	28 (11.6)
Median	28	24	24	24
Min, Max	12, 64	12, 59	12, 59	12, 64
Age Group				
12 to < 18 Years	17 (18.5)	15 (16.3)	14 (15.6)	46 (16.8)
≥ 18 Years	75 (81.5)	77 (83.7)	76 (84.4)	228 (83.2)
Sex				
Male	42 (45.7)	41 (44.6)	32 (35.6)	115 (42.0)
Female	50 (54.3)	51 (55.4)	58 (64.4)	159 (58.0)

Characteristic	Placebo QD N = 92	Voxelotor 900 mg QD N = 92	Voxelotor 1500 mg QD N = 90	All Subjects N = 274
Race[a]				
Arab/Middle Eastern	20 (21.7)	20 (21.7)	20 (22.2)	60 (21.9)
Asian	0	1 (1.1)	1 (1.1)	2 (0.7)
Black or African American	63 (68.5)	61 (66.3)	59 (65.6)	183 (66.8)
White	5 (5.4)	7 (7.6)	12 (13.3)	24 (8.8)
Other	6 (6.5)	5 (5.4)	2 (2.2)	13 (4.7)
Region[b]				
North America	35 (38.0)	36 (39.1)	34 (37.8)	105 (38.3)
Europe	18 (19.6)	19 (20.7)	19 (21.1)	56 (20.4)
Other	39 (42.4)	37 (40.2)	37 (41.1)	113 (41.2)
SCD Genotype				
HbSS	74 (80.4)	71 (77.2)	61 (67.8)	206 (75.2)
HbSC	2 (2.2)	2 (2.2)	3 (3.3)	7 (2.6)
HbSβ^0thalassemia	11 (12.0)	13 (14.1)	18 (20.0)	42 (15.3)
HbSβ^+thalassemia	3 (3.3)	2 (2.2)	7 (7.8)	12 (4.4)
Other Sickle Cell Syndrome Variant	2 (2.2)	4 (4.3)	1 (1.1)	7 (2.6)
Number of VOCs (12 months prior to screening)				
1	39 (42.4)	41 (44.6)	35 (38.9)	115 (42.0)
≥ 2	53 (57.6)	51 (55.4)	55 (61.1)	159 (58.0)
Mean (SD)	2.5 (1.88)	2.5 (2.13)	2.5 (1.90)	2.5 (1.97)
Median	2.0	2.0	2.0	2.0
Min, Max	1, 10	1, 10	1, 10	1, 10
Number of ACS Events (12 months prior to screening)				
0	89 (96.7)	82 (89.1)	80 (88.9)	251 (91.6)
1	2 (2.2)	8 (8.7)	9 (10.0)	19 (6.9)
2	0	2 (2.2)	1 (1.1)	3 (1.1)
3	1 (1.1)	0	0	1 (0.4)
Baseline Use of Hydroxyurea	58 (63.0)	63 (68.5)	58 (64.4)	179 (65.3)

Abbreviations: ACS, acute chest syndrome; HbSβ^0thalassemia, sickle haemoglobin (S) and 1 beta thalassemia gene; HbSβ^+thalassemia, sickle haemoglobin (S) and 1 beta thalassemia gene; HbSC, haemoglobin sickle cell disease with 1 HbS sickle cell gene and 1 haemoglobin C (HbC) gene; HbSS, haemoglobin sickle cell disease with 2 sickle cell genes (SS); ITT, Intent-to-Treat; Max, maximum; Min, minimum; QD, once daily; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis.

Note: All percentages were calculated using the column heading N unless otherwise indicated. Unless noted otherwise, baseline was the last available value prior to initiation of study drug.

[a] Subjects could be included in more than one race category.

[b] Countries labeled as Other include Egypt, Jamaica, Kenya, Lebanon, and Oman. Turkey was grouped with Europe for purposes of data summary.

Table 25 Study GBT440-031: Selected baseline laboratory values in adults and paediatric subjects 12 years and older with SCD (ITT Population)

Baseline Laboratory Test	Placebo QD N = 92	Voxelotor 900 mg QD N = 92	Voxelotor 1500 mg QD N = 90
Hb (g/dL), n	92	92	90
Mean (SD)	8.6 (1.06)	8.3 (1.08)	8.6 (1.10)
Median	8.6	8.3	8.7
Min, Max	6.1, 10.5	5.9, 10.8	5.9, 10.8
Reticulocyte Percentage, n	92	92	90
Mean (SD)	11.0 (4.85)	11.7 (5.35)	10.5 (4.97)
Median	10.9	11.5	9.6
Min, Max	2.4, 24.9	2.9, 23.6	3.1, 24.9
Absolute Reticulocytes (10^9/L), n	92	92	90
Mean (SD)	318.3 (130.27)	322.1 (141.68)	299.0 (123.44)
Median	312.5	326.0	290.3
Min, Max	89.5, 636.5	92.0, 671.5	60.0, 705.0
Indirect Bilirubin (µmol/L), n	86	89	87
Mean (SD)	50.3 (43.19)	44.2 (34.16)	45.3 (44.29)
Median	34.2	31.5	28.4
Min, Max	5.7, 259.1	7.2, 172.6	9.0, 262.1
Lactate Dehydrogenase (U/L), n	88	90	90
Mean (SD)	439.2 (188.70)	432.9 (179.06)	385.1 (150.61)
Median	393.8	391.8	340.8
Min, Max	161.5, 1151.0	179.5, 1210.0	185.5, 865.0
HbF (%), n	77	75	73
Mean (SD)	10.4 (10.96)	9.9 (7.47)	9.3 (6.29)
Median	7.4	8.6	8.3
Min, Max	1.2, 86.4	0.3, 30.7	0.3, 28.8

Abbreviations: Hb, haemoglobin; HbF, fetal haemoglobin; ITT, Intent-to-Treat; Max, maximum; Min, minimum; QD, once daily; SCD, sickle cell disease; SD, standard deviation.
Note: Baseline is the average of all values on or prior to randomisation.

- ## Numbers analysed

The ITT Population, which included all randomised subjects, was the primary analysis population for efficacy analyses. Three randomised subjects (Subjects 01-043-001 and 15-001-0002 assigned to the voxelotor 1500-mg group and Subject 01-006-0005 assigned to the placebo group) did not receive any study drug and were excluded from the mITT Population (see table below**)**.

Table 26 Efficacy analysis populations and groups – All randomised subjects

	Number (%) of Subjects			
	Placebo	**Voxelotor 900 mg**	**Voxelotor 1500 mg**	**All Subjects**
Intent-to-Treat (ITT)[a]	92	92	90	274
Analysis Groups				
Groups 1 and 2a Combined	51 (55.4)	52 (56.5)	53 (58.9)	156 (56.9)
Group 1	21 (22.8)	20 (21.7)	21 (23.3)	62 (22.6)
Group 2a	30 (32.6)	32 (34.8)	32 (35.6)	94 (34.3)
Group 2b	41 (44.6)	40 (43.5)	37 (41.1)	118 (43.1)
Modified Intent-to-Treat (mITT)[b]	91 (98.9)	92 (100.0)	88 (97.8)	271 (98.9)

Note: The denominator for all percentages is the N in the ITT row.

[a] All randomized subjects. Subjects were analyzed based upon the treatment group to which they were randomly assigned. This was the primary population for efficacy analyses.

[b] All subjects who were randomly assigned to a treatment group and received at least 1 dose of study drug. Subjects were analyzed based upon the treatment group to which they were randomly assigned.

- **Outcomes and estimation**

Primary endpoint

Haemoglobin Response at Week 24

In the ITT Population, 51.1% (46/90) of subjects in the voxelotor 1500mg group and 32.6% (30/92) of subjects in the voxelotor- 900-mg group achieved a > 1 g/dL increase in Hb from baseline to Week 24, compared with 6.5% (6/92) of subjects in the placebo group. The difference in the adjusted response rate at Week 24 for voxelotor 1500 mg vs placebo was 45.0% and statistically significant (p < 0.001). For voxelotor 900 mg vs placebo, the difference was 26.4% (p < 0.001).

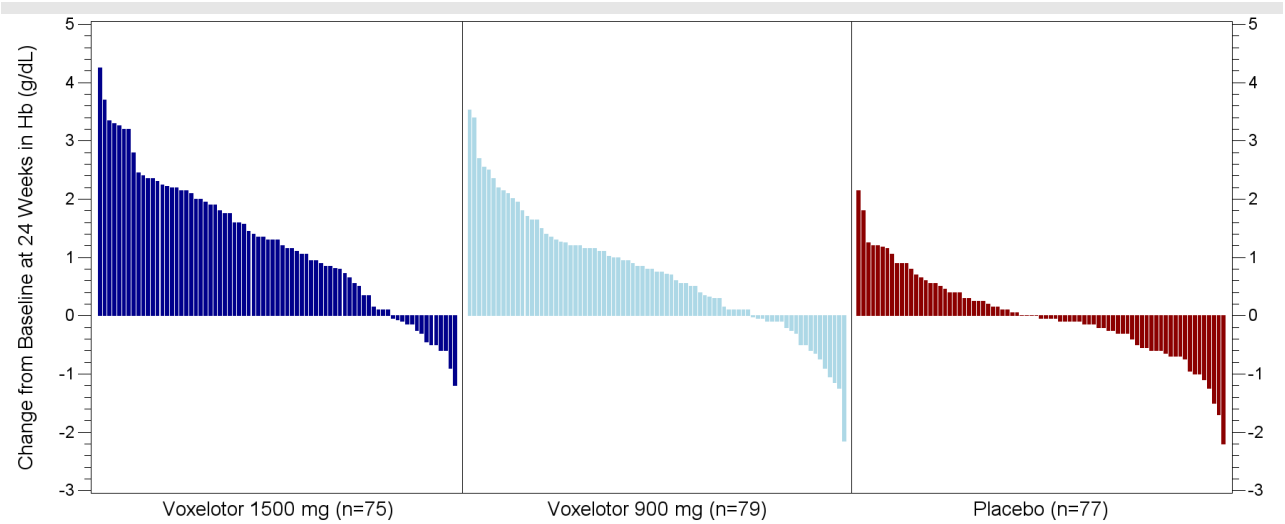
Table 27 Study GBT440-031: Haemoglobin response at week 24 in adults and paediatric subjects 12 years and older with SCD (ITT Population)

	Placebo QD (N = 92)	Voxelotor 900 mg QD (N = 92)	Voxelotor 1500 mg QD (N = 90)
N	92	92	90
Hb Increase of > 1 g/dL from Baseline to 24 Weeks, n (%)[a]	6 (6.5)	30 (32.6)	46 (51.1)
Difference in Adjusted Response Rates (vs Placebo, %)[b]		26.4	45.0
95% CI for Difference		15.5, 37.3	33.4, 56.7
P-value (vs Placebo, Exact CMH Test)		< 0.001	< 0.001[c]

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; Hb, haemoglobin; HU, hydroxyurea; ITT, Intent-to-Treat; QD, once daily; RBC, red blood cell; SCD, sickle cell disease.
Note: Baseline is the average of all values on or prior to randomisation. Hb assessed within 8 weeks post-RBC transfusion for any reason was imputed by the last Hb level prior to the transfusion. Hb response of > 1 g/dL change from baseline was derived based on change from baseline to the average of the values for Weeks 20 and 24. Subjects with any of the following scenarios are counted as nonresponders: 1) Hb missing at both Weeks 20 and 24; 2) postrandomisation HU use prior to Week 24 for subjects with no HU use at Baseline; 3) received transfusion due to anaemia within 8 weeks prior to Week 24 Hb assessment.
[a] Data presented are observed (unadjusted) counts and percentages.
[b] Difference, CI, and p-value are from pairwise comparisons adjusted for baseline HU use, age group, and geographic region.
[c] Statistically significant per pre-specified testing hierarchy.

More subjects in the voxelotor groups than in the placebo group had an increase in Hb level from baseline at Week 24, and the increases in the voxelotor groups were generally larger than those in the placebo group). Higher percentages of subjects in the voxelotor 1500 mg and 900 mg groups than in the placebo group achieved clinically meaningful Hb levels ≥ 10 g/dL at Week 24 (based on the average of Week 20 and Week 24 values): 41.1%, 19.6%, and 8.7%, respectively. A lower percentage of subjects in the voxelotor 1500 mg group (4.4% [4/90] of subjects) than in the placebo group (12.0% [11/92] of subjects) had acute anemic episodes (Hb decrease from baseline > 2 g/dL) during the study.

Figure 9 Study GBT440-031: Subject-level change from baseline in haemoglobin at week 24 (per-protocol analysis of observed data)



Abbreviations: Hb, haemoglobin; HU, hydroxyurea.
Note: Data displayed are changes in Hb from baseline (average of Screening and Day 1) to the average of Weeks 20 and 24. Subjects with missing values at both Weeks 20 and 24 were excluded from the summary. Laboratory results after the earliest of last dose, postrandomisation HU initiation for subjects with no HU use at baseline, withdrawal of consent, and end of study were excluded.
Note: The percentage of subjects with a change from baseline in Hb > 1 g/dL in each treatment group is shown.

The analysis of the data in the Group1+2a (analysed in the second interim analysis) and Group 2b (analysed following interim analysis) was consistent with the primary analysis.

Secondary and exploratory endpoints

Hb change from baseline at week 24, 48 and 72

Hb change from baseline at week 24 was secondary endpoint and Hb change from baseline at week 48 and 72 was exploratory endpoint.

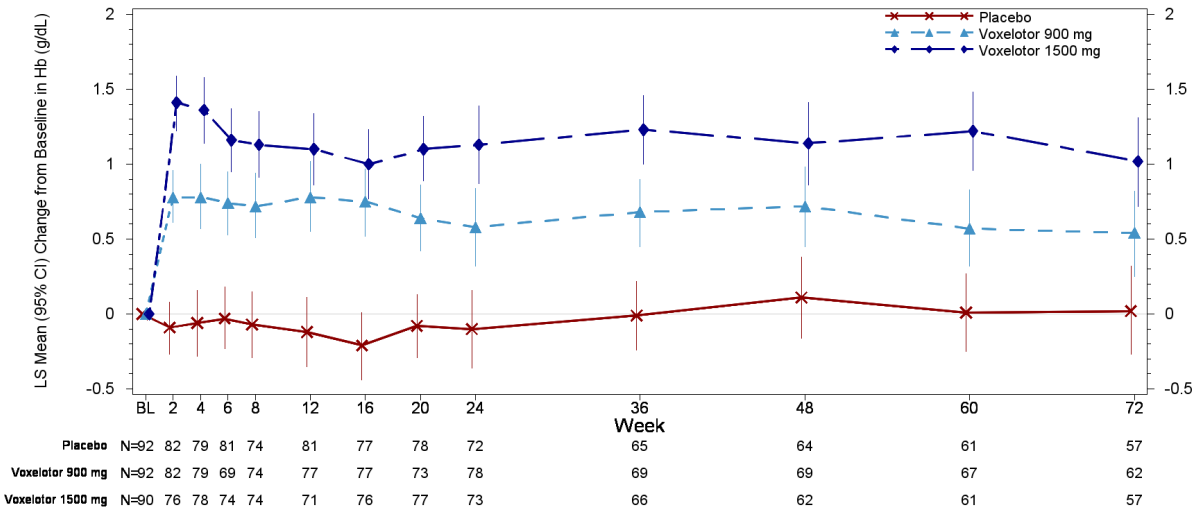
On average, an increase from baseline in Hb level was observed for the voxelotor 1500 mg group beginning at Week 2 (maximum increase) and the increase in Hb was maintained through 24 weeks (least squares [LS] mean [standard error; SE] change from baseline was 1.13 [0.111] g/dL at Week 8 and at Week 24) (CSR GBT440 031 Table 14.2.3.1).

On average, an increase from baseline in Hb level was observed for the voxelotor 1500 mg group beginning at Week 2 (maximum increase) and the increase in Hb was maintained through 72 weeks. In the placebo group, little to no change from baseline was observed in the average Hb level over time. Differences in the LS mean change from baseline in Hb between the voxelotor 1500 mg group and the placebo group were observed at all measured time points from Week 2 to Week 72 (all $p < 0.001$). At Week 24, the LS mean (SE) change from baseline was 1.13 (0.132) g/dL in the voxelotor 1500 mg group, 0.58 (0.130) g/dL in the voxelotor 900 mg group and 0.10 (0.132) g/dL in the placebo group. At Week 24, the difference between voxelotor 1500 mg and placebo was 1.23 g/dL and statistically significant ($p < 0.001$), and the difference between the voxelotor 900

mg and placebo was 0.68 g/dL (p < 0.001). The difference between the voxelotor 1500 and 900 mg groups at Week 24 was 0.55 g/dL (p = 0.003).

At Week 72, the LS mean (SE) change from baseline (g/dL) was 1.02 (0.149) in the voxelotor 1500 mg group, 0.54 (0.143) in the voxelotor 900 mg group, and 0.02 (0.148) in the placebo group. The difference between voxelotor 1500 mg and placebo was 0.99 g/dL (95% CI: 0.58 to 1.41 g/dL; p < 0.001), and the difference between voxelotor 900 mg and placebo was 0.51 g/dL (95% CI: 0.11 to 0.92 g/dL; p = 0.014).

Figure 10 Least squares mean change from baseline in haemoglobin over time up to week 72 – ITT Population



Abbreviations: BL, baseline; CI, confidence interval; Hb, haemoglobin; HU, hydroxyurea; ITT, Intent-to-Treat; LS, least-squares; MMRM, mixed-effect model for repeated measures; RBC, red blood cell.
Note: The MMRM model includes treatment, study visit, treatment by visit interaction, baseline HU use, age group, and region as fixed-effects terms, and baseline value as a covariate, and uses an unstructured covariance matrix for within-subject variability. The summary omitted laboratory assessments after postrandomisation initiation of HU (for subjects with no HU use at baseline), withdrawal of consent, and end of study. Laboratory assessments within 8 weeks post-RBC transfusion, for any reason, were imputed by the last laboratory value prior to the transfusion.

The analysis of the 24-week data in the Group1+2a (analysed in the second interim analysis) and Group 2b (analysed following interim analysis) was consistent with the ITT analysis.

The annualised IR of acute anaemic episodes was 3-fold lower (0.05 vs 0.15 per person years) with voxelotor 1500 mg than placebo.

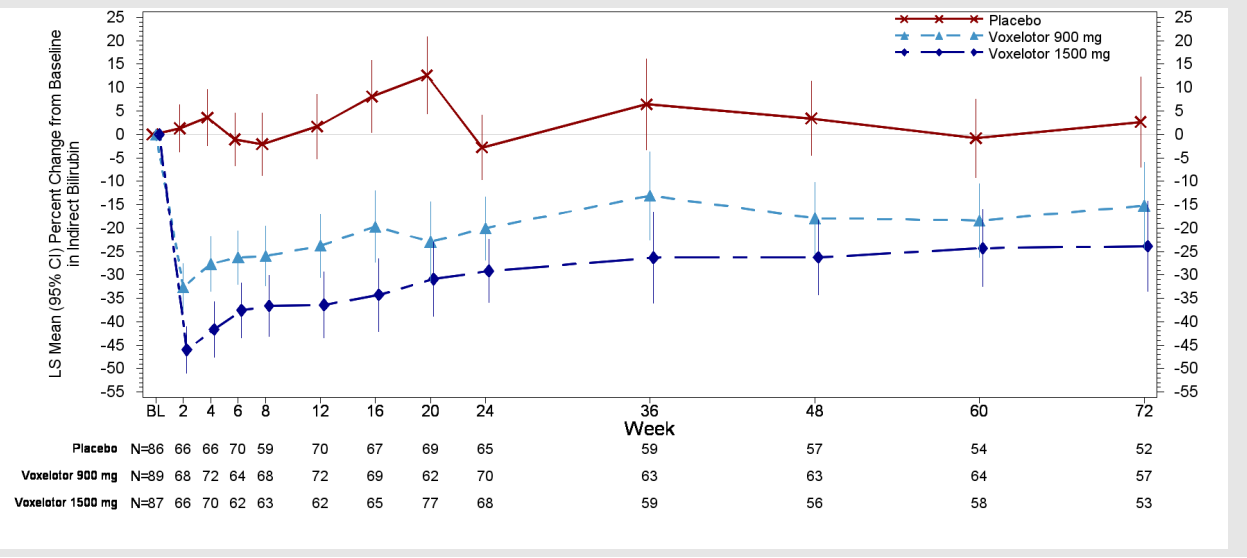
Change From Baseline in Measures of Haemolysis at Week 24, 48 and 72

Change in haemolysis markers from baseline at week 24 was secondary endpoint and change in haemolysis markers from baseline at week 48 and 72 was exploratory endpoint.

