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HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

CTX001 for transfusion-dependent beta (β)-thalassaemia

NIHRIO ID	24357	**NICE ID**	10586
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 under clinical development for the treatment of patients with beta-thalassaemia who require blood transfusions. Thalassaemia is a commonly inherited blood disorder resulting from an abnormality in one of the genes that affects the production of haemoglobin, a protein in red blood cells that carries oxygen throughout the body. Beta-thalassaemia is a subtype caused by a specific gene mutation. People with thalassaemia produce either little or no normal haemoglobin. Current treatment options for beta-thalassaemia are limited to blood transfusions with its associated risks and complications.

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 foetal haemoglobin (HbF; haemoglobin F) in red blood cells. The elevation of HbF by CTX001 has the potential to improve transfusion requirements for beta-thalassaemia patients. If licensed CTX001 will offer a treatment for patients with transfusion-dependent beta-thalassaemia.

PROPOSED INDICATION

This briefing reflects the evidence available at the time of writing 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. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

For the treatment of adolescent and adult patients aged 12 to 35 years with transfusion-dependent beta-thalassaemia (TDT).[1,2]

TECHNOLOGY

DESCRIPTION

CTX001 is an ex vivo CRISPR investigational gene-edited therapy that is currently being assessed for patients suffering from transfusion dependent beta-thalassemia (TDT) 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 foetal haemoglobin when transplanted back to the patient.[3,4]

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 elevates HbF and has the potential to improve transfusion requirements for TDT patients.[4]

CTX001 is currently in phase I/II clinical trial (NCT03655678; NCT04208529) for TDT. Participants will receive an intravenous (IV) injection following myeloablative conditioning with busulfan.[1,2]

INNOVATION AND/OR ADVANTAGES

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

CTX001 is a new approach for TDT patients. 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). It is also currently an advanced approach to gene-editing for TDT.[4]

CTX001 is the first-in-human, CRISPR-Cas9–modified autologous hematopoietic stem and progenitor cells (HSPC) product.[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:[3,6,7]

- EMA orphan drug designation in October 2019
- EMA PRIME designation in April 2021
- FDA orphan drug designation in May 2020
- FDA Regenerative Medicine Advanced Therapy in May 2020

PATIENT GROUP

DISEASE BACKGROUND

Thalassaemia is an inherited blood disorder that decreases the production of functional haemoglobin (the protein in red blood cells that carries oxygen). This leads to a shortage of normal functioning red blood cells and low levels of oxygen in the bloodstream. There are two main types of thalassaemia: alpha thalassaemia and beta thalassaemia, which affect a different part of the haemoglobin molecule. Haemoglobin is made up of two different components (subunits): alpha globin and beta globin.[8] Beta-thalassaemia is caused by mutations in the HBB gene, which provides instructions for making beta globin, and is typically inherited in an autosomal recessive manner. This means that individuals with thalassemia intermedia or thalassemia major have a mutation in both of their copies of the HBB gene. People who have only one HBB gene mutation (carriers) are typically said to have thalassemia minor (or trait) and usually do not have symptoms, but may have some symptoms of anaemia.[9]

Beta-thalassaemia comprises a number of different phenotypes with varying severity, including:[9]

- Transfusion-dependent thalassaemia: Includes patients with beta-thalassaemia major or severe forms of beta-thalassaemia intermedia which require regular red blood cell transfusions.
- Non-transfusion dependent thalassaemia: Includes patients with mild-to-moderate beta-thalassaemia intermedia who may require infrequent transfusions to manage the disease and its complications.
- Beta-thalassaemia trait (minor): heterozygous patients with mild, usually asymptomatic anaemia that generally does not require treatment (excluded from the luspatercept target patient population).

The signs and symptoms of thalassemia vary depending on the severity of the condition. People affected by milder forms of thalassemia can develop mild anaemia or may have no signs or symptoms of the condition at all. Intermediate forms of thalassemia can cause mild to moderate anaemia and iron overload, which may be associated with other health problems, including: slowed growth, delayed puberty, bone problems and/or an enlarged spleen. In addition to the signs and symptoms seen in intermediate thalassemia, people with severe forms of thalassemia may also experience severe anaemia, iron overload, poor appetite, paleness, dark urine, yellow discoloration of skin (jaundice), and enlarged liver or heart.[8]

The long-term prognosis for people with thalassaemia depends on the type and severity of the condition. For example, severe thalassaemia can cause early death due to heart failure or liver complications, while less severe forms of thalassaemia often do not shorten lifespan. Improved treatment options have resulted in increased survival and better quality of life for people affected by moderate to severe thalassaemia.[8]

According to a Greek study, even with optimal care with access to regular transfusions and iron chelating therapy, the overall survival of a patient with TDT is significantly reduced compared to people without the disease, with only 65% surviving to age 50.[10] A Cypriot study demonstrated that most common cause of mortality in TDT is cardiac failure related to iron overload.[11]

CLINICAL NEED AND BURDEN OF DISEASE

Globally, about 80-90 million people, or 1.5% of the population, are carriers of the beta thalassemia causing mutation, with an estimated 60,000 symptomatic individuals born

annually.[12,13] Approximately 1,000 people are affected by thalassaemia with around 214,000 carriers in England. The highest prevalence of thalassaemia is found in Bangladeshi, Chinese, Cypriot, Indian and Pakistani communities.[14]

In England in 2019-2020 there were 15,101 hospital admissions, 15,156 finished consultant episodes and 1,665 bed days for a primary diagnosis of beta-thalassaemia (ICD-10 code D56.1)[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Individuals with thalassaemia major or other serious types require specialist care throughout their lives. Currently, the main treatments for beta thalassaemia are:[16]

- Blood transfusions – once a month.
- Chelation therapy – treatment with medications to remove the excess iron from the body that builds up as a result of the disease and the regular blood transfusions. Some people experience a build-up of iron even without transfusions and need treatment for this.

