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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

CTX001 for severe sickle cell disease

NIHRIO ID	28065	**NICE ID**	10589
Developer/Company	Vertex Pharmaceuticals Inc, CRISPR Therapeutics	**UKPS ID**	Not available

Licensing and market availability plans	Currently in phase II clinical trials.

SUMMARY

CTX001 is in clinical development for patients with severe sickle cell disease (SCD). SCD is a group of inherited disorders where the red blood cells become hard and sticky and look like a C-shaped farm tools called a "sickle" and these sickle red blood cells die early. Individuals with SCD have inherited the gene for sickle haemoglobin from one parent and a gene for an abnormal haemoglobin variant from their other parent. Sickle-shaped red blood cells do not flow easily through the blood vessels and can cause episodic blockages (vaso-occlusive crises) in different parts of the body. Currently the only curative treatment option available for severe SCD patients is a stem cell transplant from a donor but many people will require lifelong treatment. Management focuses on reducing the chances of experiencing a sickle cell crisis by avoiding dehydration, sudden changes in temperature and infection.

CTX001 is an ex vivo CRISPR investigational gene-edited therapy that is administered intraveneously. The patient's haematopoietic stem cells are genetically engineered to produce high levels of fetal haemoglobin (HbF) in red blood cells. The elevation of HbF by CTX001 has the potential to reduce painful and debilitating sickle crises for SCD patients. If licensed CTX001 will offer a treatment for patients with severe SCD.

PROPOSED INDICATION

For the treatment of individuals aged 12 to 35 years with severe sickle cell disease (SCD).[1]

TECHNOLOGY

DESCRIPTION

CTX001 is an ex vivo CRISPR investigational gene-edited therapy that is currently being assessed for patients suffering from severe sickle cell disease in which their immature bone marrow (haematopoietic) cells are retrieved. These cells are engineered to make them produce gamma-globin, one of the components of foetal haemoglobin (haemoglobin F; HbF) present in red blood cells, which is normally not produced beyond one year after birth. The modified cells are expected to produce gamma-globin which will in turn lead to the production of HbF when transplanted back to the patient. CTX001 elevates HbF and has the potential to reduce debilitating and painful sickle cell crises for patients with severe sickle cell disease (SCD).[2,3]

This process is expected to increase the formation of new red blood cells and reduce anaemia. The engineering of the cells is made using CRISPR-cas9, an enzyme combined with a small piece of genetic material (RNA) that is capable of editing a specific gene. CTX-001 causes CRISPR-cas9 to create defects in a gene for a protein called BCL11A which normally stops the production of gamma-globin. These defects prevent the production of BCL11A and allow gamma-globin to be produced.[3]

CTX001 is in clinical development for the treatment of adolescents and adults with SCD. CTX001 is currently in phase I/II clinical trial (NCT03745287; NCT04208529). Participants will receive an intravenous (IV) injection of CTX001 following myeloablative conditioning with busulfan.[1]

INNOVATION AND/OR ADVANTAGES

Currently the only curative treatment option available for severe SCD patients is a stem cell transplant from a donor.[4]

Where a donor is not available, CTX001 can provide a stem cell treatment option; as the transplanted stem cells are autologous (meaning that a donor is not required), this approach may avoid complications such as graft versus host disease (GvHD).[4] It is also an advanced approach to gene-editing for SCD.[2]

CTX001 is the first-in-human, CRISPR-Cas9–modified autologous hematopoietic stem and progenitor cells (HSPC) product. Preliminary data demonstrates that CTX001 is a potential functional therapy for the treatment of SCD.[5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

CTX001 does not currently have Marketing Authorisation in the EU/UK for any indication.

CTX001 was granted the following drug designations:[2,3,6]

- EMA orphan drug designation in October 2019
- EMA PRIME designation in September 2020
- FDA Regenerative Medicine Advanced Therapy in May 2020

PATIENT GROUP

DISEASE BACKGROUND

Sickle cell disease (SCD) is an inherited chronic haemolytic anaemia that results from a single amino acid substitution in the β-globin chain, producing the abnormal haemoglobin-S (HbS). The condition causes red blood cells to become rigid and misshapen, to resemble a crescent (or sickle). Sickle-shaped red blood cells do not flow easily through the blood vessels and can cause blockages (vaso-occlusion) in different parts of the body. Episodes of vaso-occlusion are known as vaso-occlusive crises. These lead to insufficient oxygen being delivered to tissues and organs, causing ischaemic injuries and excruciating pain.[7]