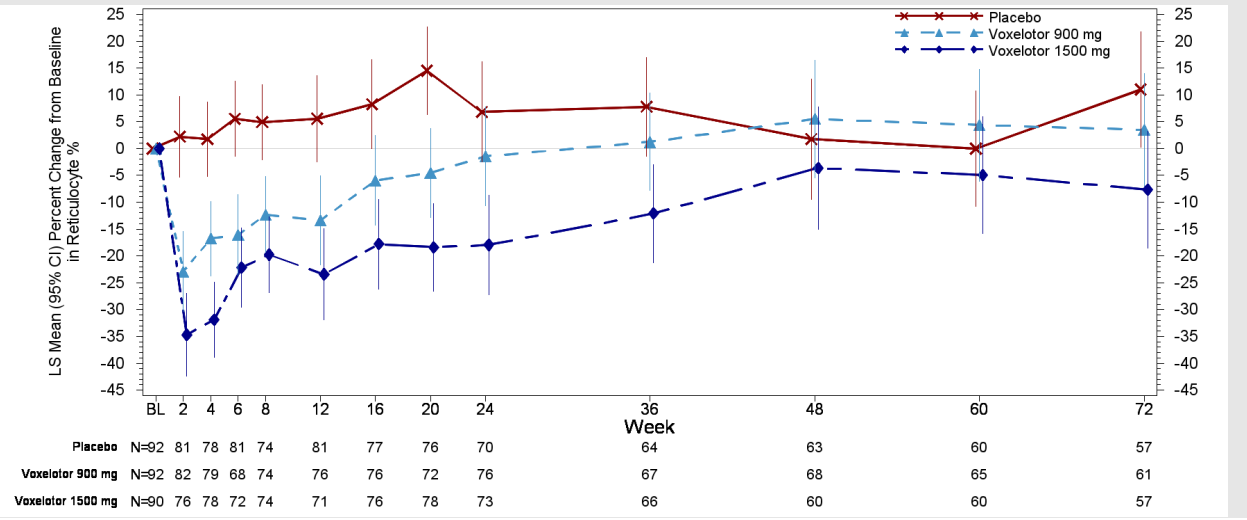
Consistent with the increase from baseline in Hb, dose dependent decreases in clinical measures of haemolysis were observed with voxelotor treatment. Improvements in haemolysis measures and Hb occurred within 2 weeks of treatment initiation. Following this initial reduction in haemolysis measures, indirect bilirubin and reticulocyte percentage demonstrated a durable treatment effect over 72 weeks with the voxelotor 1500 mg dose compared to placebo, but not the decrease in LDH or absolute reticulocyte number (Figure 11 and Table 28).

Figure 11 Least-squares mean percentage change from baseline in a) Indirect bilirubin, b) Reticulocytes percentage, c) Absolute reticulocytes, and d) Lactate dehydrogenase over time up to week 72—ITT Population

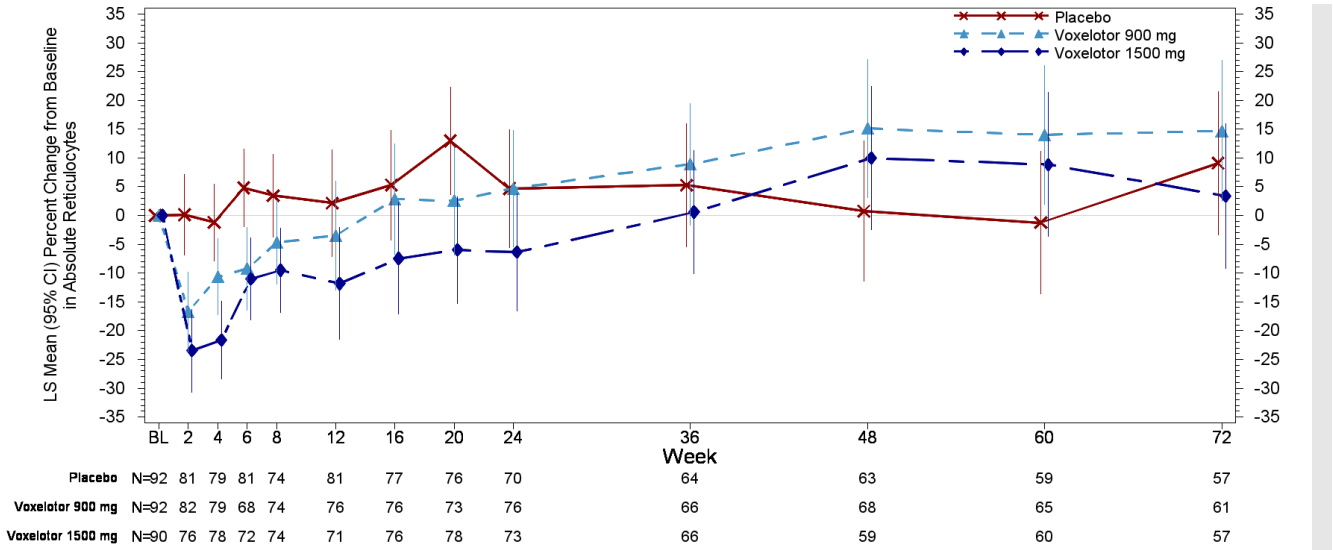
a: Indirect bilirubin



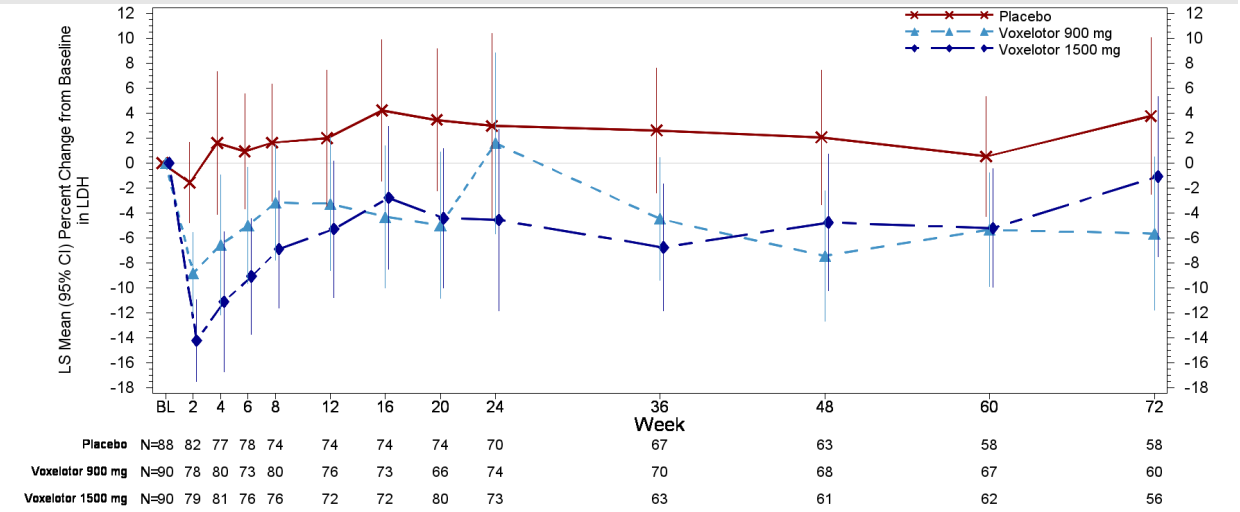
b: Reticulocyte percentage



c: Absolute reticulocytes



d: Lactate dehydrogenase



Abbreviations: BL, baseline; CI, confidence interval; HU, hydroxyurea; ITT, Intent-to-Treat; LDH, lactate dehydrogenase; LS, least-squares; MMRM, mixed-effect model for repeated measures; RBC, red blood cell.
Note: The MMRM model includes treatment, study visit, treatment by visit interaction, baseline HU use, age group, and region as fixed-effects terms, and baseline value as a covariate, and uses an unstructured covariance matrix for within-subject variability. The summary omitted laboratory assessments after post-randomisation initiation of HU (for subjects with no HU use at baseline), withdrawal of consent, and end of study. Laboratory assessments within 8 weeks post–RBC transfusion, for any reason, were imputed by the last laboratory value prior to transfusion.
Source: CSR GBT440-031, Figures 14.2.2.1, 14.2.3.1, 14.2.4.1, and 14.2.5.1.

Table 28 Study GBT440-031: Analysis of percent change from baseline in measures of haemolysis at week 24 in adults and paediatric subjects 12 years and older with SCD (ITT Population)

Parameter	Placebo QD N = 92	Voxelotor 900 mg QD N = 92	Voxelotor 1500 mg QD N = 90
Indirect Bilirubin			
Number of Subjects Included in the MMRM	85	88	85
N at Week 24	65	70	68
LS Mean Percent Change in Indirect Bilirubin from Baseline at Week 24 (SE)	-2.8 (3.51)	-20.1 (3.41)	-29.1 (3.46)
95% CI of LS Mean	-9.7, 4.1	-26.8, -13.3	-36.0, -22.3
Difference (95% CI) in LS Mean (vs Placebo)	—	-17.3 (-26.9, -7.6)	-26.4 (-36.1, -16.6)
P-value (vs Placebo)	—	< 0.001	< 0.001[a]
Reticulocytes %			
Number of Subjects Included in the MMRM	91	92	88
N at Week 24	70	76	73
LS Mean Percent Change in Reticulocyte % from Baseline to Week 24 (SE)	6.8 (4.73)	-1.4 (4.65)	-18.0 (4.70)
Reticulocytes % (continued)			
95% CI of LS Mean	-2.5, 16.1	-10.6, 7.7	-27.2, -8.7
Difference (95% CI) in LS Mean (vs Placebo)	—	-8.3 (-21.3, 4.8)	-24.8 (-37.9, -11.6)
P-value (vs Placebo)	—	0.215	< 0.001[a]
Absolute Reticulocytes			
Number of Subjects Included in the MMRM	91	92	88
N at Week 24	70	76	73
LS Mean Percent Change in Absolute Reticulocytes from Baseline to Week 24 (SE)	4.7 (5.19)	4.7 (5.13)	-6.4 (5.17)
95% CI of LS Mean	-5.6, 14.9	-5.4, 14.8	-16.5, 3.8
Difference (95% CI) in LS Mean (vs Placebo)	—	0.0 (-14.3, 14.4)	-11.0 (-25.4, 3.4)
P-value (vs Placebo)	—	0.995	0.134
LDH			
Number of Subjects Included in the MMRM	87	90	88
N at Week 24	70	74	73

Parameter	Placebo QD N = 92	Voxelotor 900 mg QD N = 92	Voxelotor 1500 mg QD N = 90
LS Mean Percent Change in LDH from Baseline at Week 24 (SE)	3.0 (3.75)	1.6 (3.68)	-4.6 (3.69)
95% CI of LS Mean	-4.4, 10.4	-5.7, 8.8	-11.8, 2.7
Difference (95% CI) in LS Mean (vs Placebo)	—	-1.4 (-11.7, 9.0)	-7.5 (-17.9, 2.8)
P-value (vs Placebo)	—	0.791	0.154

Abbreviations: CI, confidence interval; HU, hydroxyurea; ITT, Intent-to-Treat; LDH, lactate dehydrogenase; LS, least-squares; MMRM, mixed-effect model for repeated measures; QD, once daily; RBC, red blood cell; SCD, sickle cell disease; SE, standard error.
Note: Baseline is the average of all values on or prior to randomisation. All data through Week 72 are included in the model. The MMRM model includes treatment, study visit, treatment by visit interaction, baseline HU use, age group, and region as fixed-effect terms, and baseline value as a covariate, and uses an unstructured covariance matrix for within-subject variability. The summary omitted laboratory assessments after postrandomisation initiation of HU (for subjects with no HU use at baseline), the withdrawal of consent, and the end of study date. Laboratory assessments within 8 weeks post–RBC transfusion, for any reason, were imputed by the last laboratory value prior to the transfusion.
a Statistically significant per prespecified testing hierarchy.

Table 29 Analysis of percentage change from baseline at weeks 48 and 72 in indirect bilirubin, reticulocyte percentage, absolute reticulocytes, and lactate dehydrogenase—ITT Population

	Week 48			Week 72		
	Placebo (N = 92)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N = 90)	Placebo (N = 92)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N = 90)
Indirect Bilirubin						
Number of Subjects Included in the MMRM	85	88	85	85	88	85
N	57	63	56	52	57	53
LS Mean Percentage Change from Baseline (SE)	3.4 (4.02)	-17.9 (3.84)	-26.2 (4.04)	2.7 (4.89)	-15.2 (4.68)	-23.9 (4.86)
95% CI of LS Mean	(-4.5, 11.3)	(-25.5, -10.3)	(-34.2, -18.3)	(-7.0, 12.3)	(-24.4, -6.0)	(-33.5, -14.3)
Difference (95% CI) in LS Mean (vs Placebo)	—	-21.3 (-32.3, -10.3)	-29.6 (-40.9, -18.4)	—	-17.9 (-31.2, -4.5)	-26.6 (-40.2, -12.9)
P-value (vs Placebo)	—	< 0.001	< 0.001	—	0.009	< 0.001

	Week 48			Week 72		
	Placebo (N = 92)	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 90)**	**Placebo (N = 92)**	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 90)**
Reticulocyte Percentage						
Number of Subjects Included in the MMRM	91	92	88	91	92	88
N	63	68	60	57	61	57
LS Mean Percentage Change from Baseline (SE)	1.8 (5.70)	5.5 (5.57)	-3.6 (5.80)	11.0 (5.47)	3.5 (5.35)	-7.6 (5.52)
95% CI of LS Mean	(-9.5, 13.0)	(-5.5, 16.5)	(-15.1, 7.8)	(0.2, 21.8)	(-7.1, 14.0)	(-18.5, 3.3)
Difference (95% CI) in LS Mean (vs Placebo)	—	3.8 (-12.0, 19.5)	-5.4 (-21.4, 10.6)	—	-7.5 (-22.6, 7.6)	-18.6 (-33.9, -3.3)
P-value (vs Placebo)	—	0.638	0.507	—	0.327	0.017
Absolute Reticulocytes						
Number of Subjects Included in the MMRM	91	92	88	91	92	88
N	63	68	59	57	61	57
LS Mean Percentage Change from Baseline (SE)	0.8 (6.20)	15.1 (6.07)	10.0 (6.32)	9.1 (6.30)	14.7 (6.17)	3.4 (6.36)
95% CI of LS Mean	(-11.5, 13.0)	(3.2, 27.1)	(-2.5, 22.4)	(-3.3, 21.5)	(2.5, 26.9)	(-9.2, 15.9)
Difference (95% CI) in LS Mean (vs Placebo)	—	14.4 (-2.7, 31.5)	9.2 (-8.2, 26.6)	—	5.6 (-11.8, 23.0)	-5.8 (-23.4, 11.9)
P-value (vs Placebo)	—	0.099	0.299	—	0.526	0.521
Lactate Dehydrogenase						
Number of Subjects Included in the MMRM	87	90	88	87	90	88
N	63	68	61	58	60	56
LS Mean Percentage Change from Baseline (SE)	2.1 (2.73)	-7.4 (2.64)	-4.8 (2.77)	3.8 (3.19)	-5.6 (3.11)	-1.1 (3.24)
95% CI of LS Mean	(-3.3, 7.5)	(-12.6, -2.2)	(-10.2, 0.7)	(-2.5, 10.0)	(-11.8, 0.5)	(-7.5, 5.3)

	Week 48			Week 72		
	Placebo (N = 92)	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 90)**	**Placebo (N = 92)**	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 90)**
Difference (95% CI) in LS Mean (vs Placebo)	—	-9.5 (-17.0, -2.0)	-6.8 (-14.5, 0.9)	—	-9.4 (-18.2, -0.6)	-4.8 (-13.8, 4.1)
P-value (vs Placebo)	—	0.013	0.081	—	0.036	0.289

Abbreviations: CI, confidence interval; HU, hydroxyurea; ITT, Intent-to-Treat; LDH, lactate dehydrogenase; LS, least-squares; MMRM, mixed-effect model for repeated measures; RBC, red blood cell; SE, standard error.

Note: Baseline is the average of all values on or prior to randomisation. All data through Week 72 are included in the model. The MMRM model includes treatment, study visit, treatment by visit interaction, baseline HU use, age group, and region as fixed-effects terms, and baseline value as a covariate, and uses an unstructured covariance matrix for within-subject variability. The summary omitted laboratory assessments after postrandomisation initiation of HU (for subjects with no HU use at baseline), withdrawal of consent, and end of study. Laboratory assessments within 8 weeks post–RBC transfusion, for any reason, were imputed by the last laboratory value prior to the transfusion.

Annualised Incidence Rate of Vaso-Occlusive Crisis

In the mITT Population, the total number and annualised IR of on-treatment events of VOC were as follows:

- voxelotor 1500 mg (219 events; adjusted IR of 2.4 events/year),
- voxelotor 900 mg (251 events; adjusted IR of 2.4 events/year), and
- placebo (293 events; adjusted IR of 2.8 events/year).

The IR of on treatment VOCs was also analysed by subgroups of VOC history prior to study entry. For subjects **with 1 VOC in the prior year**, the adjusted IR of on treatment VOCs was 2.1 events/year in the voxelotor 1500 mg group, 1.6 events/year in the voxelotor 900 mg group, and 2.2 events/year in the placebo group.

For subjects with ***≥ 2 VOCs in the previous year***, the total number of on treatment VOC events were numerically fewer for subjects who received voxelotor 1500 mg group (134 events) compared with the voxelotor 900 mg group (174 events) and placebo group (197 events). The adjusted IR of on treatment VOCs for this subpopulation was 2.5 events/year in the voxelotor 1500 mg group, 3.0 events/year in the voxelotor 900 mg group, and 3.1 events/year in the placebo group.

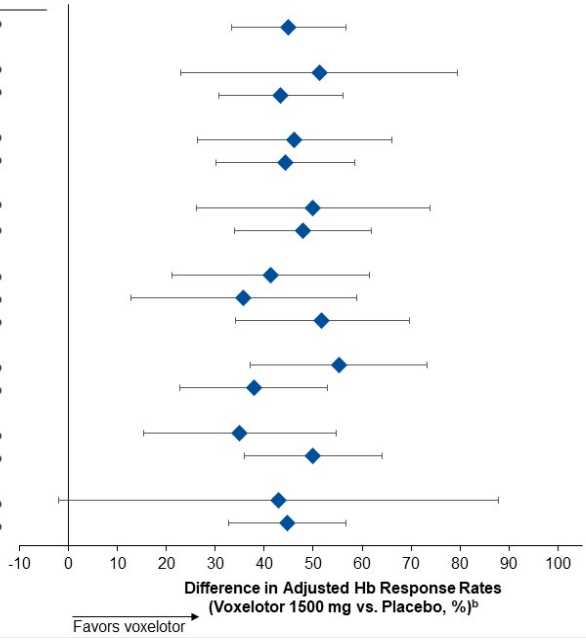
- **Ancillary analyses**

In the pivotal Study GBT440-031, the efficacy of voxelotor based on Hb response at Week 24 was explored across subgroups based on age (12 to < 18 years vs 18 to ≤ 65 years), sex, race (Black or African American vs Arab or Middle Eastern), geographic region (North America vs Europe vs Other), VOC history (1 episode vs ≥ 2 episodes within previous 12 months), baseline HU use (yes vs no), and anaemia severity (baseline Hb < 7 vs ≥ 7 g/dL).

A consistent treatment benefit with respect to Hb response rate at Week 24 (voxelotor 900 mg and 1500 mg vs placebo) was observed across all subgroups examined (Figure 12 , only data for voxelotor 1500 mg is shown).

Figure 12 Study GBT440-031: Haemoglobin response at week 24 by subgroup (voxelotor 1500 mg vs placebo) in adults and paediatric subjects 12 years and older with SCD (ITT Population)

	Placebo		Voxelotor 1500 mg	
	N	Response Rate[a]	N	Response Rate[a]
ITT (Groups 1 and 2)	92	6.5%	90	51.1%
Age				
12 to <18 years	17	5.9%	14	57.1%
18 to 65 years	75	6.7%	76	50.0%
Sex				
Male	42	9.5%	32	56.3%
Female	50	4.0%	58	48.3%
Race				
Arab or Middle Eastern	20	5.0%	20	55.0%
Black or African American	63	4.8%	59	52.5%
Geographic Region				
North America	35	11.4%	34	52.9%
Europe	18	0%	19	36.8%
Other	39	5.1%	37	56.8%
VOC History (prior 12 months)				
1 episode	39	5.1%	35	60.0%
≥2 episodes	53	7.5%	55	45.5%
Baseline HU Use				
No	34	8.8%	32	43.8%
Yes	58	5.2%	58	55.2%
Baseline Hb				
<7 g/dL	7	14.3%	7	57.1%
≥7 g/dL	85	5.9%	83	50.6%



Abbreviations: CI, confidence interval; Hb, haemoglobin; HU, hydroxyurea; ITT, Intent-to-Treat; SCD, sickle cell disease; VOC, vaso-occlusive crisis.
[a] Data presented are observed (unadjusted) percentages.
[b] Difference and associated CIs are from pairwise comparisons adjusted for baseline HU use, as applicable. Unadjusted differences and associated CIs are presented for subgroups of 12 to < 18 years of age, Arab and Middle Eastern race, and baseline Hb < 7 g/dL due to small sample size.

- ## Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 30 Summary of efficacy for trial GBT440-031

Title: A PHASE 3, DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED, MULTICENTER STUDY OF VOXELOTOR ADMINISTERED ORALLY TO PATIENTS WITH SICKLE CELL DISEASE	
Study identifier	Protocol Number: GBT440-031 EudraCT Number: 2016-003370-40
Design	Study GBT440-031 was a double-blind, randomised, placebo-controlled, multicentre study of subjects aged 12 to 65 years with sickle cell disease (SCD), including Hb sickle cell disease with 2 sickle cell genes (HbSS), Hb sickle cell disease with 1 HbS sickle cell gene and 1 haemoglobin C gene

	(HbSC), HbSβ thalassemia, or other sickle cell syndrome variants. Subjects were randomised in a 1:1:1 ratio to voxelotor 900 mg once daily (QD), voxelotor 1500 mg QD, or placebo.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		72 weeks not applicable not applicable
Hypothesis	Superiority		
Treatment groups	Placebo		Placebo QD up to 72 weeks 92 subjects randomised
	Voxelotor 900 mg		Voxelotor 900 mg QD up to 72 weeks 92 subjects randomised
	Voxelotor 1500 mg		Voxelotor 1500 mg QD up to 72 weeks 90 subjects randomised
Endpoints and definitions	Primary endpoint	Hb Response rate at Week 24	Hb response is defined as an increase of Hb from baseline by > 1 g/dL at 24 weeks. Hb at 24 weeks is determined by the average value of Hb levels at Week 20 and Week 24.
	Secondary	Change from baseline in Hb at Week	Change from baseline in Hb at Week 24
	Secondary	Change from baseline in measures of haemolysis	Change and percent change from baseline in measures of haemolysis including unconjugated bilirubin, absolute reticulocytes, reticulocytes %, and lactate dehydrogenase (LDH) at Week 24
	Secondary	Annualised incidence rate (IR) of vaso-occlusive	Annualised IR of VOC over 72 weeks
	Exploratory	Clinical Global Impression of Change (CGIC) at	Clinical Global Impression (CGIC)
Database lock	22 November 2019		
Results and Analysis			
Analysis description	**Primary Analysis (prespecified): Hb response rate (increase of > 1 g/dL from Baseline) at Week 24**		
Analysis population and time point description	Intent-to-treat (ITT): all randomised subjects Time point: 24 weeks		

Descriptive statistics and estimate variability	Treatment group	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg
	Number of subjects	92	92	90
	Responders: n (%)	6 (6.5)	30 (32.6)	46 (51.1)
Effect estimate per comparison	Primary endpoint: Hb response rate	Comparison groups		Voxelotor 1500 mg vs placebo
		Difference in adjusted response rates (%)		45.0
		95% confidence interval for difference		33.4, 56.7
		P-value (CMH)		< 0.001
	Primary endpoint: Hb response rate	Comparison groups		Voxelotor 900 mg vs placebo
		Difference in adjusted response rates (%)		26.4
		95% confidence interval for difference		15.5, 37.3
		P-value (CMH)		< 0.001
Notes	The Hb response rate at Week 24 was analysed using an exact Cochran-Mantel-Haenszel (CMH) general association test. Each voxelotor dose group (900 mg or 1500 mg) was compared to placebo while stratifying for the randomisation stratification factors of hydroxyurea (HU) use, age group (< 18 vs 18 to 65 years old), and geographic region (North America, Europe, or Other)			
Analysis description	**Exploratory Analysis (prespecified): Change from baseline in Hb at Week 72**			
Analysis population and time point description	Intent-to treat (ITT): all randomised subjects Time point: 72 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg
	Number of subjects randomised	92	92	90
	Number of subjects in mixed effect model for repeated measures (MMRM) analysis	91	92	88
	Least squares (LS) mean change in	0.02	0.54	1.02

	Hb from baseline at Week 72 (g/dL)			
	Standard error (SE)of LS mean	0.148	0.143	0.149
	95% CI of LS Mean	-0.27, 0.32	0.25, 0.82	0.72, 1.31
Effect estimate per comparison	Exploratory endpoint: Change from baseline in Hb at Week 72 (g/dL)	Comparison groups		Voxelotor 1500 mg vs placebo
		Difference in LS Mean (vs Placebo)		0.99
		95% CI for difference		0.58, 1.41
		P-value (MMRM)		< 0.001
	Exploratory endpoint: Change from baseline in Hb at Week 72 (g/dL)	Comparison groups		Voxelotor 900 mg vs placebo
		Difference in LS Mean (vs Placebo)		0.51
		95% CI for difference		0.11, 0.92
		P-value (MMRM)		0.014
Notes	The MMRM model included treatment, study visit, treatment by visit interaction, baseline HU use, age group, and geographic region as fixed effect terms, and baseline value as a covariate, and used an unstructured covariance matrix for within subject variability. All visits through Week 72 were included in the model. The summary omitted laboratory assessments after post-randomisation initiation of HU (for subjects with no HU use at baseline), the withdrawal of consent, and the end of study date. Laboratory assessments within 8 weeks post–RBC transfusion, for any reason, were imputed by the last laboratory value prior to the transfusion.			
Analysis description	**Exploratory Analysis (prespecified): Percent change from baseline in measures of haemolysis at Week 72 (indirect bilirubin)**			
Analysis population and time point description	Intent-to treat (ITT): all randomised subjects Time point: 72 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg
	Number of subjects	92	92	90
	Number of subjects in MMRM	85	88	85
	LS Mean percent change from baseline in indirect bilirubin at Week 72	2.7	-15.2	-23.9

	SE of LS mean	4.89	4.68	4.86
	95% CI of LS	-7, 12.3	-24.4, -6	-33.5, -14.3
Effect estimate per comparison	Exploratory endpoint: Percent change from baseline in indirect bilirubin at Week 72	Comparison groups		Voxelotor 1500 mg vs placebo
		Difference in LS Mean (vs Placebo)		-26.6
		95% CI for difference		-40.2, -12.9
		P-value (MMRM)		< 0.001
	Exploratory endpoint: Percent change from baseline in indirect bilirubin at Week 72	Comparison groups		Voxelotor 900 mg vs placebo
		Difference in LS Mean (vs Placebo)		-17.9
		95% CI for difference		-31.2, -4.5
		P-value (MMRM)		0.009
Notes	The MMRM model included treatment, study visit, treatment by visit interaction, baseline HU use, age group, and geographic region as fixed effect terms, and baseline value as a covariate, and used an unstructured covariance matrix for within subject variability. All visits through Week 72 were included in the model. The summary omitted laboratory assessments after postrandomisation initiation of HU (for subjects with no HU use at baseline), the withdrawal of consent, and the end of study date. Laboratory assessments within 8 weeks post–RBC transfusion, for any reason, were imputed by the last laboratory value prior to the transfusion.			
Analysis description	**Exploratory Analysis (prespecified): Percent change from baseline in measures of haemolysis at Week 72 (reticulocytes %)**			
Analysis population and time point description	Intent-to treat (ITT): all randomised subjects Time point: 72 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg
	Number of subjects	92	92	90
	Number of subjects in MMRM	91	92	88
	LS mean % change from baseline in reticulocytes % at Week 72	11	3.5	-7.6
	SE of LS mean	5.47	5.35	5.52
	95% CI of LS Mean	0.2, 21.8	-7.1, 14	-18.5, 3.3

Effect estimate per comparison	Exploratory endpoint: % change from baseline in reticulocytes % at Week 72	Comparison groups		Voxelotor 1500 mg vs placebo
		Difference in LS Mean (vs Placebo)		-18.6
		95% CI for difference		-33.9, -3.3
		P-value (MMRM)		0.017
	Exploratory endpoint: % change from baseline in reticulocytes % at Week 72	Comparison groups		Voxelotor 900 mg vs placebo
		Difference in LS Mean (vs Placebo)		-7.5
		95% CI for difference		-22.6, 7.6
		P-value (MMRM)		0.327
Notes	The MMRM model included treatment, study visit, treatment by visit interaction, baseline HU use, age group, and geographic region as fixed effect terms, and baseline value as a covariate, and used an unstructured covariance matrix for within subject variability. All visits through Week 72 were included in the model. The summary omitted laboratory assessments after post-randomisation initiation of HU (for subjects with no HU use at baseline), the withdrawal of consent, and the end of study date. Laboratory assessments within 8 weeks post–RBC transfusion, for any reason, were imputed by the last laboratory value prior to the transfusion.			
Analysis description	**Exploratory Analysis (prespecified): Percent change from baseline in measures of haemolysis at Week 72 (absolute reticulocytes)**			
Analysis population and time point description	Intent-to treat (ITT): all randomised subjects Time point: 72 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg
	Number of subjects	92	92	90
	Number of subjects in MMRM	91	92	88
	LS mean % change from baseline in absolute reticulocytes at Week 72	9.1	14.7	3.4
	SE of LS mean	6.30	6.17	6.36
	95% CI of LS Mean	-3.3, 21.5	2.5, 26.9	-9.2, 15.9

Effect estimate per comparison	Exploratory endpoint: Percent change from baseline in absolute reticulocytes at Week 72	Comparison groups		Voxelotor 1500 mg vs placebo
		Difference in LS Mean (vs Placebo)		-5.8
		95% CI for difference		-23.4, 11.9
		P-value (MMRM)		0.521
	Exploratory endpoint: % change from baseline in absolute reticulocytes at Week 72	Comparison groups		Voxelotor 900 mg vs placebo
		Difference in LS Mean (vs Placebo)		5.6
		95% CI for difference		-11.8, 23.0
		P-value (MMRM)		0.526
Notes	The MMRM model included treatment, study visit, treatment by visit interaction, baseline HU use, age group, and geographic region as fixed effect terms, and baseline value as a covariate, and used an unstructured covariance matrix for within subject variability. All visits through Week 72 were included in the model. The summary omitted laboratory assessments after post-randomisation initiation of HU (for subjects with no HU use at baseline), the withdrawal of consent, and the end of study date. Laboratory assessments within 8 weeks post–RBC transfusion, for any reason, were imputed by the last laboratory value prior to the transfusion.			
Analysis description	**Exploratory Analysis (prespecified): Percent change from baseline in measures of haemolysis at Week 72 (LDH)**			
Analysis population and time point description	Intent-to treat (ITT): all randomised subjects Time point: 72 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg
	Number of subjects	92	92	90
	Number of subjects in MMRM	87	90	88
	LS mean percent change from baseline in LDH at Week 72	3.8	-5.6	-1.1
	SE of LS mean	3.19	3.11	3.24
	95% CI of LS Mean	-2.5, 10.0	-11.8, 0.5	-7.5, 5.3

Effect estimate per comparison	Exploratory endpoint: % change from baseline in LDH at Week 72	Comparison groups		Voxelotor 1500 mg vs placebo
		Difference in LS Mean (vs Placebo)		-4.8
		95% CI for difference		-13.8, 5.3
		P-value (MMRM)		0.289
	Exploratory endpoint: % change from baseline in LDH at Week 72	Comparison groups		Voxelotor 900 mg vs placebo
		Difference in LS Mean (vs Placebo)		-9.4
		95% CI for difference		-18.2, -0.6
		P-value (MMRM)		0.036
Notes	The MMRM model included treatment, study visit, treatment by visit interaction, baseline HU use, age group, and geographic region as fixed effect terms, and baseline value as a covariate, and used an unstructured covariance matrix for within subject variability. All visits through Week 72 were included in the model. The summary omitted laboratory assessments after postrandomisation initiation of HU (for subjects with no HU use at baseline), the withdrawal of consent, and the end of study date. Laboratory assessments within 8 weeks post–RBC transfusion, for any reason, were imputed by the last laboratory value prior to the transfusion.			
Analysis description	**Secondary Analysis (prespecified): Annualised IR of VOC over 72 weeks**			
Analysis population and time point description	Modified Intent-to treat (mITT): Excludes 3 randomised subjects (1 in placebo group and 2 in voxelotor 1500 mg group) who were not treated Time point: up to 72 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg
	Number of subjects	92	92	90
	Number of subjects in mITT	91	92	88
	Total person-years (on treatment)	100.4	107.3	96.8
	Subjects with any VOCs postbaseline, n (%)	70 (76.9)	64 (69.6)	61 (69.3)
	Total number of events	293	251	219

	Adjusted annualised IR (events/year)	2.787	2.395	2.374
	95%CI of adjusted IR	2.185, 3.556	1.871, 3.065	1.835, 3.071
Effect estimate per comparison	Secondary endpoint: Annualised IR of VOC over 72 weeks	Comparison groups		Voxelotor 1500 mg vs placebo
		IRR vs placebo		0.852
		95% CI for IRR vs placebo		0.598, 1.213
		P-value (negative binomial regression)		0.373
	Secondary endpoint: Annualised IR of VOC over 72 weeks	Comparison groups		Voxelotor 900 mg vs placebo
		IR ratio (IRR) vs placebo		0.859
		95% CI for IRR vs placebo		0.607, 1.217
		P-value (negative binomial regression)		0.394
Notes	The number of VOC events was modelled using a negative binomial regression model with the independent variable of treatment group and adjusted for baseline HU use, age group, and geographic region. The P-value describes testing the null hypothesis: IRR = 1 (vs Placebo).			
Analysis description	**Exploratory Analysis (prespecified): CGIC at Week 72**			
Analysis population and time point description	Intent-to treat (ITT): all randomised subjects Time point: 72 weeks			
Descriptive statistics and estimate variability	Treatment group	Placebo	Voxelotor 900 mg	Voxelotor 1500 mg
	Number of subjects	92	92	90
	Number of subjects at	51	58	53
	Moderately or very much improved CGIC from baseline at Week 72: n (%)	24 (47.1)	32 (55.2)	39 (73.6)

Effect estimate per comparison	Exploratory endpoint: Percent of subjects with moderately or very much improved CGIC from baseline at Week 72	Comparison groups	Voxelotor 1500 mg vs placebo
		Difference in % (vs placebo)	26.5%
		95% CI for difference	8.4, 44.7
		P-value (Chi-square test)	0.006
	Exploratory endpoint: Percent of subjects with moderately or very much improved CGIC from baseline at Week 72	Comparison groups	Voxelotor 900 mg vs placebo
		Difference in % (vs placebo)	8.1
		95% CI for difference	-10.6, 26.9
		P-value (Chi-square test)	0.398
Notes			

Note: Secondary endpoints "the change from baseline in Hb at Week 24" and "the percent change from baseline in measures of haemolysis at Week 24" are not presented in the table. However, they can be found in the section 3.3.1 "Results" in the Clinical AR.

2.6.5.3. Clinical studies in special populations

The maximum age of the patients included into the voxelotor clinical programme was 64. Paediatric subjects ≥12 years of age were included in the pivotal trial, as well as a separate paediatric study GBT440- 007.

Study GBT440- 007 Part B

Study GBT440 007 is an ongoing Phase 2a, multicentre, open label study of voxelotor in paediatric subjects with SCD. The study is composed of 4 parts; only efficacy data from the multiple dose Part B is discussed here. Part B was designed to evaluate the safety, tolerability, and PK of voxelotor and to provide supportive evidence of the efficacy of voxelotor 900 or 1500 mg administered QD for 24 weeks in paediatric subjects 12 to < 18 years old with SCD (HbSS or HbSβ0 thalassemia) and Hb levels ≤ 10.5 g/dL. This part of the study is currently completed.

In total, 25 subjects were involved in the voxelotor 900 mg group and 15 subjects in voxelotor 1500 mg group. The median age of participants was 14 years of age, normal weight and, similar to the pivotal GBT440-031 study, most of the participants were Black or African American, had HbSS genotype and used HU at baseline. Around 50% of participants had a history of pain crisis and >60% had a history of ACS. Median baseline Hb levels were: 8.9 (6.3, 11.0) in the voxelotor 900 mg group and 8.8 (6.2, 10.6) in the voxelotor 1500 group. Reticulocyte or indirect bilirubin levels were not part of the inclusion criteria. However, all adolescents had increased reticulocyte % at the time of the enrolment.

Efficacy assessments included clinical measures of anaemia (Hb) and haemolysis (reticulocyte percentage, indirect bilirubin, and LDH).

Consistent with the results of the pivotal study, improvements in Hb were observed as early as Week 2 with voxelotor treatment and were maintained through Week 24: median change in Hb was 0.7 g/dL for both treatment groups. Concurrent improvements in haemolysis measures (reticulocyte percentage, indirect bilirubin, and LDH) were observed at Week 24: decrease in reticulocyte % at 24 weeks was 17.4% (-35.6, -36.5), decrease in indirect bilirubin was - 42.8% (-50.5, -15.4), and decrease in LDH was -5.8% (-12.5, 11.7) in the voxelotor 1500 mg group.

2.6.5.4. Supportive studies

Study GBT440- 034 (OLE study of pivotal study GBT440-031)

Study GBT440-034 is an ongoing open-label extension (OLE) study for subjects 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), are receiving voxelotor 1500 mg once daily.

Long-term efficacy and safety data as of 31 December 2020 from Study GBT440-034 were provided. A total of 179 subjects were enrolled and 178 subjects have been treated with voxelotor 1500 mg in Study GBT440 034; 43.8% (78/178) of subjects have completed 72 weeks of treatment, and 11.8% (21/178) of subjects have completed 96 weeks of treatment in Study GBT440-034. Of the 78 subjects with ≥ 72 weeks of treatment in this study, 52 subjects received up to 72 weeks of treatment with voxelotor previously in the antecedent Study GBT440-031 for a cumulative voxelotor treatment duration of ≥ 144 weeks. As of the data cut-off date, 100 subjects remain ongoing in this study.

Haemoglobin

The effect of voxelotor on Hb increase showed durability. For subjects who previously received voxelotor 900 mg or 1500 mg, the mean Hb level was 9.0 g/dL and 9.5 g/dL, respectively, prior to dosing in Study GBT440-034. After receiving voxelotor 1500 mg in GBT440-034, the mean change from GBT440-034 baseline was 0.7 g/dL and 0.2 g/dL, respectively, at Week 48. Subjects who previously received placebo in Study GBT440-031 had an improvement in Hb over time in Study GBT440-034 compared to baseline: the mean Hb level was 8.8 g/dL prior to dosing in Study GBT440-034 and the mean change from baseline in Hb was 1.4 g/dL, 0.9 g/dL, and 1.3 g/dL at Weeks 12, 24, and 48, respectively.

Haemolysis markers

Significant decrease in indirect bilirubin levels observed in voxelotor groups in the main Study GBT440-031 was sustained in the OLE study. Patients who switched from placebo in study GBT440-031 to voxelotor 1500 mg showed similar decrease in indirect bilirubin levels as patients on voxelotor 1500 mg in the Study GBT440-031. Thus, the mean percentage change from baseline at 48 weeks in the OLE study was -39.5 (SD, 40.96), -2.0 (66.13) and 1.1 (85.55) for patients who received placebo, voxelotor 900 mg and voxelotor 1500 mg in the Study GBT440-031, respectively.

The decrease in % reticulocyte observed in the Study GBT440-031 continued to be seen in the OLE study. The mean percentage change from baseline at 48 weeks was -28.6 (SD, 55.29), -14.6 (56.25) and -21.0 (81.29)

for patients who received placebo, voxelotor 900 mg and voxelotor 1500 mg in the Study GBT440-031, respectively. A slight decrease in the absolute reticulocyte number was observed in the OLE study, with the decrease being more pronounced in the groups that previously received placebo and voxelotor 900 mg in the pivotal study compared to voxelotor 1500 mg. The mean percentage change from baseline at 48 weeks was -17.4 (SD, 45.33), -17.0 (55.92) and -12.0 (58.12) for patients who received placebo, voxelotor 900 mg and voxelotor 1500 mg in the Study GBT440-031, respectively.

For LDH, the mean percentage change from baseline at 48 weeks was -4.7 (38.03), 2.0 (26.41) and -1.3 (31.38) for patients who received placebo, voxelotor 900 mg and voxelotor 1500 mg in the Study GBT440-031, respectively.

VOC

In the mITT Population, the total number and annualised IR of on treatment events of VOC were as follows:

- voxelotor 1500 mg (86 events; adjusted IR of 1.1 events/year),
- voxelotor 900 mg (71 events; adjusted IR of 1.0 events/year), and
- placebo (129 events; adjusted IR of 1.7 events/year).

2.6.6. Discussion on clinical efficacy

The application is based on efficacy data from a single pivotal trial (GBT440-031), an open-label extension of the pivotal trial (GBT440-034) and Phase 2a study in paediatric patients (GBT440-007). The data from phase 1 study GBT440-001 and its open-label extension (GBT440-024) were used for dose determination for the Phase 3 study.

Dose selection. No formal dose-finding study was performed. Instead, the doses for the pivotal study GBT440-031 of 900 mg and 1500 mg were determined based on the data from phase 1 Study GBT440-001, where the maximum multiple dose tested was 900 mg (>90 days) and 1000 mg (28 days) QD. The % Hb occupancy target of >20% was used for dose selection, as potentially being of significant clinical benefit from reducing HbS polymerisation. The rationale for this target is based on the knowledge that in patients with both HbS and hereditary persistence of foetal haemoglobin (s/HPFH), the dilution of HbS by the presence of 20% to 30% foetal haemoglobin (HbF) in all RBCs suffices to inhibit Hb polymerisation. The increase in Hb and reduction in haemolysis markers was seen with 900 mg QD dose. However, the majority of patients did not reach the % Hb occupancy target of 20-30% and no plateau was reached with respect to the effect on haemolysis markers in SCD patients with the doses tested in the GBT440-001 study. Based on the population pharmacokinetic and PK/PD analyses of data from the Phase 1 Study GBT440-001, a prediction was made that with the dose of 1500 mg the % Hb occupancy target of >20% will be reached for 76% of subjects. Also, the model predicted a larger beneficial response on haemolysis markers with 1500 mg dose compared to 900 mg dose. As a result, based on this modelling, two doses were chosen to be tested in Phase 3 study – 900mg and 1500 mg. The approach used to determine the doses for Phase 3 studies is not considered optimal, but the model predictions with respect to %Hb occupancy were confirmed in the pivotal phase 3 trial. The predicted effects of the 1500 mg dose on haemolysis markers (e.g. -66% and -84% decrease in indirect bilirubin and % reticulocytes, respectively), however, were not all achieved in the pivotal trial.

Design and conduct of the main clinical study (GBT440-031)

Study GBT440-031 was a double-blind, randomised, placebo-controlled, multicentre study of subjects aged 12 to 65 years with sickle cell disease (SCD), including haemoglobin (Hb) sickle cell disease with 2 sickle cell genes (HbSS), haemoglobin sickle cell disease with 1 HbS sickle cell gene and 1 haemoglobin C gene (HbSC), HbSβ thalassemia, or other sickle cell syndrome variants. This study used placebo as a comparator on the background of best clinical standard-of-care treatment, including hydroxyurea (HU), which is considered appropriate. The dose of HU used needed to be stable before study entry. Subjects were randomly assigned to receive voxelotor 900 mg, voxelotor 1500 mg, or matching placebo QD on the background of best clinical standard-of-care treatment for up to 72 weeks. Clinical standard of care included pain control, HU, L-glutamine, blood transfusions. Subject randomisation was stratified by concomitant hydroxyurea (HU) use, geographic region, and age group.

