

**NIHR Innovation Observatory
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Voxelotor for sickle cell disease

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LAY SUMMARY

Sickle cell disease (SCD) describes a group of inherited diseases. People with SCD have abnormal haemoglobin, a protein found in red blood cells that carries oxygen throughout the body. This abnormal haemoglobin is called haemoglobin S or sickle haemoglobin. Red blood cells that contain normal haemoglobin are disc shaped. This shape allows the cells to be flexible so that they can move through large and small blood vessels to deliver oxygen. Sickle-shaped cells are not flexible and can stick to vessel walls, causing a blockage that slows or stops the flow of blood. When this happens, oxygen cannot reach tissues and organs. SCD varies in severity from person to person. It sometimes can be a serious condition that can have a significant impact on a person's life. It can lead to problems such as strokes, serious infections and lung problems, which can occasionally be fatal. It is estimated that about 350 babies are born each year in England with SCD.

Voxelotor is as an oral, once-daily therapy that is being developed for treatment of SCD. It is designed to work by helping haemoglobin hold onto more oxygen as the red blood cells travel through the body. This keeps red blood cells in their normal shape and helps stop sickling. As there is a desperate need for new treatments for SCD, voxelotor, if licensed, will offer a new treatment option for patients with SCD.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Sickle cell disease (SCD)

TECHNOLOGY

DESCRIPTION

Voxelotor (GBT440) is a haemoglobin S allosteric modulator. It is designed to work by helping haemoglobin (Hb), the molecules inside red blood cells, hold onto more oxygen as the red blood cells travel through the body, thereby inhibiting polymerization in SCD. This keeps red blood cells in their normal shape and helps reduce sickling of the cells.^{1,2}

Voxelotor is an oral, once-daily therapy.¹ In the phase III HOPE study (NCT03036813), voxelotor is being investigated in two different doses (900 mg daily or 1500 mg daily) for 24 weeks in adolescents and adults aged (12 Years to 65 Years).^{2,3}

Voxelotor does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

If licensed, voxelotor will offer a new treatment option for patients with SCD. SCD represents a global health problem and new treatment options are desperately needed. Beginning in early childhood, SCD patients suffer unpredictable and recurrent episodes or crises of severe pain due to hypoxia (inadequate oxygen delivery to body tissues) and haemolytic anaemia (the destruction of red blood cells). This can lead to multi-organ damage and early death. SCD is also associated with high treatment costs.¹

DEVELOPER

Global Blood Therapeutics Inc.

AVAILABILITY, LAUNCH or MARKETING

Voxelotor is a designated orphan drug in the EU/USA for sickle cell disease.¹

Voxelotor was awarded PRIME status for sickle cell disease by EMA in June 2017.⁴

Voxelotor was designated Fast Track for sickle cell disease by FDA in Oct 2015.⁵

PATIENT GROUP

BACKGROUND

The term sickle cell disease (SCD) describes a group of inherited red blood cell disorders. People with SCD have abnormal haemoglobin, called haemoglobin S or sickle haemoglobin (HbS), in their red blood cells. This disease is passed by genes from parents to their children therefore it is an inherited disease. Patients with SCD inherit an abnormal haemoglobin gene (genetic mutation) from each parent.⁶ At least one of those two inherited abnormal genes causes a person's body to make HbS. When a person has two HbS genes (Hb SS) the disease is called sickle cell anaemia which is the most common and the most severe form of SCD. There are two other common forms of SCD these are haemoglobin SC disease and haemoglobin S β thalassaemia.⁶

Haemoglobin is a protein found in red blood cells that carry oxygen throughout the body.¹ Red blood cells that contain normal haemoglobin are disc shaped (like a doughnut without a hole). This shape allows the cells to be flexible so that they can move through large and small blood vessels to deliver oxygen. HbS is not like normal Hb. It can form stiff rods within the red blood cell, changing it into a crescent or sickle shape. Sickle-shaped cells are not flexible and can stick to vessel walls, causing a blockage that slows or stops the flow of blood. When this happens, oxygen can't reach nearby tissues. This can cause attacks of sudden, severe pain, called pain crises. These pain attacks can occur without warning, and a person often needs to go to the hospital for effective treatment.⁶

People born with sickle cell disease sometimes experience problems from early childhood, although most children have few symptoms and lead normal lives most of the time. The main symptoms of SCD are pain crises also called sickle cell crises, an increased risk of serious infections, and anaemia. Some people also experience other problems such as delayed growth, strokes and lung problems.⁷

SCD varies in severity from person to person. Most children with it will lead normal lives. However, it can still be a serious condition that can have a significant impact on a person's life. It can lead to problems such as strokes, serious infections and lung problems, which can occasionally be fatal. Generally, the life expectancy for a person with SCD tends to be shorter than normal, but this can vary depending on the exact type of SCD they have, how it's treated, and the problems they experience. Currently, people with sickle cell anaemia (the most severe form of SCD) typically live until 40-60 years of age. Milder types of SCD may have no impact on life expectancy.⁷