Currently, the only possible cure for thalassaemia is a stem cell or bone marrow transplant, however, this is not often done because of donor availability or the significant risks involved.[16]

CURRENT TREATMENT OPTIONS

To remove excess iron from the body, chelating agents are used.There are 3 chelating agents currently available:[16]

- Desferrioxamine (DFO) – given as an infusion, where a pump slowly feeds the liquid medicine through a needle into your skin over 8 to 12 hours; this is done 5 or 6 times a week
- Deferiprone (DFP) – taken as a tablet or liquid 3 times a day; it's sometimes used alongside DFO to reduce the number of infusions you need
- Deferasirox (DFX) – taken once a day as a tablet that you dissolve in a drink.

PLACE OF TECHNOLOGY

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

CLINICAL TRIAL INFORMATION

Trial	**NCT03655678, 2018-001320-19; A Phase 1/2 Study of the Safety and Efficacy of a Single Dose of Autologous CRISPR-Cas9 Modified CD34+ Human Hematopoietic Stem and Progenitor Cells (hHSPCs) in Subjects With Transfusion-Dependent β-Thalassemia** **Phase I/II - Recruiting**	**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)** **Location(s): 5 EU countries, UK,USA and Canada**

	Location(s): 3 EU countries, UK, USA and Canada **Estimated primary completion date: February 2021**	
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 TDT as defined by documented homozygous β-thalassaemia or compound heterozygous β-thalassaemia including β-thalassaemia/haemoglobin E (HbE). Subjects can be enrolled based on historical data, but a confirmation of the genotype using the study central laboratory will be required before busulfan conditioning. History of at least 100 mL/kg/year or ⩾10 units/year of packed RBC transfusions in the prior 2 years before signing the consent or the last rescreening for patients going through re-screening; eligible for autologous stem cell transplant as per investigator's 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 infusion following myeloablative conditioning with busulfan.	Participants will receive CTX001 infusion
Comparator(s)	-	-
Outcome(s)	- Proportion of subjects achieving transfusion reduction for at least 6 months (TR6) [Time Frame: From 3 to 24 months post-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 neutrophil and platelet engraftment [Time Frame: Days post-infusion to engraftment]	- 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]

	- Frequency and severity of collected adverse events (AEs) [Time Frame: Signing of informed consent through Month 24 visit] - Incidence of transplant-related mortality (TRM) [Time Frame: Baseline (pre-transfusion) to 100 days and 1 year post-CTX001 infusion] - All-cause mortality [Time Frame: Signing of informed consent through Month 24 visit]	- CTX001-related AEs [Time Frame: Signing of informed consent up to 15 years post CTX001 infusion]
Results (efficacy)	• Increases in total Hb and HbF occurred early and were maintained over time. • Pancellular expression of HbF following CTX001 infusion demonstrates homogenous • distribution of HbF. – The mean proportion of circulating RBCs expressing HbF (F-cells) increased to >95%. • All 15 patients were transfusion-free at the time of this analysis (within a median of 0.9 months after CTX001 infusion [range: 0.7 to 2.0 months]), with up to 26.2 months of total follow-up.[17]	-
Results (safety)	• The safety profile of CTX001 is generally consistent with myeloablation and autologous • hematopoietic stem cell transplant. • 1 patient had 4 serious AEs (SAEs) assessed by the investigator as related or possibly related to CTX001: headache, haemophagocytic lymphohistiocytosis(HLH), acute respiratory distress	-

	syndrome, and idiopathic pneumonia syndrome (latter also • related to busulfan), all in the context of HLH. • 3 patients experienced SAEs assessed as related or possibly related to busulfan only: • venoocclusive liver disease (2 patients), febrile neutropenia (1 patient), colitis (1 patient), • and pneumonia (1 patient). All were previously reported, except for the SAE of pneumonia. • All of these SAEs have resolved. • In addition to the safety data presented above, which includes all patients dosed with CTX001 with ≥3 months of follow-up as of the data cut of 30 March 2021, an additional SAE is included here, in a patient with <3 months of follow-up as of the data cut of 30 March 2021. This patient experienced an SAE of cerebellar hemorrhage, assessed by the investigator to be life-threatening, related to busulfan-induced thrombocytopenia, • and not related to CTX001. The SAE has since resolved.[17]	

ESTIMATED COST

The cost of CTX001 is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- No relevant guidance identified.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Specialised Services for Haemoglobinopathy care (all ages). B08/S/a.

OTHER GUIDANCE

- UK Thalassemia Society. Standards for the Clinical Care of Children and Adults with Thalassaemia in the UK. 2016.[18]

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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