The **trial population** is reflective of the population with SCD and is adequate to evaluate the proposed indication. In order to evaluate secondary endpoint – VOC (vaso-occlusive crisis) rates – the study was enriched with patients who had at least 1 VOC in the previous 12 months. The required minimum baseline VOC rate is considered low to allow the evaluation of beneficial effect of voxelotor on VOC rates. In general, the currently proposed indication reflects the study population. However, several modifications to the wording of the indication were accepted in the second round of assessment in order to better specify the origin of the haemolytic anaemia (i.e. due to SCD) and to reflect that voxelotor can be used as monotherapy or in combination with hydroxycarbamide.

Haemolytic anaemia is a hallmark of SCD. Therefore, Hb and haemolysis endpoints are relevant endpoints and can support efficacy in the claimed indication. The **primary endpoint** was the percentage of subjects achieving an increase of > 1 g/dL in Hb from baseline to Week 24. The size of the benefit and clinical relevance of this increase might depend upon baseline levels and individual tolerance to anaemia. Nevertheless, it can be agreed that an increasing in Hb levels > 1g/dL is likely to be relevant. However, uncertainties were raised with respect to the anticipated beneficial effects of the Hb increase in patients with SCD, considering the MoA of voxelotor. It was not clear if the increase in stabilised Hb (the pharmacodynamic effect that accounts for the observed total Hb increase) translates into better tissue oxygenation, since stabilised Hb by voxelotor may release oxygen less easily. The duration of 24 weeks treatment used for assessment of the primary endpoint is quite short to establish the sustainability of the beneficial effect. However, Hb change from baseline at week 48 and 72 are listed as **exploratory endpoints** to support the primary endpoint. Other **secondary endpoints** (haemolysis markers and VOC rates) and exploratory endpoints are all relevant to evaluate the clinical impact of the observed Hb increase and are supported. As SCD is a chronic disease characterised by chronic pain and end-organ damage, the inclusion of PROs are of importance.

Initially, the Study GBT440-031 was designed as a seamless adaptive design trial to investigate and select the most effective dose and then confirm it. Therefore, in the original protocol, the study population was divided in three groups: Group 1 (60 patients) was to be used to choose a dose for the confirmatory part of the trial (Group 3). Group 2 was designed to allow continued enrolment between Group 1 and Group 3. The Group 3 and the patients on the selected dose in the Group 2, who were not included in the interim analysis, were to be used for the Primary Analysis. Two interim analyses took place: first interim analysis to analyse the data from Group 1 and second interim analysis to analyse the data from Groups 1+ Group 2a. Following the second interim analysis, the latest **protocol amendment#4** was implemented that brought substantial changes to the study design. The primary analysis is currently performed on the participants from Group 1 and Group 2

combined (274 subjects in total, including 156 subjects that were used in the second interim analysis), with Group 3 not being used at all in the primary analysis. Group 3 was not open for enrolment. The **sample size** for the total study was changed in protocol amendment #4 based on the results of the second interim analysis. Since the sample size adjustment was downwards (from 370 to 274), was based on interim data with an information fraction of 57% and the amendment allowed the interim data to be incorporated in the final dataset rather than using patients after the interim to confirm the interim results, this results in an inflation of the type I error rate. However, since the primary endpoint is highly significant for both the total population and the 'confirmatory' Group 2b, this is not further pursued.

A number of secondary endpoints were changed following protocol amendment #4, and a new endpoint, CGIC (Clinical Global Impression – Improvement scale), was added to the protocol. Introduction of this scale at a later time point in the study reduces the reliability of this endpoint. Overall, considering the number and the nature of the protocol amendments, as well as their timing in relation to the interim analysis and general study timeline, unblinding of certain sponsor members, there was a concern that the changes might have been data-driven. Whatsoever the primary Hb endpoint, as well as haemolysis endpoint are objective markers offer sufficient reassurance. However some of the other secondary endpoints are less objective (e.g. CGIC, PRO's) and, therefore, need to be interpreted with caution.

Analysis sets and the **statistical analysis.** The definitions of the analysis populations are considered standard and acceptable. The analysis model for the primary endpoint, Hb response, uses the Cochran-Mantel-Haenszel test, adjusting for the randomisation stratification factors, which is considered standard and acceptable. Change from baseline in Hb and haemolysis measurements were analysed using mixed-effects model for repeated measures (MMRM) including visit, treatment by visit interaction, baseline and stratification factors. Haemolysis measurements were analysed using a similar MMRM model. This can be an acceptable method as well, provided missing data is handled appropriately. All analyses were adjusted for the randomisation stratification factors, except for the Group 2b analysis, which was only adjusted for baseline HU use due to small sample size. This can be considered acceptable, a sensitivity analysis using all stratification factors did not influence the results.

The incidence rate of VOC events were analysed using a negative binomial model and time to event endpoints (VOC, ACS, pneumonia and RBC transfusion) were analysed using Kaplan Meier. Both are considered appropriate. However, the current analysis excludes VOC events after HU initiation, which may be an optimistic representation. Two sensitivity analyses were performed to test whether omitting data after HU initiation introduced bias: a treatment policy analysis using all data; and a time to VOC analysis with HU initiation as event rather than censored. These analyses did not show any impact of handling HU initiators on the primary VOC analysis.

Hb response was based on the difference between the average two post-baseline levels (week 20 and 24) and baseline. If there was missing data for one of the postbaseline levels, the other level was used, if both were missing, the patient was considered a non-responder. Data collected after non-anaemia related transfusion was set to missing and imputed using LOCF. These are conservative approaches and are considered acceptable. Non-response was also imputed after HU initiation or recent anaemia-related RBC transfusion (8 weeks). Since these two intercurrent events can be seen as treatment failure, non-response imputation is adequate. Several sensitivity analyses were performed: using the mITT population; and imputation after recent transfusion was repeated using 12 weeks instead of 8 as definition of 'recent'.

For change from baseline in haemolysis measurements, missing data after study discontinuation or VOC hospitalisation or data set to missing after HU initiation were all considered missing at random and handled by

the MMRM model. Since discontinuation, VOC and HU initiation are likely treatment related, it is not considered adequate to consider the data afterwards to be missing at random. Measurements after RBC transfusion were imputed using LOCF. Similar sensitivity analyses were performed as for the primary endpoint, additionally, LOCF imputation was used after VOC instead of assuming missing at random. Furthermore, a sensitivity analysis testing the missing data assumption by using a pattern mixture model was performed, using placebo-based imputation after HU initiation, RBC transfusion or study discontinuation. The results differed slightly but the conclusions remain the same, showing that the primary analysis was reasonably robust to the missing data handling.

Multiplicity due to the two interim analyses was handled by a Lan-DeMets alpha spending function using O'Brien-Fleming boundaries. Subsequent multiplicity during the final analysis, due to two doses and primary and secondary endpoints, was handled by a hierarchical testing procedure. Technically, this could provide protection of the type I error rate. However, in this case, type I error rate is not protected, since the multiplicity procedure was informed by, and protocolised after, the interim analyses, the population for the interim analyses was part of the final analysis population, and the ordering of the secondary endpoints was changed after the interim analysis. Therefore, no p-values for the secondary endpoints, suggesting statistical significance, should be mentioned in the product information.

Since the primary endpoint was not amended after the interim analysis, this can still be reported with a p-value. Although there may have been type I error inflation for this endpoint as well, due to the changes in the primary analysis population after the interim, this endpoint is highly significant and the interim analysis was confirmed in Group 2b.

Efficacy data and additional analyses

The **baseline characteristics** of the patients in the placebo and voxelotor groups were in general well balanced.

With regard to the **primary efficacy endpoint**, more subjects treated with voxelotor 1500mg and voxelotor 900mg had an increase in Hb levels >1 g/dL compared to placebo: 51.1%, 32.6% and 6.5% respectively. The response rate was similar in subjects who were or were not receiving HU concurrently. The treatment with voxelotor resulted in a fast (within 2 weeks), statistically significant and sustained (up to 72 weeks) increase in **Hb levels** when compared to baseline levels, as well as to placebo, with 1500 mg dose being more effective compared to 900 mg dose, resulting in the LS mean change in Hb from baseline at 72 weeks of 1.02 g/dL (CI 0.72, 1.31). The observed Hb effects were consistent in the Group1+2a (that was analysed in the second interim analysis) and Group 2b (that was analysed following interim analysis), which is important considering the amendments in the protocol. However, it is not clear to what extent the observed increase in Hb translates into better tissue oxygenation, as difficulties in offloading O_2 in tissue capillaries is seen as competing phenomena that may potentially cancel part of a beneficial effect of voxelotor. These concerns are also strengthened by the *in vitro* and animal studies. However, the annualised **incidence rate of acute anaemic episodes** was 3-fold lower (0.05 vs 0.15 per person years) with voxelotor 1500 mg than placebo.

Further, voxelotor treatment resulted in a rapid decrease in all the haemolysis markers (indirect bilirubin, LDH, reticulocyte % and in absolute numbers) in the initial treatment phase, with the magnitude of the decrease being different for every marker, and indirect bilirubin levels decreasing the most. This initially observed decrease attenuated somewhat over time, achieving a new balance, with the decrease in indirect bilirubin and

slight decrease in % reticulocyte still being significant at 72 weeks. This is expected as indirect bilirubin most directly 121nalyzing121zes haemolysis state, while regulation of other parameters, i.e. reticulocytes, is known to be complex and affected by various factors, including persistent hypoxia. Long-term clinical benefits of voxelotor are yet unclear, as the studies of voxelotor were of short duration and small in size.

The pivotal study was not powered to detect the effect of the treatment on the **VOC rate** and also, about 40% of subjects enrolled in the study had a history of only 1 VOC in the previous 12 months, making the detection of the beneficial effect on VOC incidence more difficult. The percent of subjects without any VOC occurrence on study and VOC rates were comparable between groups. When analyzing subjects with higher baseline annual VOC rate (≥ 2 VOCs), a trend of improvement was observed for subjects who received voxelotor 1500 mg group (134 events) compared to placebo group (197 events).

No effect of the treatment was observed between groups on the **endpoints that reflect disease burden and patient wellbeing**: RBC transfusions, concomitant opioid use or PROs. PRO's baseline scores indicate that the majority of the patients on the study had relatively little limitations, which hampers to detect improvement in these endpoints. The results of the CGIC scale showed improvement on voxelotor treatment. However, the introduction of this subjective endpoint to the study only after amendment #4 reduces the interpretability of the results. The improvement in leg ulceration was noted upon voxelotor treatment. However, the numbers are very low, and the data needs to be interpreted with caution.

The **subgroup analysis** performed for the primary endpoint of Hb increase showed consistency in the efficacy of voxelotor between different groups. Age, race, region, gender, baseline Hb levels or baseline HU use did not have an influence on the voxelotor efficacy based on the 24- and 72-week analysis. No patients >65 years of age were included in the study. An appropriate warning is included in section 4.4 of the SmPC.

The cut-off date of the ongoing extension study of GBT440-031 – OLE GBT440-034 – is 31 December 2020. The data available so far on haemoglobin, haemolysis markers and VOC rates from the OLE GBT440-034 study show durability of the effects that were observed in the main GBT440-031 study for patients who were treated with voxelotor. For patients who switched from placebo to voxelotor, positive trends were observed in haematological parameters, as well as VOC, similar to the pivotal study.

The **dose** of 1500 mg was shown to be more effective compared to 900 mg dose based on the primary Hb endpoint and decrease in indirect bilirubin. Therefore, the choice of this dose to be marketed is supported.

Assessment of paediatric data on clinical efficacy

The data from the **supportive** paediatric study GBT440-007 in patients 12 to < 18 years of age is consistent with the results of the pivotal phase 3 trial GMT440-031 and can be considered supportive.

2.6.7. Conclusions on the clinical efficacy

Efficacy of voxelotor is shown to be superior to placebo in terms of increase in Hb levels and decrease in the haemolysis markers – indirect bilirubin and % reticulocytes. However, the extent to which this Hb increase contributes to better tissue oxygenation is difficult to estimate given the potential difficulty in oxygen offloading

from voxelotor-bound Hb. Long-term clinical benefits of voxelotor were not investigated, as the studies with voxelotor were of short duration and small in size. The decrease in haemolysis and positive trend in the VOC incidence are, however, acknowledged and considered of clinical relevance for the applied target population. Further data are expected from the ongoing open label extension study.

2.6.8. Clinical safety

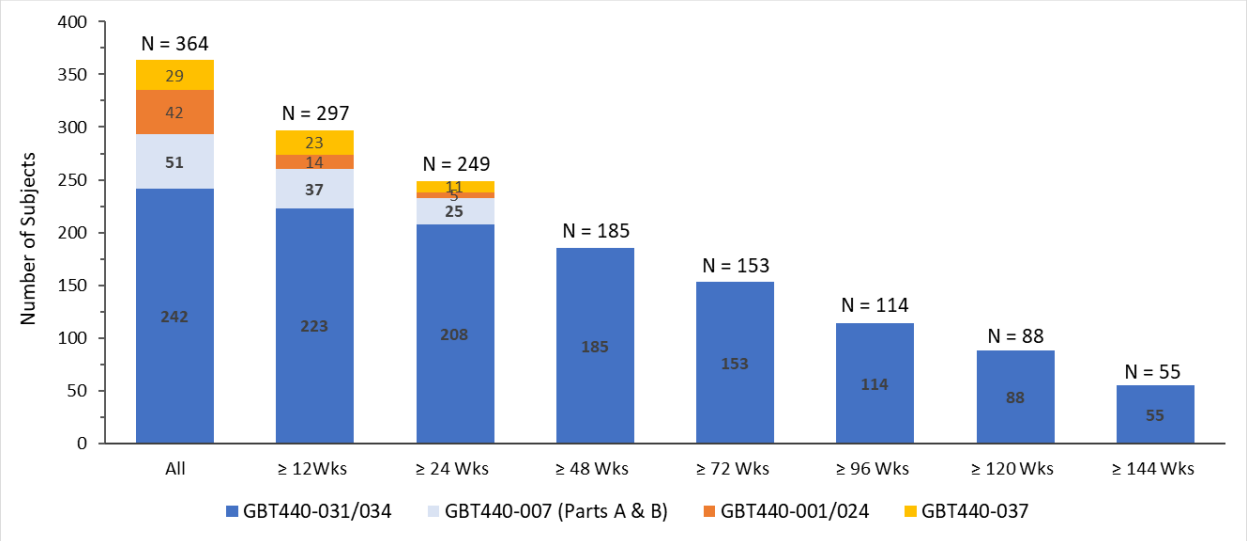
The mean safety data is based on a single **Phase 3 Study GBT440-031**, a randomised, placebo controlled, double blind **72-week** study in adults and paediatric subjects 12 to < 18 years of age, with the safety profile in paediatric subjects 12 to < 18 years of age supported by data from the open-label Phase 2a Study GBT440-007 Part B. Interim data are also available from Study GBT440-034, the ongoing long-term extension (OLE) of Study GBT440-031 (cumulative voxelotor exposure for in total ≥ **144 weeks**).

2.6.8.1. Patient exposure

The overall duration of exposure to voxelotor (all dose levels) for subjects with SCD in Studies GBT440-031, GBT440-034 (data cut-off date of 31 December 2020), GBT440-007 Parts A and B, GBT440-001, GBT440-024, and EAP GBT440-037 is shown in

. By combining data from Study GBT440-031 and the ongoing open-label extension Study GBT440 034, 153 adult and paediatric subjects aged 12 to < 18 years have been exposed to voxelotor for ≥ 72 weeks, and 55 subjects have been exposed to voxelotor for ≥ 144 weeks.

Figure 13 Duration of exposure to voxelotor (all dose levels) in adult and paediatric subjects (12 to < 18 years) with SCD in studies GBT440-031, GBT440-034, GBT440-007 (Parts A and B), GBT440-001, GBT440-024, and EAP GBT440 037



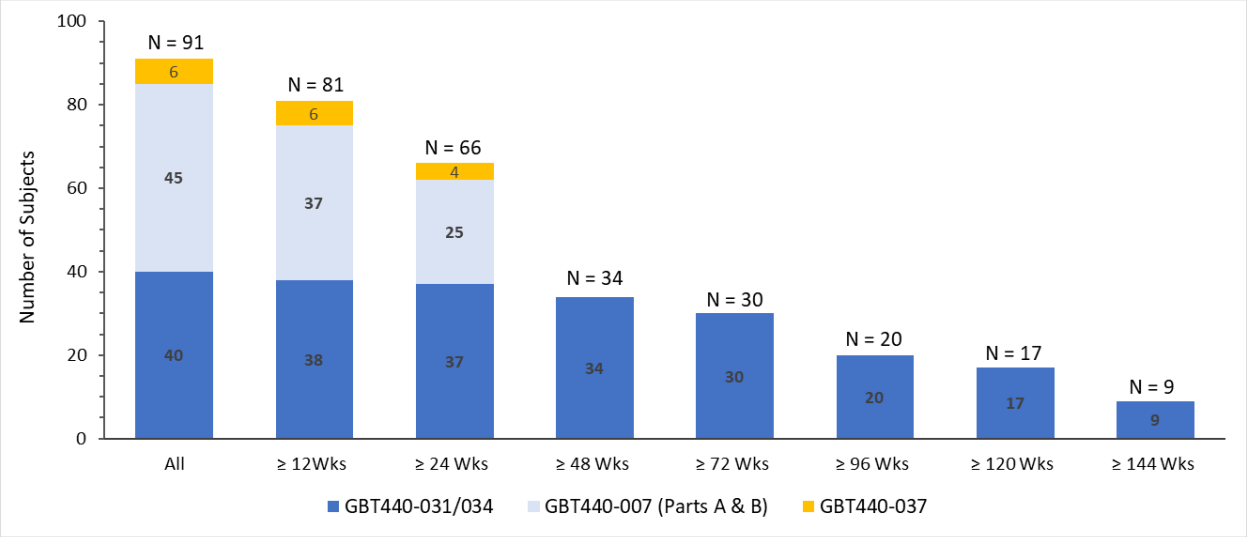
Abbreviations: EAP, expanded access programme; eIND, emergency investigational new drug; SCD, sickle cell disease; SCS, Summary of Clinical Safety.
Note: Voxelotor exposure includes all dose levels. Data cutoff date for Study GBT440-034 is 31 December 2020 and for Study GBT440-037 is 01 October 2020. For subjects who were treated in both Study GBT440-031 and the open-label extension Study GBT440-034, duration of exposure is based on first day of treatment with voxelotor in Study GBT440 031 (or Study GBT440-034 for subjects who received placebo in Study GBT440-031) and last day of exposure in Study GBT440-034. Of the 55 subjects with ≥ 144 weeks of voxelotor exposure, 52 subjects had approximately 72 weeks in Study GBT440-031 and ≥ 72 weeks in Study GBT440-034, and 3 subjects had > 72 weeks in Study GBT440-031 and < 72 weeks in Study GBT440-034. In the expanded access programme (collection of single-patient, investigator-sponsored eIND protocols), an additional nine subjects were exposed to voxelotor for a total of 20.1 subject-years. Data cutoff date for the collection of single-patient, investigator-sponsored eIND protocols is 20 October 2020.

Exposure in paediatric patients

The overall duration of exposure to voxelotor (all dose levels) for paediatric subjects aged 12 to < 18 years in SCD Studies GBT440-031, GBT440-034 (data cut-off date of 31 December 2020), GBT440-007 Parts A and B, and EAP GBT440-037 is shown in table below.

. In the combined dataset from Study GBT440-031 and the ongoing open-label extension Study GBT440-034, 30 paediatric subjects aged 12 to < 18 years have a voxelotor exposure duration of ≥ 72 weeks, and nine paediatric subjects have a voxelotor exposure duration of ≥ 144 weeks.

Figure 14 Duration of exposure to voxelotor (all dose levels) in paediatric subjects (12 to < 18 years) with SCD in studies GBT440-031, GBT440-034, GBT440 007 (Parts A and B), and EAP GBT440-037



Abbreviations: EAP, expanded-access programme; SCD, sickle cell disease; SCS, Summary of Clinical Safety.
Note: Voxelotor exposure includes all dose levels. Subjects are included in the summary based on age at time of first exposure to voxelotor. Data cutoff date for Study GBT440-034 is 31 December 2020 and for Study GBT440-037 is 01 October 2020. For subjects who were treated in both Study GBT440-031 and the open-label extension Study GBT440-034, duration of exposure is based on first day of treatment with voxelotor in Study GBT440 031 (or Study GBT440-034 for subjects who received placebo in Study GBT440-031) and last day of exposure in Study GBT440-034.

2.6.8.2. Adverse events

For Studies GBT440-031, GBT440-034, and GBT440-007, all treatment emergent adverse events (TEAEs) were summarised separately by ***non SCD–related TEAEs*** and ***SCD related TEAEs*** to minimise confounding of the overall safety profile of voxelotor by underlying SCD comorbidities.

SCD-related TEAEs include the following SCD morbidities and complications: *sickle cell anaemia with crisis, ACS, pneumonia, priapism, and osteonecrosis* (pneumonia was included because of the difficulty in distinguishing the diagnosis from ACS).

The overall incidence of TEAEs, distribution of severity of TEAEs, and incidence of serious TEAEs were similar between the voxelotor treatment groups and the placebo group. The majority of TEAEs were related to the underlying SCD disease. Long-term dosing with voxelotor (≤ 144 weeks cumulative exposure beyond Study GBT440-031) in Study GBT440-034 show that the incidence and pattern of non-SCD-related and SCD-related TEAEs in adults and paediatric subjects 12 to < 18 years of age are generally consistent with those reported in Study GBT440-031.

Non-SCD–Related Adverse Events

Most of the subjects in the study experienced at least 1 non-SCD-related AE: 90.1% in the placebo group, 93.5% in the voxelotor 900mg 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 the study drug. Number of subjects with any serious non-SCD-related TEAEs ranged between 22-28%. More serious non-SCD-related TEAEs were assessed as related to the study drug or led to discontinuation in voxelotor groups compared to placebo (see table below).