The frequency, severity and duration of these crises vary. Painful (known as pain crises) or damaging blockages, for example to the lung (known as acute chest syndrome) or brain (leading to a stroke), are called acute sickle cell crises. Other complications of vasoocclusive crises include blindness because of damage to the retina, skin ulcers if small blood vessels are blocked, and increased risk of infection if there is sustained damage to the spleen.[7]

Other sickle cell crises are a result of severe anaemia. These include splenic sequestration (the spleen gets enlarged because sickle red blood cells get trapped in the spleen), aplastic crisis (the bone marrow suddenly stops producing red blood cells because of a virus), and haemolytic crisis (increased rate of red blood cell destruction).[7]

CLINICAL NEED AND BURDEN OF DISEASE

SCD is estimated to affect 1 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 sickle cell disease and a further 9500 babies are found to be carriers of the disease.

There are more than 12,500 people with sickle cell disease in England, and about 240,000 are carriers. The highest prevalence of sickle cell disease is among Black African and Black Caribbean people, but cases also occur in families originating from the Middle East, parts of India, the eastern Mediterranean, and South and Central America; the common factor to this geographical distribution is a history of malaria, or migration from a malarial area. Due to population migration, however, sickle cell disease is an important part of clinical practice in most countries.[8]

Life expectancy of those with SCD has improved considerably over the last decades, due to improvements in the management of infections and other complications in childhood; new interventions; active health maintenance for adults and counselling. It is estimated that more than 90% of people of all phenotypes will survive past 20 years of age, and significant numbers are older than 50 years of age.[9] However, their lifespan is shortened by 20 to 30 years compared to the general population, with a median age at death of approximately 40 to 50 years.[10-14]

In 2019-2020 in the UK there were 27,924 hospital admissions with a primary diagnosis of sickle-cell disorders (ICD-10 code D57), 33,003 finished consultant episodes and 46,631 bed

days. In 2019-2020 in the UK there were 76,689 hospital admissions with a primary diagnosis of disorders of iron metabolism (ICD-10 code E83.1), 76,750 finished consultant episodes and 1,047 FCE bed days.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

SCD usually requires lifelong treatment. Management focuses on reducing the chances of experiencing a sickle cell crisis by avoiding dehydration, sudden changes in temperature and infection. Patients with SCD are supported by a team consisting of different healthcare professionals usually working together at a specialist sickle cell centre. The healthcare team allocated to the patient helps the patient learn about SCD and come up with a tailored care plan that considers the health concerns and health needs of the patient.[4,7]

CURRENT TREATMENT OPTIONS

There are different approaches to the management of SCD depending on whether the patient is experiencing a sickle cell crisis or chronic complications. The current management approaches include:[4,7]

- Pain management with paracetamol, non-steroidal anti-inflammatory drugs and opiates appropriate to the age and severity of symptoms. Prevention of painful episodes or crisis through water consumption to reduce dehydration, wearing warm clothes to keep warm and avoiding a sudden change in temperature.
- Administration of medicine such as hydroxycarbamide can also be used to increase the production of foetal haemoglobin, which improves blood cell hydration and reduces red blood cell adhesion which can reduce both acute painful crises and, acute chest syndrome (caused by reduced blood flow in the lungs) in people with recurrent painful crises
- Pain medicines during painful crises
- Blood transfusions including exchange transfusions (where sickle red blood cells are replaced with healthy red blood cells) and simple (top-up) transfusions can help to maintain a healthy proportion of normal red blood cells to sickle red blood cells
- Allogeneic stem cell transplant may be considered in children, and more recently in adults, who have severe disease

There are no NICE guidelines published on appropriate treatment or chronic management of SCD, which indicates the limited effectiveness and evidence base of current treatments.

PLACE OF TECHNOLOGY

If licensed, CTX001 will offer a treatment option for patients with severe SCD.