CLINICAL NEED and BURDEN OF DISEASE

SCD is estimated to affect one in every 2000 live births in England, and it is now the most common genetic condition at birth. It is estimated that about 350 babies are born each year in England with SCD and a further 9500 babies are found to be carriers of the disease. Also it is estimated that there are more than 12,500 people with sickle cell disease in England, and about 240,000 are carriers.⁸

In England in 2016 to 2017, there were 24,586 admissions for sickle cell disorder (ICD-10: D57), 12,279 day cases, 44,865 bed days, and 29,031 finished consultant episodes (FCE).⁹

A study on trends in hospital admissions for SCD in England, 2001/02 to 2009/10 showed that the overall admission rate per 100,000 population has risen from 21.2 per 100,000 in 2001/02 to 33.5 per 100,000 in 2009/10. This rise in admission rates has occurred in every age and sex group with the exception of women aged 30–39 years, whose admission rate per 100,000 population declined from 52.4 to 45.3 over the time period.¹⁰

The long-term effects of SCD often begin to emerge during the teenage years and this may be a time of increased episodes of sickle cell crisis, especially in young men. This evidently can have a major impact on education, career, future employment prospects, and social relationships. With improvements in health and social care, especially access to health care, the life span of those with sickle cell disease has improved tremendously and many are living into their fifth and sixth decade, especially in the UK.¹¹

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Clinical guideline. Sickle cell disease: managing acute painful episodes in hospital (CG143). June 2012.
- NICE Quality standard. Sickle cell disease (QS58). April 2014.
- NICE Medical technologies guidance. Spectra Optia for automatic red blood cell exchange in patients with sickle cell disease (MTG28). March 2016.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2016/17 NHS public health functions agreement: Service specification No. 18 NHS sickle cell and thalassaemia screening programme.
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OTHER GUIDANCE

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CURRENT TREATMENT OPTIONS

Stem cell or bone marrow transplants are the only cure for SCD, but they are not often undertaken due to the significant risks involved. The main risk is graft versus host disease, which is a life-threatening problem where the transplanted cells start to attack the other cells in the body. For better chances a successful transplant, donated stem cells need to carry a special genetic marker that is identical or very similar to that of the person receiving the transplant. Therefore, stem cell transplants are generally only considered in children with SCD who have severe symptoms that have not responded to other treatments, when the long-term benefits of a transplant are thought to outweigh the possible risks.^{19, 20}

The main treatments of SCD involve the prevention and treatment of painful episodes (sickle cell crisis). To reduce the chance of sickle cell crisis, the patient may need to avoid dehydration by drinking plenty of fluids, stop getting cold by wearing appropriate clothing, and to avoid sudden changes in temperature. For the treatment of sickle cell crisis, over-the-counter pain killers can be used to relieve the pain, also drinking plenty of fluids and using warm towels or heat pads on the affected part of the body. Hydroxycarbamide (hydroxyurea) may be recommended if the patient continues to experience pain episodes. Hydroxycarbamide is a medication that is usually taken orally. It can lower the amount of other blood cells, such as white blood cells and platelets (clotting cells), so regular blood tests will usually be recommended to monitor patient's health.¹⁹

Treatment of anaemia caused by SCD may require dietary supplements such as folic acid especially for children with restricted diet, such as vegetarian or vegan diet. Anaemia caused by sickle cell disease is not the same as the more common iron deficiency anaemia. Patients should not take iron supplements to treat it without seeking medical advice as it could be dangerous. If anaemia is particularly severe or persistent, treatment with blood transfusions or hydroxycarbamide may be necessary.¹⁹ NICE recommends the use of spectra optia for automated red blood cell exchange in patients with sickle cell disease who need regular transfusion.²¹

EFFICACY and SAFETY

Trial	GBT_HOPE, NCT03036813, ABC-123; voxelotor dose 1 (900mg) vs voxelotor dose 2 (1500mg) vs placebo; phase III
Sponsor	Global Blood Therapeutics
Status	Ongoing
Source of Information	Poster, ² trial registry, ³ global data. ²²
Location	EU (incl UK), USA, and other countries.
Design	Randomized, double-blind, placebo-controlled, multicentre
Participants	n=400 (planned); aged 12-65 years; males and females; have had at least 1 episode of vaso-occlusive crisis (VOC) in the past 12 months; haemoglobin (Hb) ≥ 6.0 and ≤ 10.5 g/dL during screening; for participants taking hydroxyurea (HU), the dose of HU (mg/kg) must be stable for at least 3 months prior to signing the ICF.
Schedule	Randomised to 900 mg of voxelotor, orally; or 1500 mg of voxelotor, orally; or placebo orally.
Follow-up	Active treatment for 24 weeks, follow-up 24 weeks.
Primary Outcomes	Proportion of participants with increase in Hb >1 g/dL from baseline to week 24
Secondary Outcomes	Time frame from baseline to 24 weeks. <ul style="list-style-type: none"> • Proportion of days with SCD symptom exacerbation • Change in the sickle cell disease severity measure (SCDSM) total symptom score
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as June 2019.