Table 31 Study GBT440-031: Overview of non-SCD–related treatment-emergent adverse events (safety population)

	Number (%) of Subjects		
	Placebo (N = 91)	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 88)**
Subjects with Any Non-SCD-Related TEAE	82 (90.1)	86 (93.5)	85 (96.6)
Maximum Severity Grade = 5	1 (1.1)	1 (1.1)	2 (2.3)
Maximum Severity Grade = 4	3 (3.3)	2 (2.2)	1 (1.1)
Maximum Severity Grade = 3	30 (33.0)	27 (29.3)	26 (29.5)
Subjects with Any Non-SCD-Related Serious TEAE	23 (25.3)	20 (21.7)	25 (28.4)
Study Drug–Related	1 (1.1)	4 (4.3)	3 (3.4)
Leading to Treatment Discontinuation	2 (2.2)	5 (5.4)	4 (4.5)
Subjects with Any Non-SCD-Related Drug-Related TEAE	24 (26.4)	30 (32.6)	35 (39.8)
Subjects with Any Non-SCD-Related TEAE Leading to Treatment Discontinuation	6 (6.6)	7 (7.6)	9 (10.2)

Abbreviations: SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: The table summarizes only TEAEs, defined as adverse events with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. SCD-related adverse events of sickle cell anaemia with crisis, acute chest syndrome, pneumonia grouped term, priapism, and osteonecrosis are excluded from the summary. Source: CSR GBT440-031 Table 14.3.2.1.A

Common non-SCD–related TEAEs

Non-SCD–related TEAEs that occurred in ≥ 10% of subjects in any treatment group are summarised by PT in table below.

Gastrointestinal Disorders was the most commonly reported SOC in each treatment group: 62.5% (55/88), 59.8% (55/92), and 54.9% (50/91) of the subjects in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively.

Incidence of Nervous System Disorders SOC was higher in the voxelotor 1500 mg (40.9% [36/88 subjects]) and placebo (35.2% [32/91 subjects]) groups and lower in the voxelotor 900-mg group (30.4% [28/92 subjects]).

Events in the Respiratory, Thoracic, and Mediastinal Disorders SOC occurred in similar proportions of subjects in the voxelotor 1500-mg group (28.4% [25/88 subjects]) and placebo group (30.8% [28/91 subjects]), but were lower in the voxelotor 900-mg group (20.7% [19/92 subjects]).

Incidences of Skin and Subcutaneous Tissue Disorders SOC were similar in the voxelotor 1500-mg treatment group (27.3% [24/88] subjects]), the voxelotor 900-mg group (23.9% [22/92 subjects]), and the placebo group (24.2% [22/91 subjects]).

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

Table 32 Study GBT440-031: Non-SCD–related treatment-emergent adverse events in ≥ 10% of subjects in any treatment group (safety population)

Preferred Term	Number (%) of Subjects		
	Placebo (N = 91)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N = 88)
Headache	23 (25.3)	20 (21.7)	28 (31.8)
Diarrhoea	10 (11.0)	17 (18.5)	20 (22.7)
Arthralgia	13 (14.3)	14 (15.2)	19 (21.6)
Nausea	9 (9.9)	17 (18.5)	17 (19.3)
Back Pain	12 (13.2)	13 (14.1)	15 (17.0)
Pain	18 (19.8)	15 (16.3)	15 (17.0)
Abdominal Pain	10 (11.0)	13 (14.1)	13 (14.8)
Pyrexia	7 (7.7)	12 (13.0)	13 (14.8)
Rash (Grouped PTs)[a]	10 (11.0)	13 (14.1)	13 (14.8)
Upper Respiratory Tract Infection	14 (15.4)	22 (23.9)	13 (14.8)
Fatigue	12 (13.2)	13 (14.1)	12 (13.6)
Pain in Extremity	19 (20.9)	20 (21.7)	12 (13.6)
Vomiting	15 (16.5)	13 (14.1)	11 (12.5)
Non-Cardiac Chest Pain	10 (11.0)	13 (14.1)	10 (11.4)
Urinary Tract Infection	13 (14.3)	6 (6.5)	9 (10.2)
Abdominal Pain Upper	6 (6.6)	14 (15.2)	8 (9.1)
Cough	10 (11.0)	6 (6.5)	8 (9.1)

- Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
- Note: AEs were coded using MedDRA version 22.0. The table summarizes only TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. SCD-related AEs of sickle cell anaemia with crisis, acute chest syndrome, pneumonia grouped term, priapism, and osteonecrosis are excluded from the summary. Multiple occurrences of a given PT in a subject were counted only once.
- [a]Rash (grouped PTs) includes the following PTs: rash, urticaria, rash generalised, rash maculo-papular, rash pruritic, rash papular, rash erythematous, rash vesicular, and rash macular.

Treatment-related non-SCD-related TEAEs

The incidence of treatment-related Non-SCD–related TEAEs considered by the investigator and reported in ≥ 2 subjects in any treatment group are summarised in table 33.

The overall incidence of treatment-related non-SCD–related TEAEs was higher in the voxelotor treatment groups than in the placebo group. The dose-response relationship was driven primarily by the incidence of diarrhoea and abdominal pain.

Table 33 Study GBT440-031: Study drug–related non-SCD–related treatment-emergent adverse events reported in ≥ 2 subjects in any treatment group (safety population) (safety population)

Preferred Term	Number (%) of Subjects		
	Placebo (N = 91)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N = 88)
Subjects with Any Drug-Related Event	24 (26.4)	30 (32.6)	35 (39.8)
Drug-Related TEAE in ≥ 2 Subjects in Any Treatment Group			
Diarrhoea	3 (3.3)	8 (8.7)	12 (13.6)
Nausea	5 (5.5)	6 (6.5)	7 (8.0)
Abdominal Pain	1 (1.1)	6 (6.5)	6 (6.8)
Rash (grouped PTs)[a]	4 (4.4)	2 (2.2)	6 (6.8)
Headache	3 (3.3)	3 (3.3)	5 (5.7)
Abdominal Pain Upper	2 (2.2)	3 (3.3)	2 (2.3)
Angina Pectoris	0	0	2 (2.3)
Vomiting	4 (4.4)	3 (3.3)	1 (1.1)
Aspartate Aminotransferase Increased	0	2 (2.2)	0
Decreased Appetite	0	2 (2.2)	0
Fatigue	0	2 (2.2)	0
Pyrexia	0	2 (2.2)	0
Dizziness	3 (3.3)	0	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: AEs were coded using MedDRA version 22.0. The table summarizes only TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. SCD-related AEs of sickle cell anaemia with crisis, acute chest syndrome, pneumonia grouped term, priapism, and osteonecrosis are excluded from the summary. Multiple occurrences of a given PT in a subject were counted only once.
[a]Rash (grouped PTs) includes the following PTs: rash, urticaria, rash generalised, rash maculo-papular, rash pruritic, rash erythematous, rash papular, rash vesicular, and rash macular. PTs contributing to this table include rash, urticaria, rash generalised, and rash pruritic.

SCD-Related Adverse Events

A brief summary of SCD-related TEAEs is provided in table below

Similar number of subjects in every group experienced at least one SCD-related AE in the GBT440-031 study (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 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).

Table 34 Study GBT440-031: Overview of SCD-related treatment-emergent adverse events (safety population)

	Number (%) of Subjects		
	Placebo (N = 91)	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 88)**
Subjects with Any SCD-Related TEAE	73 (80.2)	69 (75.0)	69 (78.4)
Maximum Severity Grade = 5	1 (1.1)	1 (1.1)	1 (1.1)
Maximum Severity Grade = 4	1 (1.1)	0	0
Maximum Severity Grade = 3	50 (54.9)	51 (55.4)	49 (55.7)
Subjects with Any SCD-Related Serious TEAE	48 (52.7)	48 (52.2)	46 (52.3)
Study drug-related	1 (1.1)	1 (1.1)	4 (4.5)
Leading to treatment discontinuation	2 (2.2)	3 (3.3)	3 (3.4)
Subjects with Any SCD-Related Drug-Related TEAE	5 (5.5)	3 (3.3)	5 (5.7)
Subjects with Any SCD-Related TEAE Leading to Treatment Discontinuation	2 (2.2)	3 (3.3)	4 (4.5)

Abbreviations: AE, adverse event; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: SCD-related AEs include sickle cell anaemia with crisis, acute chest syndrome, pneumonia grouped term, priapism, and osteonecrosis.
Source: CSR GBT440-031 Table 14.3.2.1.B.

All SCD-related TEAEs

SCD-related TEAEs are summarised in **Error! Reference source not found.**

The majority of SCD-related TEAEs were sickle cell anaemia with crisis. The incidence of sickle cell anaemia with crisis was evenly balanced across groups, and its occurrence was widely distributed throughout the study. 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.

Table 35 Study GBT440-031: SCD-related treatment-emergent adverse events (safety population)

	Number (%) of Subjects		
	Placebo (N = 91)	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 88)**
Subjects with Any Event	73 (80.2)	69 (75.0)	69 (78.4)

	Number (%) of Subjects		
	Placebo (N = 91)	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 88)**
Sickle Cell Anaemia with Crisis	72 (79.1)	69 (75.0)	67 (76.1)
Priapism (Male Subjects Only) [a]	1/42 (2.4)	6/41 (14.6)	4/31 (12.9)
Acute Chest Syndrome or Pneumonia	13 (14.3)	15 (16.3)	16 (18.2)
Acute Chest Syndrome	6 (6.6)	8 (8.7)	12 (13.6)
Pneumonia	9 (9.9)	9 (9.8)	6 (6.8)
Osteonecrosis	1 (1.1)	0	0

Abbreviations: AE, adverse event; TEAE, treatment-emergent AE; SCD, sickle cell disease.
Note: AEs were coded using MedDRA version 22.0. The table summarizes TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. Pneumonia includes all preferred terms of pneumonia reported in this study including pneumonia mycoplasmal.
[a] Percentages are calculated based on number of male subjects in the Safety Population. Source: CSR GBT440-031 Table 14.3.7 and Listing 16.2.

The majority of SCD-related AEs were considered by the investigator to be related to underlying SCD. The incidence of TEAEs that were considered by the investigator to be related to study drug was low and similar across treatment groups (3.3% to 5.7%). Of the 13 subjects with events related to study drug, 12 subjects had sickle cell anaemia with crisis and 1 subject had priapism.

Adverse Events by Organ System or Syndrome:

Among the common non-SCD–related TEAEs in the pivotal study, gastrointestinal disorders (ie, diarrhoea, nausea, and abdominal pain) and rash (grouped PTs) both occurred with greater frequency at the voxelotor 1500-mg dose than with placebo and demonstrated a dose response. Arthralgia was also a common non-SCD–related TEAE but demonstrated a minimal dose response, and exposure-response analysis showed no relationship to exposure. Furthermore, drug hypersensitivity, while infrequently observed (2 events) in the voxelotor clinical programme, is discussed due to the potential seriousness of this TEAE.

Analysis of Gastrointestinal Events

In the pivotal Phase 3 Study GBT440-031, the most frequently reported TEAEs in the Gastrointestinal Disorders SOC were diarrhoea, nausea, vomiting, and abdominal pain, with both diarrhoea and nausea showing a dose-dependent effect. Diarrhoea was the most common and was reported in 22.7%, 18.5%, and 11.0% of subjects in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively.

Data from the open-label extension Study GBT440-034 indicated that with long term voxelotor treatment (> 72 weeks), the incidence of diarrhoea did not increase. Gastrointestinal SAEs were infrequent and did not result in study drug discontinuation. The majority of reported gastrointestinal events have been Grade 1 or 2 self-

limiting and clinically manageable without the need for dose interruption or reduction or treatment discontinuation. No events of bloody diarrhoea or fatty stools, or associated complications such as dehydration were reported.

Analysis of Rash Events

In the pivotal Phase 3 study, rash was reported in 14.8%, 14.1%, and 11.0% of subjects in the voxelotor 1500-mg, 900-mg, and placebo groups, respectively. This was similar to the incidence reported in paediatric subjects in Study GBT440-007 (13.3% in the 1500-mg group and 8.0% in the 900-mg group); similar or lower rates of rash were reported in healthy subjects and subjects with IPF. Additionally, rash was reported in 2.2% (4/178) of subjects in the OLE Study GBT440-034, including 2.6% (3/116) of subjects who were previously treated with voxelotor for up to 72 weeks in Study GBT440-031. With long term voxelotor treatment (> 72 weeks), the incidence of rash did not increase.

In the analysis of paediatric subjects, 2 subjects treated with placebo in Study GBT440-031 and 2 subjects in each voxelotor treatment group in Study GBT440-007 reported events of rash. None of the events resulted in discontinuation of study drug. One of the events (Grade 3 urticaria; voxelotor 900 mg) resulted in dose modifications, with dose escalation back to 900 mg with no reoccurrence.

Serious TEAEs of rash were infrequent and rarely resulted in study drug discontinuation in the SCD population. The majority of rash events were similar in appearance (consistent with typical maculopapular drug eruptions) and distribution, were not associated with extradermal concurrent TEAEs such as pyrexia and arthralgia, and were manageable with or without treatment including oral antihistamines or topical corticosteroids.

Although rash appears to be drug related, exposure-response analysis did not reveal a statistically significant dose- or exposure-response relationship. No events of Stevens-Johnson syndrome were reported.

Analysis of Hypersensitivity

Across all studies in the voxelotor clinical development programme to date, 2 TEAEs of drug hypersensitivity in adult patients were assessed by the investigator as related to voxelotor have occurred: 1 subject with SCD in Study GBT440-031 and 1 subject with IPF in Study GBT440-006.

Both subjects were receiving voxelotor 1500 mg. The event of drug hypersensitivity in the subject with SCD was reported as an SAE and evaluated as Grade 3 in severity. The event in the subject with IPF was reported as a nonserious AE and evaluated as Grade 2 in severity. The observed symptoms in the 2 subjects included generalised morbilliform rash, urticaria, mild shortness of breath, mild facial swelling, fever, headache, and diarrhoea. Elevated eosinophils were also noted for both subjects. Symptoms abated after study drug was withheld; and recurrence was observed after reintroduction of voxelotor despite 2 dose reductions in the SCD subject. Subjects received oral antihistamine and/or oral steroid treatment to resolve observed events.

Treatment exposure to time of event onset varied in these 2 subjects, occurring on Study Day 40 for the subject with SCD and Study Day 10 for the subject with IPF. Confounding factors in both subjects included the use of other medications with known risk of drug hypersensitivity reactions (platelet-rich plasma for hair growth in the subject with SCD and anti-fibrotics for the subject with IPF).

In summary, the occurrence of serious drug hypersensitivity is uncommon (2/819 [0.24%] voxelotor-treated subjects) and reversible after discontinuation of study drug and symptomatic treatment. No events of anaphylaxis or anaphylactoid reactions have been reported across the voxelotor clinical development programme.

Analysis of Vaso-Occlusive Crisis Following Study Drug Discontinuation (28-day follow-up)

There was a numerically higher incidence of VOCs in the voxelotor arm compared with placebo after treatment discontinuation: IR: 0.365 (95% CI: 0.158, 0.720), 0.184 (95% CI: 0.050, 0.470), and 0.455 (95% CI: 0.218, 0.836) events/28-days for the placebo, voxelotor 900 mg, and voxelotor 1500 mg groups, respectively.

Analysis of Acute Chest Syndrome and Pneumonia

While the overall baseline (in the 12 months prior to study entry) incidence of VOC was balanced between treatment groups, the placebo group had a lower percentage of subjects at baseline with a history of ACS (prior 12 months; 3.3% [3/92 subjects] compared with 10.9% [10/92 subjects] and 11.1% [10/90 subjects] in the voxelotor 900-mg and 1500-mg groups, respectively).

Although the incidence of on-treatment sickle cell anaemia with crisis was observed to be evenly distributed across treatment groups, there was an imbalance in ACS incidence across treatment groups: 13.6% (12/88 subjects), 8.7% (8/92 subjects), and 6.6% (6/91 subjects) in the voxelotor 1500-mg, voxelotor 900-mg, placebo groups, respectively. When combined with pneumonia events, the incidences were 18.2% (16/88 subjects), 16.3% (15/92 subjects), and 14.3% (13/91 subjects) in the voxelotor 1500-mg, voxelotor 900 mg, and placebo groups, respectively, with a difference of 3 subjects between voxelotor 1500-mg and placebo.

ACS and pneumonia events as reported were also assessed within subject subgroups as defined by baseline ACS status (with or without ACS episodes in the 12 months prior to study entry). This analysis showed that across treatment groups, subjects with similar matched baseline ACS histories had similar ACS incidence during the treatment period. Additionally, an exposure safety analysis of ACS as a function of % haemoglobin occupancy was performed. No statistically significant exposure-response relationship was observed between voxelotor PK exposure and the incidence of ACS (GBT-CP-006).

In Study GBT440-034 (OLE), 7.3% (13/178) of subjects experienced events of ACS or pneumonia. Seven of the 13 subjects had a history of ACS at any point prior to entry into the parent Study GBT440-031. These events were assessed by the investigator as not related to voxelotor. Although Study GBT440-007 Part B (paediatric study) was not placebo controlled, it is notable that ACS events on study showed an inverse treatment relationship with a 6.7% incidence at the 1500-mg dose and a 12.0% incidence at the 900-mg dose of voxelotor.

Overall, the applicant assesses the events of ACS as not related to voxelotor but related to complications associated with SCD.

Analysis of Priapism

Overall, priapism occurred infrequently in Study GBT440-031; a total of 11 subjects experienced at least 1 event during the treatment period, with no apparent dose-dependent effect. Overall, there was an imbalance in reported events of priapism between treatment groups in Study GBT440-031, with an incidence of 4/31 (12.9%), 6/41 (14.6%), and 1/42 (2.4%) in the voxelotor 1500-mg, voxelotor 900-mg, and placebo groups, respectively. The imbalance in Study GBT440-031 was assessed as not likely due to a treatment effect for the following reasons:

- Overall, there was a small number of subjects with priapism events and a small absolute difference (3 subjects) between the voxelotor 1500-mg and placebo groups.

- Most subjects with priapism on treatment also had a history of priapism (8/11 subjects); therefore, recurrent events were not unexpected in these subjects. More subjects had a history of priapism in the voxelotor treatment groups; this may have contributed to the observed imbalance in the treatment period. In Study GBT440-031, there were slightly more male subjects with a prior history of priapism in the voxelotor 1500-mg and 900 mg groups than in the placebo group: 8/32 (25.0%), 10/41 (24.4%), and 7/42 (16.7%), respectively.
- There was a lack of a dose-dependent effect, with lower incidence in the voxelotor 1500-mg group than in the voxelotor 900-mg group and minimally higher incidence in the 1500-mg group than in the placebo group.

In Study GBT440-007 Part B, 3/19 male paediatric subjects reported priapism: 2 in the voxelotor 1500-mg group and 1 in the voxelotor 900-mg group. One subject in the voxelotor 1500-mg group had a prior history of priapism. This is similar to the incidence observed in paediatric subjects enrolled in Study GBT440-031.

In Study GBT440-034, 7 adult subjects experienced priapism. Five of the 7 subjects had a history of priapism prior to enrollment into Study GBT440-031, of which 4 also experienced priapism during the treatment period in Study GBT440-031.

The applicant assessed the events of priapism as not related to voxelotor but related to a complication associated with SCD.

Analysis of Assessments Related to Tissue Oxygen Availability

With voxelotor, there is a theoretical risk that at a high enough percentage of Hb occupancy, offloading of O2 from voxelotor-bound Hb in the tissues could be decreased. If present, a clinically relevant decrease in O2 offloading could lead to end organ tissue hypoxic stress and dysfunction.

Overall, no clinical safety concerns consistent with inadequate tissue oxygenation were identified in the voxelotor clinical development programme, including in subjects with SCD. To further assess the potential for reduced O2 offloading from voxelotor-bound Hb, maximal exercise physiology tests were performed and hematologic measures to assess for compensatory erythropoiesis (erythropoietin and reticulocyte counts) in SCD studies were studied.

Maximal exercise testing

In Study GBT440-0111 in healthy subjects receiving voxelotor 900 mg (8 subjects) or 1500 mg (6 subjects) QD for 14 days, maximal exercise was performed under the hypoxic (12.5% O2) and normoxic conditions. Three subjects from the 1500-mg cohort discontinued from the study, 2 due to TEAEs assessed as possibly/probably related to voxelotor and one subject was withdrawn at the discretion of the investigator. Maximal exercise tests were performed on Days 1 and 15 under. The effects of voxelotor on end-organ function were measured, comparing subjects to their baseline (off voxelotor). No detrimental effects of voxelotor were seen on clinically relevant physiologic parameters that would indicate hypoxic tissue stress (eg, vital signs, cardiac output, lactate, exercise capacity, dyspnea and perceived exertion, mental status).

Maximal exercise testing in SCD patients in Study GBT440-001 showed similar results when voxelotor was administered for up to 90 days, with no impairment in workload or tissue oxygen consumption.

Erythropoiesis

No evidence of a compensatory erythropoietic response was seen in Study GBT440 031: erythropoietin did not increase, and reticulocytes decreased. No correlation was observed between the model-predicted % Hb occupancy at steady-state Cmax and percent change from baseline (%CFB) erythropoietin at Week 72. As in Study GBT440-031, no relationship between erythropoietin levels and exposure was observed in Study GBT440-007.

%Hb occupancy over time

The median %Hb occupancy after the administration of voxelotor 1500 mg in subjects with SCD reaches the 20% to 30% target occupancy quickly within the first weeks of treatment and is subsequently stable for the entire treatment period. Results indicate that the time spent above 30% Hb occupancy represents 34% of total treatment duration. The upper limits of the 95% confidence intervals stay below 50% for both dose levels. The data are consistent between Studies GBT440007 and GBT440-031.