CLINICAL TRIAL INFORMATION

Trial	**NCT03745287, 2018-001320-19; A Phase 1/2 Study to Evaluate the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and**	**NCT04208529, 2018-002935-88; A Long-term Follow-up Study of Subjects With β-thalassemia or Sickle Cell Disease Treated With Autologous CRISPR-Cas9 Modified Hematopoietic Stem Cells (CTX001)**

	Progenitor Cells (CTX001) in Subjects With Severe Sickle Cell Disease **Phase I/II - Recruiting** **Location(s): 3 EU countries, UK, USA and Canada**	**Location(s): 4 EU countries, UK,USA and Canada**
Trial design	Open label and single group assignment	Observational, prospective and cohort
Population	n=45 (planned); aged 12 to 35 years with a diagnosis of SCD as defined by a documented severe SCD genotype, a history of at least two severe vaso-occlusive crisis events per year for the previous two years prior to enrolment, and eligibility for autologous stem cell transplant as per investigators judgment.	n=90 (planned) adults aged 18 years and over who complete or discontinue the parent study (CTX001-111 or CTX001-121) after CTX001 infusion; subjects or legal representative or guardian (if applicable) must sign and date informed consent form (ICF).
Intervention(s)	Participants will receive CTX001 IV infustion following myeloabltive conditioning with busulfan.	Participants will receive CTX001 infusion
Comparator(s)	-	-
Outcome(s)	• Proportion of subjects with HbF ⩾20%, sustained for at least 3 months at the time of analysis, starting 6 months after CTX001 infusion [Time Frame: 6 months up to 2 years after CTX001 infusion] • Proportion of subjects with engraftment (absolute neutrophil count [ANC] ⩾500/µL for three consecutive days) [Time Frame: Within 42 days after CTX001 infusion] • Time to engraftment [Time Frame: From CTX001 infusion up to 2 years after CTX001 infusion] • Frequency and severity of collected adverse events (AEs) [Time Frame: From screening to 2 years after CTX001 infusion] • Incidence of transplant-related mortality (TRM) within 100 days after CTX001 infusion [Time	• New malignancies [Time Frame: Signing of informed consent up to 15 years post CTX001 infusion] • New or worsening hematologic disorders [Time Frame: Signing of informed consent up to 15 years post CTX001 infusion] • All-cause mortality [Time Frame: Signing of informed consent up to 15 years post CTX001 infusion] • Serious adverse events (SAEs) occurring up to 5 years after CTX001 infusion [Time Frame: Signing of informed consent up to 5 years post CTX001 infusion] • CTX001-related AEs [Time Frame: Signing of informed consent up to 15 years post CTX001 infusion] See trial records for full list of other outcomes

	Frame: Within 100 days after CTX001 infusion] • Incidence of TRM within 1 year after CTX001 infusion [Time Frame: Within 1 year after CTX001 infusion] • All-cause mortality [Time Frame: 2 years after mobilization] See trial records for full list of other outcomes	
Results (efficacy)	• Increases in total Hb and HbF occurred early and were maintained over time; mean %HbF increased to >30% by 3 months following infusion. • Pancellular expression of HbF following CTX001 infusion demonstrates homogenous distribution of HbF. – The mean proportion of circulating red blood cells expressing HbF (F-cells) increased to >95%. • All 7 patients have remained VOC-free from CTX001 infusion to the time of this analysis, with up to 22.4 months of total follow-up.[16]	-
Results (safety)	• The safety profile of CTX001 is generally consistent with myeloablation and autologous haematopoietic stem cell transplant. • Post-CTX001 infusion, 1 patient experienced a serious AE (SAE) related to busulfan: sepsis; resolved. • No SAEs related to CTX001 were reported.[16]	-

ESTIMATED COST

The cost of CTX001 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE quality standard. Sickle cell disease (QS58). April 2014.
- NICE clinical guidelines. Sickle cell disease: managing acute painful episodes in hospital. June 2012.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Services for Haemoglobinopathy Care (All Ages). B08/S/a.
- NHS England. Allogeneic haematopoietic stem cell transplantation for adults with sickle cell disease. 190138P.

OTHER GUIDANCE

- Sickle Cell Society. Sickle Cell Disease in Childhood: Standards and Recommendations for Clinical Care. 2019.[17]
- Sickle Cell Society. Standards for the clinical care of adults with sickle cell disease in the UK. 2018.[18]
- NICE Clinical Knowledge Summary. Sickle cell disease. November 2016.[19]

ADDITIONAL INFORMATION

Vertex Pharmaceuticals Inc did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines.

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.