Trial	NCT02850406, GBT440-007; children aged 12-17 years; voxelotor; phase II
Sponsor	Global Blood Therapeutics
Status	Ongoing
Source of Information	Trial registry, ²³ Manufacturer, ²⁴ global data. ²⁵
Location	USA
Design	Single group assignment, open label.
Participants	n=41 (planned); aged 12-17 years; males or females; homozygous haemoglobin SS (HbSS) or haemoglobin S beta0 thalassemia (HbS $\beta 0$ thal); for subjects taking hydroxyurea, the dose must be stable for at least 3 months with no anticipated need for dose adjustments during the study and no sign of haematological toxicity.
Schedule	Subjects to receive daily oral dosing of voxelotor for 1 day (single dose) or up to 24 weeks (multiple dose)
Follow-up	Active treatment for 24 weeks, follow-up 24 weeks.

Primary Outcomes	<p>Part A: Time Frame: pre-dose to day 15</p> <ul style="list-style-type: none"> • Pharmacokinetic profile of voxelotor including maximum concentration • Pharmacokinetic profile of voxelotor including the time taken to reach the maximum concentration • Pharmacokinetic profile of voxelotor including the total drug concentration over time <p>Part B: Change in haemoglobin [time frame: baseline to week 24]</p>
Secondary Outcomes	<p>Part A: Number of participants with treatment-related adverse events as assessed by CTCAE v4.03 [time frame: days 1 - 15]</p> <p>Part B:</p> <ul style="list-style-type: none"> • Multiple dose effect on clinical measures of haemolysis [time frame: day 1 - week 24] • Part B: Pharmacokinetic profile of voxelotor including maximum concentration [time frame: pre-dose to week 24] • Part B: Pharmacokinetic profile of voxelotor including the time taken to reach the maximum concentration [time frame: pre-dose to week 24] • Part B: Pharmacokinetic profile of voxelotor including the total drug concentration over time [time frame: pre-dose to week 24]
Key Results	Preliminary results in adolescents who received a single oral dose of 600 mg of voxelotor showed that the pharmacokinetics and half-life of voxelotor were similar in adolescents and adults, with results supporting once-daily dosing and a high specificity for haemoglobin.
Adverse effects (AEs)	Preliminary results in adolescents who received a single oral dose of 600 mg of voxelotor showed that voxelotor was well tolerated, with no serious or severe adverse events related to study drug observed.
Expected reporting date	Study completion date reported as May 2018.

Trial	NCT03041909, GBT440-024; adults aged 18-60 years; voxelotor; phase II
Sponsor	Global Blood Therapeutics
Status	Ongoing, not recruiting
Source of Information	Trial registry, ²⁶ global data. ²⁷
Location	UK
Design	Single group assignment, open label
Participants	n=16 (planned); aged 18-60 years; male or females; >50 kg who have participated in the GBT440-001 study; if female and of child bearing potential, agree to continue to use highly effective methods of contraception prior to enrolment in this study and for 3 months after the last dose of study drug; if male, are willing to continue to use barrier methods of contraception, prior to enrolment in this study to 3 months after the last dose of study drug.
Schedule	voxelotor 900mg oral drug
Follow-up	Active treatment for 6 months, follow-up 6 months.
Primary Outcomes	The incidence of treatment-emergent adverse events during dosing of GBT440 for up to 6 months. [time frame: 2 - 6 months]
Secondary Outcomes	<p>Time frame: 2 - 6 months</p> <ul style="list-style-type: none"> • To assess the efficacy of voxelotor as measured by improvements in anemia • To observed pharmacokinetics in plasma and whole blood.

	<ul style="list-style-type: none"> • To characterize the effect of voxelotor on haemolysis.
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as August 2017.

ESTIMATED COST and IMPACT

COST

The cost of voxelotor is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other: | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|--|
| <input type="checkbox"/> Increased use of existing services | <input checked="" type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other: | <input type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input checked="" type="checkbox"/> Other reduction in costs: <i>reduced use of secondary care/specialist services and reduced need for interventional procedures</i> |
| <input type="checkbox"/> Other | <input type="checkbox"/> None identified |

OTHER ISSUES

- Clinical uncertainty or other research question identified: None identified

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