At a dose of 1500 mg voxelotor daily, the maximum Hb% occupancy is on average 37.9% and 38.1% for Studies GBT440-007 and GBT440-031, respectively. Values of 60% and above were reached in 1 subject in Study GBT440-007 and 3 subjects in Study GBT440-031.

The table below provides an overview of the number of subjects with SCD who exceeded %Hb occupancy levels of 30%, 40%, and 50% in Studies GBT440-007 and GBT440-031 after administration of 1500 mg voxelotor. Out of 96 subjects overall, 79, 38, and 10 subjects exceeded the %Hb occupancy level of 30%, 40%, and 50% at least once, respectively. For subjects who exceeded the %Hb occupancy level, the time above the %Hb occupancy of 30% and 40% was on average 33% to 37% and 15% to 20% of the treatment duration, respectively, depending on the study. For the 2 subjects in Study GBT440-007 who had %Hb occupancy levels above 50%, the average time above that level was 3.7% of the treatment duration, and for the 8 subjects in Study GBT440-031 who had %Hb occupancy levels above 50%, the average time above that threshold was 15%.

Table 36 Subjects with sickle cell disease who reached %Hb occupancy above 30%, 40%, or 50% after administration of 1500 mg voxelotor daily in studies GBT440-007 and GBT440-031

Study	Total Subjects	Subjects Exceeding %Hb Occupancy Threshold	Mean	Minimum	Maximum
Time at > 30% Hb Occupancy			**Number of Hours With > 30% Hb Occupancy (% of Treatment Duration [24 or 72 Weeks])**		
GBT440-007	15	11	1313 (33%)	44 (1.1%)	3189 (79%)
GBT440-031	81	68	4442 (37%)	4 (< 1%)	11580 (96%)
Time at > 40% Hb Occupancy			**Number of Hours With > 40% Hb Occupancy (% of Treatment Duration [24 or 72 Weeks])**		
GBT440-007	15	5	793 (20%)	330 (8.2%)	1564 (39%)
GBT440-031	81	33	1835 (15%)	2 (< 1%)	11448 (95%)
Time at > 50% Hb Occupancy			**Number of Hours With > 50% Occupancy (% of Treatment Duration [24 or 72 Weeks])**		
GBT440-007	15	2	150 (3.7%)	54 (1.3%)	247 (6.1%)
GBT440-031	81	8	1820 (15%)	5 (< 1%)	2725 (56%)

Source: Studies GBT440-007 and GBT440-031.

Review of AEs in subjects with %HB occupancy > 30% targeted Hb occupancy

The AE safety profile of subjects whose %Hb occupancy profile at Cmax exceeded the levels of > 30, > 40, and > 50% was assessed. Overall, the AE profile in subjects whose %Hb occupancy level at Cmax exceeded levels of > 30, > 40 and > 50% were either consistent with the known safety profile of voxelotor (e.g. headache, pyrexia, gastrointestinal disorders, and fatigue); or the AEs were expected in a subject with underlying SCD (e.g. sickle cell anaemia with crisis, infectious AEs, pain, priapism, arthralgia, and acute chest syndrome/pneumonia). Also, these findings were consistent among subjects with the longest time spent at %Hb occupancy levels of > 30%, > 40%, or > 50%. In addition, none of the AEs were suggestive of having an underlying aetiology of tissue hypoxia.

2.6.8.3. Serious adverse event/deaths/other significant events

Non-SCD-Related Serious Adverse Events

Non-SCD–related SAEs reported in ≥ 2 subjects in any treatment group are summarised in Table 37 and non-SCD–related SAEs considered by the investigator to be related to study drug are summarised by PT in **Error! Reference source not found.**

Non-SCD–related SAEs in the Respiratory, Thoracic, and Mediastinal Disorders SOC were more common in the voxelotor 1500-mg group (6.8% [6/88 subjects]) than in the voxelotor 900-mg group (0.0%) or the placebo group (2.2% [2/91 subjects]). In the voxelotor 1500-mg group, these events included pleural effusion and pulmonary embolism (in 2 subjects each) and acute respiratory failure and respiratory failure (in 1 subject each).

In the Gastrointestinal Disorders SOC, SAEs included nausea (1.1% [1/88 subjects]) in the voxelotor 1500-mg group, gastritis (2.2% [2/92 subjects]), diarrhoea (1.1% [1/92 subjects]), and gastritis haemorrhagic (1.1% [1/92 subjects]) in the voxelotor 900-mg group, and odynophagia (painful swallowing) (1.1% [1/92 subject]) in the placebo group.

Six subjects had a total of 7 Grade 4 treatment emergent SAEs (1 subject in voxelotor 1500 mg group, 2 subjects in the voxelotor 900 mg and 3 subjects in the placebo group. Type 2 diabetes mellitus (voxelotor 900-mg group) was the only one of these events considered by the investigator as related to study drug; this event also led to discontinuation of study drug. Anaemia (voxelotor 900-mg group) and respiratory failure (voxelotor 1500-mg group) also led to discontinuation of study drug.

Table 37 Study GBT440-031: Non-SCD–related serious adverse events reported in ≥ 2 subjects in any treatment group (safety population)

Preferred Term	Number (%) of Subjects		
	Placebo (N = 91)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N = 88)
Subjects with Any Event	23 (25.3)	20 (21.7)	25 (28.4)
Anaemia	2 (2.2)	3 (3.3)	0
Pyrexia	3 (3.3)	3 (3.3)	2 (2.3)
Pleural Effusion	0	0	2 (2.3)
Pulmonary Embolism	1 (1.1)	0	2 (2.3)
Malaria	0	3 (3.3)	1 (1.1)
Gastritis	0	2 (2.2)	0
Musculoskeletal Chest Pain	1 (1.1)	2 (2.2)	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: AEs were coded using MedDRA version 22.0. The table summarizes only TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. SCD-related AEs of sickle cell anaemia with crisis, acute chest syndrome, pneumonia grouped term, priapism, and osteonecrosis are excluded from the summary. Multiple occurrences of a given PT in a subject were counted only once. Source: CSR GBT440-031 Table 14.3.9.

Table 38 Study GBT440-031: Study drug–related non-scd–related serious adverse events (safety population)

Preferred Term	Number (%) of Subjects		
	Placebo (N = 91)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N = 88)
Subjects with Any Event	1 (1.1)	4 (4.3)	3 (3.4)
Drug Hypersensitivity	0	0	1 (1.1)
Headache	0	0	1 (1.1)
Pulmonary Embolism	0	0	1 (1.1)
Anaemia	0	1 (1.1)	0
Hepatitis Acute	0	1 (1.1)	0
Rash Generalised	0	1 (1.1)	0
Thrombocytopenia	0	1 (1.1)	0
Type 2 Diabetes Mellitus	0	1 (1.1)	0
Thrombocytosis	1 (1.1)	0	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: AEs were coded using MedDRA version 22.0. The table summarizes only TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. SCD-related AEs of sickle cell anaemia with crisis, acute chest syndrome, pneumonia grouped term, priapism, and osteonecrosis are excluded from the summary. Multiple occurrences of a given PT in a subject were counted only once. Source: CSR GBT440-031 Table 14.3.10.

SCD-Related Serious Adverse Events

SCD-related SAEs are summarised in the Table below.

Overall, the incidence of SCD-related SAEs was similar across treatment groups and ranged from 52.2% to 52.7%. Sickle cell anaemia with crisis was the most common SAE in each treatment group. Across all treatment groups, a total of 6 subjects (4 in the voxelotor 1500-mg group, 1 in the voxelotor 900-mg group, and 1 in the placebo group) had drug-related SAEs: all drug-related SAEs were sickle cell anaemia with crisis.

The majority of events were Grade 3, and 1 subject had a Grade 4 SCD-related SAE (placebo); this event of sickle cell anaemia with crisis was not considered by the investigator to be related to study drug and did not lead to discontinuation.

Table 39 Study GBT440-031: SCD-related serious adverse events (safety population)

Preferred Term	Number (%) of Subjects		
	Placebo (N = 91)	Voxelotor 900 mg (N = 92)	Voxelotor 1500 mg (N = 88)
Subjects with Any Event	48 (52.7)	48 (52.2)	46 (52.3)
Sickle Cell Anaemia with Crisis	46 (50.5)	45 (48.9)	45 (51.1)
Acute Chest Syndrome or Pneumonia	12 (13.2)	11 (12.0)	13 (14.8)
Acute Chest Syndrome	6 (6.6)	8 (8.7)	11 (12.5)
Pneumonia	7 (7.7)	3 (3.3)	4 (4.5)
Priapism (Male Subjects Only)[a]	0/42	1/41 (2.4)	0/31
Osteonecrosis	1 (1.1)	0	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: AEs were coded using MedDRA version 22.0. The table summarizes only TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. Multiple occurrences of a given PT in a subject were counted only once. Pneumonia includes all PTs of pneumonia, including pneumonia mycoplasmal.
[a] Percentages are calculated based on number of male subjects in the Safety Population. Source: CSR GBT440-031 Table 14.3.11 and Listing 16.2.7.

Death

Overall, 6 subjects reported fatal SAEs, including 2 subjects in each of the treatment groups. Three of the 6 subjects, 1 in each treatment group, had a fatal event of sickle cell anaemia with crisis. One of these 3 subjects (Subject 11-001-0010 in the voxelotor 1500-mg group) also had acute sickle hepatic crisis (verbatim term coded to PT sickle cell anaemia with crisis) and pulmonary sepsis. Among the remaining 3 subjects, 1 subject (Subject 01-031-0003 in the voxelotor 1500-mg group) had a brain abscess and encephalopathy, 1 subject (Subject 05 002 0004 in the voxelotor 900-mg group) had reported death – unknown etiology (verbatim term), and 1 subject (Subject 01-055-0001 in the placebo group) had cardiac arrest. None of the fatal SAEs were considered by the investigator to be related to study drug.

2.6.8.4. Laboratory findings

Among the haematology parameters, mean changes in leukocytes, neutrophils and platelets were generally small and not clinically meaningful, as values were within the normal range.

The exposure response analysis showed a statistically significant relationship with Grade 1 decreases in white blood cells (WBCs). Taken together with the finding that small reductions in WBCs occurred within the normal range, this finding was considered not to be clinically meaningful.

No clinically meaningful trends in median alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK), or potassium were observed in any treatment group. The exposure-safety analysis of data from the pivotal Study GBT440-031 demonstrated a statistically significant relationship between exposure and Grade 1 but not Grade 2 ALT elevations. Due to the low-grade and isolated nature of this effect,

that there was no accompanying treatment effect on increasing bilirubin or ALK, and no cases of drug-induced liver injury, this finding is not considered to be of clinical concern. Given sensitivity of the kidney to hypoxia, creatinine was examined in an exposure safety analysis and showed no relationship to exposure.

In each treatment group, changes from baseline in median albumin to creatinine ratio were small and not clinically meaningful.

No correlation was observed between the model-predicted % Hb occupancy at steady-state Cmax and percent change from baseline (%CFB) erythropoietin at Week 72.

Vital signs and electrocardiograms

Clinically significant ECG results were reported as TEAEs as per protocol for 4 subjects in the voxelotor 1500-mg group (all were Grade 1 or 2), 7 subjects in the voxelotor 900-mg group (Grade 1 or 2), and 4 subjects in the placebo group (Grade 1 or 2). None of the TEAEs associated with the clinically significant ECG results were considered serious. All TEAEs related to ECG results were assessed by the investigator as not related to study drug except for 2 subjects. One of these subjects discontinued from the study following this event.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

No subjects ≥65 years of age were included in the study.

Intrinsic Factors: Overall, reported TEAEs were largely consistent across subgroups based on age, sex, race, and genotype. Please see the paediatric safety data below.

Renal or Hepatic Impairment

The analyses of the effect of renal or hepatic impairment were based on clinical pharmacology studies. A formal analysis of subjects enrolled in Study GBT440-031 was not performed since only a few subjects had renal function below the lower limit of normal and no subjects had hepatic impairment.

The TEAEs reported in otherwise healthy subjects with renal impairment or hepatic impairment following a single dose of 1500mg voxelotor were few, mild in severity, did not lead to discontinuation of voxelotor, and were consistent with the safety profile seen in the pivotal Study GBT440-031, including events of diarrhoea and headache.

No significant effects of renal impairment or mild or moderate hepatic impairment in otherwise healthy subjects were observed on voxelotor exposure, and no dose adjustment from the proposed registrational dose of 1500 mg QD is required in these populations. The recommendation for no dose adjustment in renally impaired patients is also supported by PPK analysis from Study GBT440-031.

Based on the increase in whole-blood and plasma exposures in subjects with severe hepatic impairment (Child Pugh C), it is recommended to reduce the daily dose of voxelotor to 1000 mg QD in this patient population.

Paediatric safety data

Comparison of TAEs in adults and Subjects 12 to < 18 Years of Age in Study GBT440-031

Treatment-emergent adverse events most commonly reported (≥ 10%) for paediatric subjects 12 to < 18 years of age as compared to adult subjects in the pivotal Study GBT440-031 are presented in the table below.

As with adults, the most commonly reported TEAEs across all treatment groups in paediatric subjects was sickle .cell anaemia with crisis. Although the pattern of all non SCD-related TEAEs was similar across the paediatric subjects and adult age groups, in the voxelotor 1500-mg dose groups compared to placebo, paediatric subjects had a higher incidence of arthralgia, and adults had a higher incidence of headache, diarrhoea and rash.

Table 40 Study GBT440-031: Treatment-emergent adverse events for adult and paediatric subjects 12 to < 18 years of age with SCD with incidence ≥ 10% of subjects in any voxelotor treatment group (safety population)

Preferred Term	**Number (%) of Subjects**					
	Adults 72 weeks of Treatment			**Pediatrics (12 to < 18 years) 72 weeks of Treatment**		
	Placebo N = 74	**Voxelotor 900 mg N = 77**	**Voxelotor 1500 mg N = 74**	**Placebo N = 17**	**Voxelotor 900 mg N = 15**	**Voxelotor 1500 mg N = 14**
Sickle Cell Anaemia with Crisis	60 (81.1)	58 (75.3)	60 (81.1)	13 (76.5)	11 (73.3)	9 (64.3)
Headache	18 (24.3)	15 (19.5)	25 (33.8)	5 (29.4)	5 (33.3)	3 (21.4)
Diarrhoea	8 (10.8)	16 (20.8)	19 (25.7)	2 (11.8)	1 (6.7)	1 (7.1)
Abdominal Pain	6 (8.1)	9 (11.7)	9 (12.2)	4 (23.5)	4 (26.7)	4 (28.6)
Abdominal Pain Upper	5 (5.8)	13 (16.9)	8 (10.8)	1 (5.9)	1 (6.7)	0
Nausea	8 (10.8)	15 (19.5)	15 (20.3)	1 (5.9)	2 (13.3)	2 (14.3)
Rash (Grouped PTs) [a]	8 (10.8)	13 (16.9)	13 (17.6)	2 (11.8)	0	0
Acute Chest Syndrome	4 (5.4)	8 (10.4)	11 (14.9)	2 (11.8)	0	1 (7.1)
Fatigue	12 (16.2)	12 (15.6)	11 (14.9)	0	1 (6.7)	1 (7.1)
Priapism (Male Subjects Only)[b]	1/30 (3.3)	3/30 (10.0)	4/22 (8.1)	0/12	3/11 (27.3)	0/9
Arthralgia	10 (13.5)	11 (14.3)	14 (18.9)	3 (17.6)	3 (20.0)	5 (35.7)
Pyrexia	3 (4.1)	12 (15.6)	11 (14.9)	4 (23.5)	0	2 (14.3)
Upper Respiratory Tract Infection	11 (14.9)	16 (20.8)	10 (13.5)	3 (17.6)	6 (40.0)	3 (21.4)
Vomiting	13 (17.6)	10 (13.0)	10 (13.5)	2 (11.8)	3 (20.0)	1 (7.1)
Back Pain	6 (8.1)	9 (11.7)	12 (16.2)	6 (35.3)	4 (26.7)	3 (21.4)
Pain in Extremity	17 (23.0)	18 (23.4)	10 (13.5)	2 (11.8)	2 (13.3)	2 (14.3)
Non-Cardiac Chest Pain	7 (9.5)	10 (13.0)	8 (10.8)	3 (17.6)	3 (20.0)	2 (14.3)
Pneumonia	9 (12.2)	7 (9.1)	6 (8.1)	0	2 (13.3)	0
Cough	9 (12.2)	5 (6.5)	6 (8.1)	1 (5.9)	1 (6.7)	2 (14.3)
Pain	13 (17.6)	12 (15.6)	10 (13.5)	5 (29.4)	3 (20.0)	5 (35.7)
Urinary Tract Infection	11 (14.9)	6 (7.8)	8 (10.8)	2 (11.8)	0	1 (7.1)
Constipation	8 (10.8)	9 (11.7)	6 (8.1)	1 (5.9)	0	0
Anaemia	4 (5.8)	8 (10.4)	3 (4.1)	0	1 (6.7)	1 (7.1)
Ocular Icterus	3 (4.1)	7 (9.1)	4 (5.4)	5 (29.4)	2 (13.3)	2 (14.3)

Preferred Term	Number (%) of Subjects					
	Adults 72 weeks of Treatment			Pediatrics (12 to < 18 years) 72 weeks of Treatment		
	Placebo N = 74	Voxelotor 900 mg N = 77	Voxelotor 1500 mg N = 74	Placebo N = 17	Voxelotor 900 mg N = 15	Voxelotor 1500 mg N = 14
Dizziness	8 (10.8)	6 (7.8)	4 (5.4)	1 (5.9)	2 (13.3)	0
Cellulitis	1 (1.4)	2 (2.6)	2 (2.7)	0	2 (13.3)	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.
Note: AEs were coded using MedDRA version 22.0. The table summarizes TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after study drug discontinuation. Multiple occurrences of PTs in a subject were counted only once.
a Rash (grouped PTs) includes the following PTs: rash, urticaria, rash generalised, rash maculo-papular, rash pruritic, rash erythematous, rash vesicular, and rash macular (Adults); Rash (grouped PTs) includes PTs of rash and rash papular (Pediatrics).
b Percentages are calculated based on number of male subjects in the Safety Population.

Safety in Phase 2a Study GBT440 007 in Paediatric Subjects

Overall, the safety data (nature and frequency of AEs) obtained in the GBT440-007 study were consistent with the data obtained in the GBT440-031 study. The most common non-SCD AEs in the voxelotor 1500 mg group were: headache (26.7%), back pain (26.7%), arthralgia (26.7%), followed by pain in extremity, nausea, abdominal pain and oropharyngeal pain (20% for every category). The most commonly reported study drug–related TEAE in the voxelotor 1500 mg group was nausea (20%), diarrhoea (13.3%), headache (6.7%) and rash (6.7%). As for adults, the most commonly reported SCD-related TEAE in both treatment groups was sickle cell anaemia with crisis.

One subject (4%) in the voxelotor 900 mg group and 4 subjects (26.7%) in the voxelotor 1500 mg group experienced at least 1 non-SCD-related SAE during the study. None of them were attributed to the study drug by the investigator. Ten subjects (40%) in the voxelotor 900 mg group and 5 subjects (33.3%) in the voxelotor 1500 mg group experienced SCD-related SAE. Only one of them was considered to be related to the study drug: ACS in the voxelotor 900 mg group. There was no death reported.

2.6.8.7. Immunological events

Not applicable.

2.6.8.8. Safety related to drug-drug interactions and other interactions

Voxelotor is metabolised via multiple routes and therefore DDIs with inhibitors on the PK of voxelotor is unlikely. A clinical DDI study with a strong CYP3A4 inhibitor (itraconazole) in healthy volunteers showed no effect on the PK of voxelotor, indicating that the other enzymes are able to take over if CYP3A4 is inhibited.

In vitro data indicates that voxelotor is an inhibitor of CYP2B6, 2C8, 2C9, 2C19 and 3A4 at maximal systemic concentrations and of CYP3A4 at maximal intestinal concentrations. Furthermore, voxelotor is an inhibitor of OATP1B1, OAT3, and MATE1 at maximal systemic concentrations. The clinical relevancy of the inhibition

effect of voxelotor on medicinal products that are substrates of these enzymes or transporters was not sufficiently investigated. Therefore, the DDI risk of voxelotor on other medicinal products is unknown and may lead to safety issues with these other medicinal products.

2.6.8.9. Discontinuation due to adverse events

TEAEs leading to study drug discontinuation

TEAEs leading to study drug discontinuation in at least 2 subjects are summarised in the table below.

Overall, the incidence of TEAEs that led to discontinuation of study drug was 12.5% (11/88) of the subjects in the voxelotor 1500-mg group, 8.7% (8/92) of the subjects in the voxelotor 900-mg group, and 7.7% (7/91) of the subjects in the placebo group. No pattern of TEAEs leading to discontinuation of study drug was observed within or across treatment groups.

Table 41 Study GBT440-031: Treatment-emergent adverse events leading to discontinuation of study drug (safety population) in ≥ 2 subjects

Preferred Term	**Number (%) of Subjects**		
	Placebo (N = 91)	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 88)**
Subjects with Any Event	7 (7.7)	8 (8.7)	11 (12.5)
Sickle Cell Anaemia with Crisis	2 (2.2)	2 (2.2)	3 (3.4)
Abdominal Pain	0	1 (1.1)	1 (1.1)
Nausea	2 (2.2)	0	1 (1.1)
Anaemia	0	2 (2.2)	0
Diarrhoea	1 (1.1)	1 (1.1)	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; TEAE, treatment-emergent adverse event.
Note: AEs were coded using MedDRA version 22.0. The table summarizes only TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. Multiple occurrences of a given PT in a subject were counted only once.

