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Public summary of opinion on orphan designation

Autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene for the treatment of sickle cell disease

On 9 January 2020, orphan designation EU/3/19/2242 was granted by the European Commission to Vertex Pharmaceuticals (Ireland) Limited, Ireland, for autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene (CTX001) for the treatment of sickle cell disease.

What is sickle cell disease?

Sickle cell disease is a genetic disease in which the red blood cells become rigid and sticky and change from being disc-shaped to being crescent-shaped (like a sickle). The change in shape is caused by the presence of an abnormal form of haemoglobin, the protein in red blood cells that carries oxygen around the body.

In patients with sickle cell disease, the abnormal red blood cells attach to the walls of blood vessels and block them, restricting the flow of oxygen-rich blood to the internal organs such as the heart, lungs and spleen. The disease causes severe pain and damage to these organs as well as repeated infections and anaemia (low red-blood-cell counts).

Sickle cell disease is a severe disease that is long-lasting and may be life-threatening because of damage to the heart and the lungs, anaemia and infections.

What is the estimated number of patients affected by the condition?

At the time of designation, sickle cell disease affected approximately 1.3 in 10,000 people in the European Union (EU). This was equivalent to a total of around 67,000 people*, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

*Disclaimer: For the purpose of the designation, the number of patients affected by the condition is estimated and assessed on the basis of data from the European Union (EU 28), Norway, Iceland and Liechtenstein. This represents a population of 518,400,000 (Eurostat 2019).

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What treatments are available?

At the time of designation, the only medicine authorised in the EU to treat sickle cell disease was hydroxycarbamide, also known as hydroxyurea. The main treatment for sickle cell disease was blood transfusion. In some cases, haematopoietic (blood) stem cell transplantation (a complex procedure where the patient receives stem cells from a matched donor to help restore the bone marrow) was used to allow the patient to produce red blood cells containing normal haemoglobin.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with sickle cell disease. This is because early studies demonstrate that a single treatment resulted in consistent production of foetal haemoglobin over at least 4 months, which reduced the need for other treatments such as transfusions. This assumption will need to be confirmed at the time of marketing authorisation in order to maintain the orphan status.

How is this medicine expected to work?

The medicine is made up of immature bone marrow (haematopoietic) cells that are taken from the patient. These cells are modified to make them produce gamma-globin, one of the components of foetal haemoglobin, which is normally not produced beyond one year after birth. When they are given back to the patient, the modified cells are expected to produce gamma-globin which will in turn lead to the production of foetal haemoglobin. This type of haemoglobin is expected to decrease the abnormal sickling of red blood cells and reduce anaemia.

The modification of the cells is made using CRISPR-Cas9, an enzyme combined with a small piece of genetic material (RNA) that is able to edit a specific gene. In this medicine, CRISPR-Cas9 creates 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.

What is the stage of development of this medicine?

The effects of the medicine have been evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials with the medicine in patients with sickle cell disease were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of sickle cell disease or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000, the COMP adopted a positive opinion on 5 December 2019, recommending the granting of this designation.

Opinions on orphan medicinal product designations are based on the following three criteria:

- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the EU) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

For more information

Sponsor's contact details:

Contact details of the current sponsor for this orphan designation can be found on EMA website.

For contact details of patients' organisations whose activities are targeted at rare diseases see:

- Orphanet, a database containing information on rare diseases, which includes a directory of patients' organisations registered in Europe;
- European Organisation for Rare Diseases (EURORDIS), a non-governmental alliance of patient organisations and individuals active in the field of rare diseases.