TEAEs leading to study drug modification

TEAEs that led to dose modification for at least 2 subjects in any treatment group are summarised in Table below

The highest rate of TEAEs that led to modification of study drug dosing occurred in the voxelotor 1500-mg group (47.7% [42/88 subjects]). The rate in the voxelotor 900-mg group (32.6% [30/92 subjects]) was similar to the rate for the placebo group (36.3% [33/91 subjects]). Overall, sickle cell anaemia with crisis was the most common TEAE that led to modification of dosing.

Across all 3 treatment groups, the majority of dosing modifications due to TEAEs were dosing interruptions rather than dose reductions. In total, 28.4% patients in the voxelotor 1500 mg group had dose reductions during the Study GBT440-031 compared to 12% in the voxelotor 900 mg group and 16.5% in the placebo group.

Table 42 Study GBT440-031: Treatment-emergent adverse events leading to modification of study drug dosing in ≥ 2 subjects in any treatment group (safety population)

	Number (%) of Subjects		
	Placebo (N = 91)	**Voxelotor 900 mg (N = 92)**	**Voxelotor 1500 mg (N = 88)**
Subjects with Any Event	33 (36.3)	30 (32.6)	42 (47.7)
Sickle Cell Anaemia with Crisis	19 (20.9)	18 (19.6)	24 (27.3)
Acute Chest Syndrome	3 (3.3)	2 (2.2)	5 (5.7)
Rash (Grouped PTs)[a]	0	1 (1.1)	4 (4.5)
Diarrhoea	0	4 (4.3)	3 (3.4)
Headache	3 (3.3)	1 (1.1)	2 (2.3)
Nausea	4 (4.4)	1 (1.1)	2 (2.3)
Non-Cardiac Chest Pain	1 (1.1)	0	2 (2.3)
Vomiting	3 (3.3)	2 (2.2)	2 (2.3)
Abdominal Pain	1 (1.1)	3 (3.3)	1 (1.1)
Pneumonia[b]	4 (4.4)	1 (1.1)	1 (1.1)
Abdominal Pain Upper	2 (2.2)	3 (3.3)	0
Pyrexia	2 (2.2)	3 (3.3)	0
Gastritis	0	2 (2.2)	0
Dyspnoea	2 (2.2)	0	0
Influenza	2 (2.2)	0	0
Pruritus Generalized	2 (2.2)	0	0

Abbreviations: AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; PT, Preferred Term; TEAE, treatment-emergent adverse event.
Note: AEs were coded using MedDRA version 22.0. The table summarizes only TEAEs, defined as AEs with an onset date on or after the initiation of study drug until 28 days after discontinuation of drug. Multiple occurrences of a given PT in a subject were counted only once.
[a] Rash (grouped PTs) includes the following PTs: rash, urticaria, rash generalised, rash maculo-papular, rash pruritic, rash erythematous, rash papular, rash vesicular, and rash macular. PTs contributing to this table include rash, rash generalized, and rash maculo-papular.
[b] Pneumonia (Grouped PTs) includes the following PTs: pneumonia and pneumonia mycoplasmal.

2.6.8.10. Post marketing experience

On 25 November 2019, Oxbryta (voxelotor) was granted accelerated approval by the US Food and Drug Administration (FDA) for the treatment of SCD in adults and paediatric patients 12 years of age and older. As of 22 August 2020, approximately 2,540 patients have received at least one dose of Oxbryta in the US.

The majority of adverse drug experiences (ADEs) reported occur under the MedDRA System Organ Class (SOC) of Gastrointestinal Disorders, Blood and Lymphatic System Disorders, Injury, Poisoning and Procedural Complications, and Nervous System Disorders. Across all PADER reports, events with fatal outcomes were uncommon, and included SCD-related complications and a single case of SARS-CoV-2 infection. All fatal events have been evaluated as not related to Oxbryta. The most commonly reported serious and unlabelled event was sickle cell anaemia with crisis. The majority of reported ADEs were nonserious and labelled and included

diarrhoea, product dose omission, nausea, headache and abdominal pain. Post-marketing experience did not identify any new safety signals that warrant any changes to the product information.

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

Main safety data

The main safety data are based on a single pivotal Phase 3 Study GBT440-031 with the safety profile in paediatric subjects 12 to < 18 years of age supported by data from the open-label Phase 2a Study GBT440-007 Part B. Interim data are also available from Study GBT440-034, the ongoing long-term extension (OLE) of Study GBT440-031 (cumulative voxelotor exposure for in total ≥ 144 weeks), with a cut-off date of 31 December 2020.

Patient exposure

Across all voxelotor doses, 153 and 114 adults and paediatric subjects 12 to < 18 years of age from Study GBT440-031 have received a cumulative voxelotor **exposure** for ≥72 weeks and ≥96 weeks, respectively. Of these, 30 and 20 adolescents were exposed for ≥72 weeks and ≥96 weeks, accordingly. With respect to the applied dose of 1500 mg, only 87 and 22 adults and adolescent subjects had exposure for ≥72 weeks, respectively, in the Study GBT440-031/Study GBT440-034. Additional 15 adolescent subjects were exposed to the registration dose of 1500 mg in the Study GBT440-007 (Part B – open label phase) for a median of 24 weeks. The data obtained in the dose ranges other than the registration dose (mostly lower doses and used for shorter durations) can only be considered as supportive.

Non-SCD-related adverse evens

Most of the subjects in the main study experienced at least 1 non-SCD-related AE (90-97%). 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 the study drug. Most of the AEs observed were mild. The number of subjects with any serious non-SCD-related TEAEs were similar across treatment groups (between 22-28%), and the incidence of non-SCD-related, drug-related TEAEs was low: 3.4% in voxelotor 1500 mg group and 1.1% in the placebo group. Gastrointestinal Disorders was the most commonly reported SOC in each treatment group, with highest incidence in voxelotor 1500 mg group. The most common non-SCD–related TEAEs within voxelotor 1500 mg group with higher incidence than in placebo were: headache (31.8%), diarrhoea (22.7%), arthralgia (21.6%) and nausea (19.3%).

The dose-response relationship of drug-related AEs was driven primarily by the incidence of diarrhoea and abdominal pain. Also, higher incidence of drug-related rash was reported for voxelotor 1500 mg group compared to placebo. Two cases of hypersensitivity were reported in the voxelotor studies, one in the pivotal study and one in the study in patients with idiopathic pulmonary fibrosis. In general, the most common adverse drug reactions (ADRs), i.e diarrhoea, abdominal pain, nausea, rash, drug hypersensitivity are listed in the SmPC.

Excluding non-clinical data, few additional data were provided by the applicant in order to better characterise the risk of vomiting with Voxelotor or explain the high incidence of GI AEs, including vomiting, in the placebo

group. Taking into consideration the possible impact of such AEs on the quality of life of patients, especially children and adolescents, while dose reductions might not be possible with a potential impact on compliance, a close monitoring of these ADRs of vomiting and associated risks will be performed within PSURs.

Risk of tissue hypoxia

As voxelotor stabilises the Hb in the oxyhaemoglobin (Hb-O2) state and increases the Hb-O2 affinity, there is a risk that at a higher percentage of Hb occupancy than the aimed target of 20%-30% Hb occupancy, the off-loading of O2 from voxelotor-bound Hb in the peripheral tissues might be decreased, which could lead to end organ tissue hypoxic stress and organ dysfunction.

- Risk of hypoxia during exercise testing

These risks were assessed by performing maximal exercise physiology tests in SCD patients in the placebo controlled Phase 1 study GBT440-001 (part B + C) in which subjects were treated up to 28 days and 90 days, respectively. Additionally, a special dedicated maximal exercise GBT440-0111 study under normoxic or hypoxic conditions in healthy volunteers was performed after treatment for 2 weeks. Even though no clear changes in clinically relevant physiologic parameters that would indicate hypoxic tissue stress were observed in both studies, it should be noted that only three volunteers were exposed to the 1500 mg dose and the SCD patients, although treated for up to 90 days, received doses up to 1000 mg only. Therefore, solely based on these exercise studies, the potential risk that decreased off-loading of O2 from voxelotor-bound Hb in the peripheral tissues on the long run can lead to tissue hypoxia, cannot be excluded.

- Safety profile of higher Hb occupancy (above 20-30% target range)

Analysis of %Hb occupancy over time revealed that the median %Hb occupancy reaches the 20% to 30% target occupancy quickly within the first weeks of treatment and subsequently remains stable for the entire treatment period. The maximum %Hb occupancy estimated for each subject for 1500 mg voxelotor was on average 37.9% and 38.1% for GBT440-007 and GBT440-031, respectively. The analysis of subjects with Hb occupancy >30% showed that 82%, 40% and 10% of the evaluated subjects (96 in total, from the Study GBT440-007 and Study GBT440-031) achieved Hb occupancy levels >30%, >40% and >50%, respectively, at any time point during the study. After the initial accumulation phase (week 4), the time spent above the %Hb occupancy of 30% and 40% was on average 33% to 37% and 15% to 20% of the treatment duration, respectively, depending on the study. The number of patients with %Hb occupancy above 50% was 10%, with average time above that level varying from 3.7% - 15% of the treatment duration. The AEs pattern recorded in patients with the longest time spent at %Hb levels of >30%, >40%, 50% appeared consistent with the known safety profile of voxelotor. In conclusion, the observed adverse event pattern in patients with %Hb occupancy above target range was comparable with that noted for patients with %Hb occupancy within the target range of 20%-30%, with no signs of AEs suggestive of tissue hypoxia.

SCD-related adverse events

A similar number of subjects in every group experienced at least one SCD-related AE in the GBT440-031 study (75- 80%). The number of subjects who experienced severe SCD-related AEs was high, but similar across the groups (52%). However, only a small part of these SAEs were attributed to the study drug (<5%). The majority of SCD-related AEs were sickle cell anaemia with crisis. The incidence of priapism and ACS was higher in voxelotor groups compared to placebo. For example, 2.4%, 14.6% and 12.9% of male subjects in the placebo, voxelotor 900 mg and voxelotor 1500 mg group experienced priapism during the GBT440-031 study. Also,

13.6% and 8.7% of subjects in the voxelotor 1500 mg and 900 mg group respectively experienced ACS versus 6.6% in the placebo group. Even though the numbers are low, the contribution of voxelotor to these differences cannot be ruled out. The applicant has committed to carefully monitor incidence of ACS, as well as priapism post-marketing and ACS and priapism are identified as an important potential risk in the PSURs.

Overall, the rate of SAEs in the study was high, but similar across groups. Most of the SAEs were attributed to sickle-cell disease manifestation. From the non-SCD–related SAEs, the Respiratory, Thoracic, and Mediastinal Disorders SOC were more common in the voxelotor 1500-mg group (6.8% vs 2.2%), that includes pleural effusion and pulmonary embolism, acute respiratory failure and respiratory failure. One case of pulmonary embolism in the voxelotor group was considered drug-related. Also, one case of diabetes type 2 was reported to be treatment-related in the voxelotor 900 mg group in a patient with BMI 44 and positive family history for DM.

In total, 6 deaths occurred in the GBT440-031 study with two deaths in each treatment arm. None of the fatal SAEs were considered by the investigator to be related to the study drug. Three of the 6 subjects, 1 in each treatment group, had a fatal event of sickle cell anaemia with crisis. Among the remaining 3 subjects, 1 subject in the voxelotor 1500 mg group had a brain abscess and encephalopathy, 1 subject in the voxelotor 900 mg group had reported death – unknown aetiology (verbatim term), and 1 subject in the placebo group had cardiac arrest.

No clear trends in median changes from baseline for most of the lab parameters were observed in safety evaluations. Reductions in white blood cells were reported more often in the voxelotor groups compared to placebo with statistically significant ER relationships for Grade ≥ 1 decreased WBC. This needs further attention, given that immunosuppressive effects of voxelotor were shown in the animal studies.

Furthermore, the statistically significant ER relationships for Grade ≥ 1 increased ALT was also confirmed for voxelotor. No clear pattern in change in erythropoietin levels over time were observed in the voxelotor studies. However, it should be noted that erythropoietin levels are known to be very high at baseline in patients with SCD, which makes it difficult to observe a possible (slow-developing) change in erythropoiesis.

No elderly subjects were included in voxelotor studies (>65 years) and the safety in this population is unknown. An appropriate warning is included in section 4.4 of the SmPC. No SCD patient with hepatic or renal impairment was included in the GBT440-031 study. Therefore, the safety of voxelotor in this population cannot be properly assessed. However, the safety data from the clinical pharmacology studies in otherwise healthy subjects with renal or hepatic impairment were consistent with the safety profile of voxelotor seen in studies with SCD patients. However, these were single-dose studies and the number of exposed patients was low and too limited to draw any definitive conclusions on the safety of voxelotor in patients with moderate/severe hepatic impairment, also given the observed effects of voxelotor on ALT elevations. An appropriate warning to cover these uncertainties is included in section 4.4 of the SmPC. Severe hepatic impairment led to the increase in whole-blood and plasma exposures. Therefore, it is recommended to reduce the daily dose of voxelotor to 1000 mg QD in this patient population, which is agreed. Age, sex, race or genotype do not seem to influence the safety profile of voxelotor. The representativeness of certain genotypes is, however, very limited and no definitive conclusions can be drawn.

Voxelotor as inhibitor of CYP2B6, 2C8, 2C9, 2C19 and 3A4 might impact safety of other medicinal products that are metabolised by these enzymes. However, currently performed studies do not allow a detailed assessment of these DDI, hence specific recommendations have been included in section 4.5 and 5.2 of the SmPC. Additional DDI studies will be performed post-marketing (please see non-clinical section).

Use during pregnancy

Due to the lack of human exposure data, voxelotor should be avoided during pregnancy. No contraceptive measures during treatment with voxelotor is necessary. However, voxelotor can be used as a combination treatment with hydroxycarbamide – a potent mutagenic agent that requires effective contraception before the start of and during the treatment. Therefore, an additional warning is mentioned in 4.4 to refer to the SmPC of hydroxycarbamide to increase an awareness of HCP.

Use during breast feeding

It is unknown whether voxelotor/metabolites are excreted in human milk. Available pharmacokinetic/ toxicological data in animals have shown readily excretion of voxelotor in milk and subsequent uptake in pups. As a risk to the newborns/infants cannot be excluded, voxelotor should not be used during breast-feeding. This has been reflected in section 4.6 of the SmPC.

Discontinuation due to AEs

The rate of AEs that led to discontinuation of the drug was slightly higher in the voxelotor groups compared to placebo in the GBT440-031 study 12.5% 7.7% in voxelotor 1500mg, and placebo groups, respectively.

Follow-up after discontinuation

There was a numerically higher incidence of VOCs in the voxelotor 1500mg arm compared with placebo after treatment discontinuation. To address this, the applicant provided haematocrit results for patients who discontinued voxelotor or completed the pivotal study without enrolling in the extension phase. Considering all submitted data, it is agreed that the causality relationship of increased incidence of VOC after treatment discontinuation with voxelotor cannot be clearly defined nor completely ruled out. The applicant has committed to closely monitor safety data from all sources in the PSURs to better characterise this potential risk. Further amendment of the RMP should also be considered when more clinical data will be available.

Safety data obtained in the ongoing OLE study are consistent with the data from the pivotal trial. Voxelotor received marketing authorisation in the USA on 25 November 2019. So far, no unexpected or new safety signals were identified post-marketing. The most common SAE was sickle cell anaemia with crisis, and the most common labelled AEs were diarrhoea, nausea, headache, and abdominal pain. Death was uncommon and was reported as related to the SCD and unrelated to voxelotor in all cases. These data are consistent with the data obtained in the clinical trials.

Assessment of paediatric data on clinical safety

Safety in paediatric subjects aged 12 to 18 years of age was assessed based on the data from pivotal study, as well as supportive GBT440-007 study. Overall safety profile of voxelotor appears to be comparable between adolescents and adults. In the voxelotor 1500-mg dose groups compared to placebo, paediatric subjects had a higher incidence of arthralgia, and adults had a higher incidence of headache, diarrhoea, and rash.

2.6.10. Conclusions on the clinical safety

Generally, the safety database is limited, but presented data so far showed that most of the non-SCD drug-related (S)AE seem to be reversible and of mild or moderate nature. Adverse events that were most frequently reported in the voxelotor groups are headache, diarrhoea, nausea, arthralgia and rash. Certain

AEs, i.e vomiting, arthralgia, ACS, priapism and VOC incidence after drug discontinuation, should be carefully monitored post-marketing in line with the agreed RMP.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 43 Summary of the safety concerns

Important identified risks	Not applicable
Important potential risks	Not applicable
Missing information	Safety in pregnancy and lactation Safety in patients with SCD with ESRD requiring dialysis Long-term safety Drug-drug interaction potential with voxelotor and OATP1B1, OAT3 and MATE1 substrates, and the drug-drug interaction potential with voxelotor on CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 substrates Safety in Immunocompromised patients (including patients with HIV)

2.7.2. Pharmacovigilance plan

Table 44 Ongoing and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities that are conditions of the marketing authorisation	No Category 1 activities			
Category 2 - Imposed mandatory additional pharmacovigilance activities that are	No Category 2 activities			

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Category 3 - Required additional pharmacovigilance activities				
GBT440-034: An Open-Label Extension Study of Voxelotor Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials (long-term follow-up study of subjects originally enrolled in GBT 440-031) Ongoing	This open-label extension study of antecedent Study GBT440-031 to assess long-term safety and treatment effect of Oxbryta	Long-term safety based on adverse events, clinical laboratory tests, physical examinations and other clinical measures	Annual progress reports	Annually in June
			Final analysis report	30 June 2025
GBT440-0120: A Phase 1, Open-Label, Fixed-Sequence, Two-Period, Drug-Drug Interaction Study to Evaluate Effect of Voxelotor on the Pharmacokinetics of Probe Substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in Healthy Subjects Planned	To evaluate effect of voxelotor on the pharmacokinetics of probe substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19 and CYP3A4 in healthy subjects	Drug-drug interaction potential with voxelotor and CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 substrates. The results of this analysis may be relevant to the description of the DDI potential of voxelotor.	Study Start	Q2 2022
			Clinical Study Report	Q1 2023
GBT440-0121: A Phase 1, Open-Label Study to Evaluate the Effect of Multiple Doses of Voxelotor on the Pharmacokinetics of Probe Substrates for MATE1, OAT3, and OATP1B1 in Healthy Subjects	To evaluate effect of voxelotor on the pharmacokinetics of probe substrates for OATP1B1, OAT3, and MATE1 in healthy subjects	Drug-drug interaction potential with voxelotor and OATP1B1, OAT3, and MATE1 substrates. The results of this analysis may be relevant to the description of the	Study Start	Q3 2022
			Clinical Study Report	Q2 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Planned		DDI potential of voxelotor.		

2.7.3. Risk minimisation measures

Table 45 Summary of risk minimisation measures and pharmacovigilance activities

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Important identified risks		
Not applicable		
Important potential risks		
Not applicable		
Missing information		
Safety in pregnancy and lactation	Routine risk minimisation measures: SmPC, Section 4.6, Section 5.3 PL Section 2 Additional risk minimisation measures: None	Routine pharmacovigilance activities: Includes review of ICSRs, periodic aggregate safety reports, and other prespecified signal detection activities.
Safety in patients with SCD with ESRD requiring dialysis	Routine risk minimisation measures: SmPC, Section 4.2, Section 4.4, Section 5.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities: Includes review of ICSRs, periodic aggregate safety reports, and other prespecified signal detection activities.

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Long-term safety	Routine risk minimisation measures: None Additional risk minimisation measures: None	Routine pharmacovigilance activities: Includes review of ICSRs, periodic aggregate safety reports, and other prespecified signal detection activities. Additional pharmacovigilance activities: GBT440-034 - An Open Label Extension Study of Voxelotor (GBT440) Administered Orally to Participants with Sickle Cell Disease Who Have Participated in Voxelotor Clinical Trials
Drug-drug interaction potential with voxelotor and OATP1B1, OAT3, and MATE1 substrates, and the drug-drug interaction potential with voxelotor and CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 substrates	Routine risk minimisation measures: SmPC, Section 4.5, Section 5.2 Additional risk minimisation measures: None	Routine pharmacovigilance activities: Includes review of ICSRs, periodic aggregate safety reports, and other prespecified signal detection activities. Additional pharmacovigilance activities: GBT440-0120: A Phase 1, Open-Label, Fixed-Sequence, Two-Period, Drug-Drug Interaction Study to Evaluate Effect of Voxelotor on the Pharmacokinetics of Probe Substrates for CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 in Healthy Subjects GBT440-0121: A Phase 1, Open-Label Study to Evaluate the Effect of Multiple Doses of Voxelotor on the Pharmacokinetics of Probe Substrates for MATE1, OAT3, and OATP1B1 in Healthy Subjects
Safety in immunocompromised patients (including patients with HIV)	Routine risk minimisation measures: SmPC, Section 4.4 Additional risk minimisation measures: None	Routine pharmacovigilance activities: Includes review of ICSRs, periodic aggregate safety reports, and other prespecified signal detection activities.

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EC) 726/2004, Oxbryta (voxelotor) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

SCD is an orphan inherited disease that has a complex pathophysiology and clinical presentation. SCD is caused by mutations in the HBB gene, which encodes haemoglobin subunit β, resulting in the presence of a mutated form of haemoglobin, haemoglobin S (HbS). HbS has the capacity to polymerise. In RBCs, this leads to increased density, reduced deformability, increased adhesivity and shortened life span to about 10-20 days. Erythrocytes that contain mostly HbS polymers assume a sickled form and are prone to haemolysis, manifesting in haemolytic anaemia. Haemolytic anaemia is experienced to various degrees by all patients with SCD and is a defining and serious feature of the disease. Haemolytic anaemia leads to reduced oxygen carrying capacity, tissue hypoxia, and clinical manifestations of end organ damage. Vaso-occlusive crisis (VOC) is another clinical hallmark of SCD. 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.

3.1.2. Available therapies and unmet medical need

Current treatment options for SCD include 2 medicinal therapies that prevent VOC, i.e. hydroxyurea (HU) and crizanlizumab (Adakveo). Hydroxyurea is indicated for patients 2 years and older, while crizanlizumab is indicated for patients 16 years and older. Crizanlizumab is indicated as an add on therapy to hydroxyurea (HU; hydroxycarbamide (HC)) or as monotherapy in patients for whom HU/HC is inappropriate or inadequate. Further, red blood cell (RBC) transfusions can be used as on-demand therapy (e.g. for acute anaemia) or as a prophylactic therapy. Even though chronic RBC transfusion can improve many SCD complications, this therapy is associated with a wide variety of (severe) adverse events, such as alloimmunisation, iron overload and infection. Chronic (prophylactic) transfusions are usually indicated for treatment of anaemia in case this anaemia is associated with high risk of severe complications such as stroke, acute chest syndrome (ACS) or very frequent and severe VOC.

Allogenic hematopoietic stem cell transplantation (alloHSCT) is the only curative treatment option for SCD patients. However, this treatment is associated with risks following transplantation and moreover, is not readily available for the majority of the SCD patients. Additionally, treatments such as preventive antibiotic use and analgesics are being used in the management of SCD.

Although some of the treatments described above will lead to an increase in haemoglobin (HU, RBC transfusions), there is currently no European approved therapy for the treatment of haemolytic anaemia associated with SCD. Especially patients who do not have recurrent VOC, have their treatment options limited to blood transfusions and alloHSCT. Therefore, SCD patients have an unmet medical need for an effective treatment for haemolytic anaemia.

Voxelotor is a Hb polymerisation inhibitor. It aims to target the underlying pathophysiological mechanism of SCD, i.e. the ability of HbS to polymerize. Voxelotor inhibits the process of Hb polymerisation by stabilizing the oxygenated state of HbS by means of increasing the Hb-oxygen (Hb-O2) affinity. This stabilisation increases the ratio of oxygenated HbS to deoxygenated HbS. This would provide a sufficiently prolonged delay time for RBCs to pass through the hypoxic environment of distal capillaries and arterioles without sickling prior to reoxygenation in the lungs (Oksenberg, 2016). As a consequence haemolytic anaemia is improved and, in the long run, a reduction in end-organ damage and morbidity is expected.

3.1.3. Main clinical studies

Study GBT440-031 is a single phase 3, double-blind, randomised, placebo-controlled, multicentre 72-week study evaluating efficacy and safety of voxelotor in subjects aged 12 to 65 years with sickle cell disease (SCD) including haemoglobin (Hb) sickle cell disease with 2 sickle cell genes (HbSS), haemoglobin sickle cell disease with 1 HbS sickle cell gene and 1 haemoglobin C gene-(HbSC), HbSβ thalassemia, or other sickle cell syndrome variants. Furthermore, subjects were required to have Hb levels at baseline ≥ 5.5 and ≤ 10.5 g/dL and experienced at least 1 VOC in the previous 12 months were included in the study..

The primary endpoint was the percentage of subjects achieving an increase of > 1 g/dL in Hb from baseline to Week 24. Important secondary and exploratory endpoints included change of Hb levels and haemolysis markers (indirect bilirubin, lactate dehydrogenase, % reticulocyte and absolute reticulocyte count) from baseline at 24, 48 and 72 weeks, as well as VOC rates at 72 weeks. The open label extension study GBT440-034 of the main study GBT440-031, provides additional long-term data on voxelotor safety and efficacy.

3.2. Favourable effects

Only results from the voxelotor 1500 mg dose will be presented here as the most relevant for the current application.

Primary endpoint: More subjects treated with voxelotor 1500 mg or voxelotor 900 mg had an **increase from baseline in Hb levels >1 g/dL** compared to placebo: 51.1%, 32.6% and 6.5% respectively ($p<0.001$) at week 24. The response rate was similar in subjects who were or were not receiving HU concurrently. Also age, race, region, gender and baseline Hb levels did not have an influence on the voxelotor efficacy based on the 24 week analysis.

Secondary endpoints: The treatment with voxelotor resulted in statistically significant and sustained (up to 72 weeks) increase in **Hb levels** when compared to baseline levels, as well as to placebo. The least-squares (LS) mean change in Hb from baseline at 72 weeks was 1.02 g/dL (CI 0.72, 1.31) in the voxelotor 1500 mg group, 0.54 (CI 0.25, 0.82) in the voxelotor 900 mg group and 0.02 (CI -0.27, 0.32) in the placebo group ($p<0.001$ for 1500 mg vs. placebo, exploratory). The incidence rate (IR) of **acute anaemic episodes** (Hb decrease > 2g/dl) decreased with voxelotor (4/90 subjects) in comparison to placebo (11/92 subjects); the annualised IR of was 3-fold lower with voxelotor 1500 mg compared to placebo (0.05 vs 0.15 per person years).

Regarding haemolysis parameters, treatment with voxelotor resulted in a decrease in **indirect bilirubin** and **% reticulocyte** at 72 weeks. LS mean percentage change from baseline in indirect bilirubin was -23.9% (CI -33.5, -14.3) compared to the increase of 2.7% (CI -7.0, 12.3) in the placebo group (p<0.001 for 1500 mg vs. placebo, exploratory). LS mean percentage change from baseline in % reticulocyte was -7.6% (CI -18.5, 3.3) compared to the increase of 11% (CI 0.2, 21.8) in the placebo group (p=0.017 for 1500 mg vs. placebo, exploratory).

An annualised incidence rate (IR) of on treatment events of **VOC** in three groups were comparable when analysing total (mITT) population: voxelotor 1500 mg (219 events; adjusted IR of 2.4 events/year), voxelotor 900 mg (251 events; 2.4 events/year), and placebo (293 events; 2.8 events/year). When analysing subjects with higher baseline annual VOC rate (≥ 2 VOCs), a trend of improvement was observed for subjects who received voxelotor 1500 mg group (134 events, 2.5 events/year) compared with the voxelotor 900 mg group (174 events, 3.0 events/year) and placebo group (197 events, 3.1 events/year).

For the **Clinical Global Impression of Change** (CGIC) scale, at the final Week 72 timepoint, 73.6% (39/53) of the subjects in the voxelotor 1500 mg group, 55.2% (32/58) of the subjects in the voxelotor 900 mg group, and 47.1% (24/51) of the subjects in the placebo group were assessed as having moderately or very much improved relative to baseline (p<0.01 for 1500 mg vs. placebo, exploratory).

The efficacy data from the OLE study GBT-440-034 are consistent with the results of the pivotal phase 3 trial GMT440-031. Voxelotor treatment results in less haemolysis as shown by durable Hb increase, indirect bilirubin decrease and decrease in % reticulocyte.

The 24-week Hb and haemolysis data from the paediatric study GBT440-007 are consistent with the results of the pivotal phase 3 trial GMT440-031.

3.3. Uncertainties and limitations about favourable effects

Study conduct. The last major protocol amendment #4 that took place following second interim analysis brought substantial changes to the study design. As a result, the primary analysis set, trial size and number and ordering of confirmatory secondary endpoints were amended. There is a potential inflation of the type I error rate, because the sample size was adjusted downwards. Also, the CGIC endpoint was added to the protocol following the protocol amendment #4. Several important secondary endpoints were downgraded to exploratory, leading to these results being supportive rather than confirmatory.

Efficacy endpoints. Even though voxelotor showed a beneficial effect on **Hb levels**, it is not clear to what extent the observed increase in Hb also translates into better tissue oxygenation. While voxelotor binding will increase Hb-O_2 affinity, which is expected to reduce Hb polymerisation, RBC sickling and haemolysis, at the same time, difficulties in off-loading O_2 in tissue capillaries is seen as competing phenomenon that may potentially cancel part of a beneficial effect of voxelotor. These concerns are also strengthened by the *in vitro* and animal data that suggest that voxelotor bound Hb is compromised in its ability to offload O2, and only voxelotor-free Hb contributes to tissue oxygenation. Additionally, 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.

The pivotal study was not powered to detect the effect of the treatment on the **VOC rate** and also, about 40% of subjects enrolled in the study had a history of only 1 VOC in the previous 12 months, hampering to definitively conclude on a beneficial effect on VOC incidence.

Health-related quality of life measures. The results of the **CGIC** scale showed improvement on voxelotor treatment. However, the introduction of this subjective endpoint was quite late in the study (at amendment #4) and only part of the patients were evaluated for this endpoint, which hampers the interpretation of the results substantially.

Although the primary endpoint of the percentage of subjects achieving an increase in Hb was met, no beneficial effect of the treatment was observed between groups on endpoints that reflect disease burden and patient wellbeing. The rate of any opioid use (approximately 80%) and the percentage of patients (approximately 35%) who received one or more RBC transfusions were similar in each treatment arm. **Patient-reported outcome** (PRO) baseline scores indicate that the majority of the patients in the study had relatively few limitations, making it more difficult to detect any improvement from baseline. As there is only a single pivotal trial, further evidence for this type of benefit to the patient is lacking.

The long-term efficacy data > 72 weeks is currently limited: only 87 adults subjects and 22 adolescents were exposed to the registration dose for more than 72 weeks; 52 patients have an exposure for 144 weeks. Currently, only 100 patients remain in the ongoing open label extension study, which adds the uncertainty on the long-term effects.

Subgroups. A subgroup analysis based on **genotypes other than HbSS** was performed, which showed comparable efficacy. As this is based on a small number of patients, definitive conclusions are hampered, though no substantial differences are expected considering the MoA of voxelotor.

3.4. Unfavourable effects

The most common **non-SCD–related TEAEs** within voxelotor 1500 mg group with higher incidence than in placebo were: **headache** (31.8% vs 25.3%), **diarrhoea** (22.7% vs 11%), **arthralgia** (21.6% vs 14.3%) and **nausea** (19.3% vs 9.9%). Also, a higher incidence of **rash** was reported for voxelotor 1500 mg group (14.8%) compared to placebo (11%). Most of these events were mild/moderate in severity (Grade 1 and Grade 2), and only few led to treatment discontinuation. The majority was assessed by the investigator as not related to the study drug. The dose-response relationship of drug-related AEs was driven primarily by the incidence of diarrhoea and abdominal pain. Two cases of **hypersensitivity** were reported in the voxelotor studies, one in the pivotal study and one in the study in patients with idiopathic pulmonary fibrosis.

Subgroups. No clear influence of age, sex, race or genotype on the voxelotor safety profile was observed. Safety profile of voxelotor in adolescents was generally comparable to adults. In the voxelotor 1500 mg dose groups compared to placebo, paediatric subjects had a higher incidence of arthralgia, and adults had a higher incidence of headache, diarrhoea, and rash. No subjects ≥65 years of age were included in voxelotor studies, which is also mentioned in the SmPC.

The rate of AEs that led to discontinuation of the drug was slightly higher in the voxelotor groups compared to placebo in the GBT440-031 study 12.5% 7.7% in voxelotor 1500mg, and placebo groups, respectively.

3.5. Uncertainties and limitations about unfavourable effects

Limited safety data set. The safety database for the registration dose is limited that brings uncertainty to the completeness of the safety assessment. An open label extension study (GBT440-034) is ongoing and will be submitted post-marketing.

Non-clinical/clinical safety findings. Even though the safety data from the clinical studies do not directly indicate particular safety issues, the nature and severity of the safety findings in the animal studies together with some observations in the clinical studies are notable:

- **Long-term safety and risk of end-organ hypoxia.** There is a potential risk that a high % Hb occupancy above the target % Hb occupancy of 20-30% may lead to a decrease in the offloading of O_2 from Hb in the peripheral tissues, leading to hypoxic tissue stress upon long-term exposure to voxelotor. The possible signs of hypoxia will be monitored by the applicant post-marketing.
- **Effect on the immune system.** In the clinical studies, exposure-dependent decrease in WBC within the normal range was observed. Even though no evident increase in the infection rates was observed during the pivotal study in the 1500 mg group, this needs further attention, given that in monkeys, treatment with voxelotor at dose levels comparable to those in clinical studies (starting already from exposure multiple of ~0.5 based on plasma C_{max} values) leads to the delayed and reduced immune response following a challenge with a standard antigen (KLH). Also, decreased lymphocyte counts in peripheral blood as well as in both primary and secondary lymphoid organs in the high-dose monkeys was noted. Decreased humoral response and changes in the relative ratio of T- and B-lymphocytes was also seen in rats at EM~4.5 of the anticipated clinical exposure. The possible impact of the drug on the immune system, therefore, is of particular importance for already immunocompromised patients who were not studied in voxelotor trials. Safety data in immunocompromised patients is mentioned as missing information in RMP. Also, an appropriate warning is added in section 4.4 of the SmPC.

Gastrointestinal Disorders was the most commonly reported SOC in each treatment group. This toxicity was also identified in non-clinical studies; including a necrotic effect. This risk is currently reflected in section 4.8 of the SmPC. High incidence of vomiting in the voxelotor group is noted, and this AE will carefully monitored post-marketing in PSUR.

SCD-related AEs. Considering SCD-related AEs, the overall incidence of any SCD event was similar across treatment groups (75.0% to 80.2%); the majority of these events were sickle cell anaemia with crisis. An increased incidence of **ACS and priapism** in the voxelotor groups compared to placebo is noted. However, due to low number of events and the fact that these are also manifestations of SCD, no hard conclusions can be drawn and their incidence will be further carefully monitored post-marketing.

The risk of **viscosity-related increase of VOCs after drug discontinuation** cannot be ruled out. The applicant will closely monitor safety data from all sources in the PSURs to better characterise this potential risk at the treatment discontinuation. Further amendment of the RMP could be considered when more clinical data will be available.

Subgroups. Subjects aged >65 years were not included in the voxelotor studies, therefore, the safety in this population is unknown. Also, even though no particular difference was observed in the safety profile of **adolescents** compared to adults, the safety data in adolescents is limited. Age, sex, race or genotype do not

seem to influence safety profile of voxelotor. The representativeness in terms of certain genotypes is very limited, but no differences in terms of safety are expected.

There are uncertainties with respect to the **drug-drug interaction** (DDI) studies. Voxelotor was shown to inhibit numerous enzymes and transporters. However, certain DDI studies were too short or performed at much lower doses than the registration dose that does not allow to properly investigate the effect of DDI. Also, some DDI studies are lacking and will be performed post-marketing.

Hepatic and renal impairment. The safety of voxelotor in SCD patients with hepatic impairment or patients with renal impairment requiring dialysis is uncertain, which is mentioned in section 4.4 of the SmPC.

3.6. Effects Table

Table 46 Effects table for voxelotor in SCD patients ≥12 years of age with haemolytic anaemia (cut-off date 31/12/2020)

Effect	Short Description Unit	1500 mg	900 mg	Placebo	Uncertainties/ Strength of evidence
Favourable Effects					
Haemoglobin Response at Week 24 (primary)	Haemoglobin Response at Week 24 N (%)	46 (51.1%)	30 (32.6%)	6 (6.5%)	SoE: p<0.001, supportive GBT440-007 study showed similar effect Unc: true clinical benefit is unclear
VOC (secondary)	Annualised IR at week 72 IR (95% CI)	2.4 (1.8, 3.07)	2.4 (1.9, 3.06)	2.8 (2.2,3.5)	SoE: nominal p=0.373, trend for improvement Unc: study was not powered to detect the effect on VOC
Hb (exploratory)	change from baseline at week 72 g/dL (95% CI)	1.02 (0.72, 1.31)	0.54 (0.25, 0.82)	0.02 (-0.27, 0.32)	SoE: nominal p< 0.001
Indirect bilirubin (exploratory)	% change from baseline at week 72 % (95% CI)	-23.9 (-33.5, -14.3)	-15.2 (24.4, -6)	2.7 (-7, 12.3)	SoE: nominal p< 0.001 Unc: effect seems to become smaller over time
% reticulocyte (exploratory)	% change from baseline at week 72 % (95% CI)	-7.6 (-18.5, 3.3)	3.5 (-7.1, 14)	11 (0.2, 21.8)	SoE: nominal p=0.017 Unc: effect seems to be smaller over time
CGIC (exploratory)	% of subjects with moderately or very much improved CGIC from baseline at Week 72	39 (73.6%)	32 (55.2%)	24 (47.1%)	SoE: nominal p=0.006 Unc: endpoint added following protocol amendment #4) and available for only 60% of the patients

Effect	Short Description Unit	1500 mg	900 mg	Placebo	Uncertainties/ Strength of evidence
Unfavourable Effects					
Headache	% of patients experiencing headache	31.8	21.7	25.3	
Diarrhoea	% of patients experiencing diarrhoea	22.7	18.5	11.0	Four grade 3 diarrhoea of which one was reported as serious with nausea, vomiting, electrolyte imbalance and dosing interruption. Similar findings reported in the nonclinical studies.
Arthralgia	% of patients experiencing arthralgia	21.6	15.2	14.3	
Nausea	% of patients experiencing nausea	19.3	18.5	9.9	
Rash	% of patients experiencing rash	14.8	14.1	11.0	Rash have consistently been reported across all voxelotor arms, including in healthy subjects, subjects with SCD, and subjects with IPF. Exposure-response analysis did not reveal a statistically significant dose- or exposure-response relationship.
Hypersensitivity	Number of patients experiencing hypersensitivity reaction (N)	1	0	0	Additional patient experienced hypersensitivity reaction on voxelotor 1500 mg dose in the Study GBT440-006 (idiopathic pulmonary fibrosis trial)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The treatment with voxelotor resulted in a fast (within 2 weeks) and sustained increase in Hb levels, with more than a half of patients having Hb increase by more than 1 g/dL after 24 weeks. Following 72 weeks of treatment the effect was sustained with a mean Hb change from baseline being 1.02 g/dL (0.72, 1.31). Importantly, the effect on Hb was observed when voxelotor was used alone or on top of HU/HC that is a current standard of care for patients with SCD. Also age gender and baseline Hb levels did not have an influence on the voxelotor efficacy further supporting the inclusion of adolescents in the indication. Even though it can be agreed that

increasing Hb levels > 1g/dL is clinically relevant, the exact effect of the increase in Hb on improved tissue oxygenation remain uncertain, since contribution of voxelotor-bound Hb (that constitute 20-30% of the total Hb) to tissue oxygenation appears to be negligible.

With respect to haemolysis as efficacy parameter, voxelotor showed a decrease in indirect bilirubin levels by more than 20% and % reticulocyte reduction by 7.6% after 72 weeks of treatment. This is indicative for reduced destruction of the RBC, which is beneficial. In fact, this can be considered the main benefit of voxelotor treatment so far, as haemolysis is an important determinant of disease severity and is a critical contributor to the activation of adhesion molecules by all blood cells, aberrant vaso-regulation and coagulation that all ultimately lead to multi-organ injury. Unfortunately, the pivotal study was not designed to demonstrate a beneficial effect of voxelotor on VOC reduction, however, a positive trend in VOC rate, even though not large, was observed on voxelotor treatment upon prolonged use that also suggests better blood rheology in line with the improvement in the haemolysis markers.

Clinical safety data is in general limited, with only 78 and 52 patients being exposed for ≥72 weeks and ≥144 weeks to the registration dose of 1500 mg, respectively. The fact that voxelotor-bound Hb is less able to release O2, raised concerns with respect to the long-term safety of the treatment with voxelotor. There is a potential risk that a higher % Hb occupancy than the target range (20-30% Hb occupancy) may substantially decrease the offloading of O2 from Hb in the peripheral tissues, which may lead to hypoxic tissue stress and organ dysfunction with prolonged use. This phenomenon was observed in animal studies, where % Hb occupancy >50% led to an appreciable degree of compensatory erythropoiesis. However, even though the follow-up in the clinical studies is still short to definitely rule out the long-term hypoxia risk, analysis of available clinical safety data, extended with new data available from the OLE study (up to >144 weeks total exposure in 52 patients), US post-marketing data, and further analysis of AEs regarding possible signs/symptoms of hypoxia so far did not present clear signals pointing out a risk of tissue hypoxia in patients in the longer term. Furthermore, even though the % Hb occupancy exceeded the target threshold of 30% in many patients (82%) at some points in the study, the mean overall Hb occupancy was within the target 20-30%, and only a small proportion of patients (10%) and during short period (up to 15% of total treatment duration) had % Hb occupancy >50%.

Overall, the presented clinical safety data so far show that voxelotor is well-tolerated since the majority of the adverse events are mild to moderate in severity, and the discontinuations due to drug-related adverse events are low. The most common adverse events are headache, arthralgia and gastro-intestinal disorders. Incidence of ACS and priapism was somewhat increased in the voxelotor groups compared to placebo, however, due to low number of events and the fact that these are also manifestations of SCD, no hard conclusions can be drawn and their incidence is to be further carefully monitored post-marketing, as should be VOC events at discontinuation of voxelotor. Additional data will be provided in the open label extension study GBT440-034.

Even though safety data on adolescents is considered limited, so far, the safety profile of voxelotor does not seem to be different in adolescents compared to adults, which is reassuring.

3.7.2. Balance of benefits and risks

Treatment with voxelotor has resulted in a beneficial effect in terms of reduction in haemolysis and an increase in Hb, which are considered of clinical relevance to the patients. The effects on long-term outcome

of SCD has not been studied, even so the beneficial effects appear to be accompanied by limited and manageable (short-term) risks.

3.8. Conclusions

The overall benefit/risk balance of Oxbryta is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Oxbryta is not similar to Adakveo within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Oxbryta is favourable in the following indication(s):

Oxbryta is indicated for the treatment of haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription.

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and

interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New active substance status

Based on the CHMP review of the available data, the CHMP considers that voxelotor is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union. Refer to Appendix on new active substance (NAS).

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0489/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.