Translations of the active ingredient and indication in all official EU languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene	Treatment of sickle cell disease
Bulgarian	Автоложни CD34+ хематопоетични стволови клетки с регион на CRISPR-редактиран еритроиден усилвател на гена *BCL11A*	Лечение на сърповидно-клетъчна анемия
Croatian	Autologne CD34+ hematopoetske matične stanice s regijom eritroidnog pojačivača gena *BCL11A* koja je uređena CRISPR-om	Liječenje bolesti srpastih stanica
Czech	Autologní CD34+ hematopoetické kmenové buňky s CRISPR-editovanou erytroidní enhancerovou oblastí genu *BCL11A*	Léčba srpkovité anémie
Danish	Autologe CD34+ hæmatopoietiske stamceller med en CRISPR-redigeret erytroid enhancer-region af *BCL11A*-genet	Behandling af seglcellesygdom
Dutch	Autologe CD34+ hematopoietische stamcellen met een CRISPR-gemodificeerd erytroïde enhancergebied van het *BCL11A*-gen	Behandeling van sikkelcelaandoening
Estonian	BCL11A geenis CRISPR-meetodil korrigeeritud erütroidse enhanser-piirkonnaga autoloogsed CD34+ vereloome tüvirakud	Sirprakulise aneemia ravi
Finnish	Autologiset CD34+ hematopoieettiset kantasolut, joissa on CRISPR-muokattu erytroidinen *BCL11A*-geenin tehostaja	Sirppisolusyndrooman hoito
French	Cellules souches hématopoïétiques CD34+ autologues avec une région amplificatrice de la lignée érythroïde du gène *BCL11A* corrigée par la technologie CRISPR	Traitement de la drépanocytose
German	Autologe CD34-positive hämatopoetische Stammzellen mit einer CRISPR-editierten erythroiden Enhancer-Region des *BCL11A*-Gens	Behandlung der Sichelzellenanämie
Greek	Αυτόλογα CD34+ αιμοποιητικά βλαστοκύτταρα με τροποποιημένη με CRISPR περιοχή ερυθροειδικού ενισχυτή του γονιδίου *BCL11A*	Θεραπεία της δρεπανοκυτταρικής αναιμίας

[1] At the time of designation

Language	Active ingredient	Indication
Hungarian	Autologinės CD34+ hematopoetinės kamieninės ląstelės su CRISPR-redaguotu eritroidų stiprintuvo regionu *BCL11A* gene	Sarlósejtes anaemia kezelése
Italian	Cellule staminali ematopoietiche autologhe CD34+ con una regione enhancer eritroide del gene *BCL11A* modificata con CRISPR	Trattamento dell'anemia falciforme
Latvian	Autologas CD34+ hematopoētiskās cilmes šūnas ar CRISPR-modificētu *BCL11A* gēna eritroīda pastiprinātāja reģionu	Sirpjveida šūnu anēmijas ārstēšana
Lithuanian	Autologinės CD34+ hematopoetinės kamieninės ląstelės su CRISPR-redaguotu *BCL11A* geno eritroidų gerinimo regionu	Siklemijos gydymas
Maltese	Ċelluli staminali ematopojetiċi CD34+ awtologi b'reġjun li jtejjeb l-eritojde editjat b'CRISPR tal-ġene *BCL11A*	Kura tal-marda taċ-ċelluli sura ta' minġel
Polish	Autologiczne krwiotwórcze komórki macierzyste o fenotypie CD34+ z wyłączonym techniką CRISPR rejonem erytroidalnym wzmacniającym ekspresję genu *BCL11A*	Leczenie niedokrwistości sierpowatokrwinkowej
Portuguese	Células estaminais hematopoiéticas autólogas CD34+ com uma região intensificadora de células eritroides do gene *BCL11A* editadas por CRISPR	Tratmento do sindrome das células falciformes
Romanian	Celule stem hematopoietice CD34+ autologe cu o regiune de potențare eritroidă a genei *BCL11A* modificată prin CRISPR	Tratamentul anemiei cu celule falciforme
Slovak	Autológne CD34+ hematopoetické kmeňové bunky s erytroidným enhancerom génu *BCL11A* upraveným CRISPR	Liečba kosáčikovej anémie
Slovenian	Autologne CD34+ hematopoetske matične stanice s regijom eritroidnog pojačivača gena *BCL11A* koja je uređena CRISPR-om	Zdravljenje bolezni srpastih celic
Spanish	Células madre hematopoyéticas CD34+ autólogas con una región eritroide potenciadora editada mediante CRISPR del gen *BCL11A*	Tratamiento de la anemia drepanocítica
Swedish	Autologa hematopoetiska CD34+-stamceller med en CRISPR-redigerad erytroidförstärkarregion i *BCL11A*-genen	Behandling av sickle cell syndrom
Norwegian	Autologe CD34+ hematopoietiske stamceller med en CRISPR-redigert erytroid forsterkerregion for *BCL11A*-genet	Behandling av sigdcellesykdom

Language	Active ingredient	Indication
Icelandic	Samgena CD34+ blóðmyndandi stofnfrumur með CRISPR-breyttu rauðkornaeflissvæði á *BCL11A* geninu	Meðferð sigðkornablóðleysis