9 January 2020
EMADOC-628903358-1532

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 beta-thalassaemia intermedia and major

On 17 October 2019, orphan designation EU/3/19/2210 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 (also known as CTX001) for the treatment of beta-thalassaemia intermedia and major.

What is beta-thalassaemia intermedia and major?

Beta-thalassaemia is an inherited disease in which patients are unable to make enough haemoglobin, the protein found in red blood cells that carry oxygen around the body. Beta thalassaemia major is a severe form of the disease in which patients need frequent blood transfusions, while beta thalassaemia intermedia is a less severe form, which may worsen with age. Both types of beta thalassaemia are caused by defects in the gene responsible for producing beta-globin, one of the components of haemoglobin, which result in low levels of haemoglobin in the blood.

Beta thalassaemia intermedia and major are life-long debilitating diseases. They may be life threatening because of severe anaemia (low red blood-cell count due to lack of haemoglobin), the need for repeated blood transfusions and the risk of complications associated with them.

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

At the time of designation, beta-thalassaemia intermedia and major affected approximately 0.80 in 10,000 people in the European Union (EU). This was equivalent to a total of around 41,000 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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

What treatments are available?

At the time of designation, the main treatments for beta thalassaemia intermedia and major were blood transfusions and the use of iron chelators (medicines for reducing 'iron overload' - the high iron levels in the body caused by repeated blood transfusions). The gene therapy medicine Zynteglo was authorised to treat beta thalassaemia in patients 12 years and older who require regular blood transfusions. In some cases, allogeneic haematopoietic stem cell transplantation was used to cure the disease. This is a complex procedure where the bone marrow of the patient is cleared of cells and replaced with healthy bone marrow cells from a matched donor, allowing the patient to produce red blood cells with normal haemoglobin.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with beta-thalassaemia intermedia and major because early results from a clinical study suggest that this medicine could restore a normal level of haemoglobin; in addition, it has a different mechanism of action compared to existing treatments. 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 is expected to increase the formation of new 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 beta-thalassaemia intermedia and major were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of beta-thalassaemia intermedia and major 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 12 September 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+ haematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene	Treatment of beta-thalassaemia intermedia and major
Bulgarian	Автоложни CD34+ хематопоетични стволови клетки с регион на CRISPR-редактиран еритроиден усилвател на гена *BCL11A*	Лечение на бета таласемия интермедия и майор
Croatian	Autologne CD34+ hematopoetske matične stanice s regijom eritroidnog pojačivača gena *BCL11A* koja je uređena CRISPR-om	Liječenje beta-talasemije intermedije i major
Czech	Autologní CD34+ hematopoetické kmenové buňky s CRISPR-editovanou erytroidní enhancerovou oblastí genu *BCL11A*	Léčení beta thalasémie intermedia a major
Danish	Autologe CD34+ hæmatopoietiske stamceller med en CRISPR-redigeret erytroidenhancerregion af *BCL11A*-genet	Behandling af beta-thalassæmia intermedia og major
Dutch	Autologe CD34+ hematopoietische stamcellen met een CRISPR-gemodificeerd erytroïde enhancergebied van het *BCL11A*-gen	Behandeling van bètathalassemie intermedia en major
Estonian	CRISPR-meetodil korrigeeritud erütroidse ehnanserpiirkonnaga *BCL11A* geeni sisaldavad autoloogsed CD34+ vereloome tüvirakud	Intermedia - ja major-tüüpi beetatalasseemia ravi
Finnish	Autologiset CD34+ hematopoieettiset kantasolut, joissa on *BCL11A*-geenin CRISPR-muokattu erytroidinen tehostaja	Beetatalassemia intermedia - ja major-tyypin 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 bêta-thalassémie intermédiaire et majeure
German	Autologe hämatopoetische CD34^{+}-Stammzellen mit einer CRISPR-editierten erythroiden Enhancerregion des *BCL11A*-Gens	Behandlung der Beta-Thalassämie (Intermediäre und Major-Form)
Greek	Αυτόλογα CD34+ αιμοποιητικά βλαστικά κύτταρα με τροποποιημένη με CRISPR περιοχή ερυθροειδικού ενισχυτή του γονιδίου *BCL11A*	Θεραπεία της β-μεσογειακής αναιμίας, ενδιάμεσης και μείζονος
Hungarian	Autológ CD34+ hematopoetikus őssejtek a *BCL11A* gén CRISPR-szerkesztett eritroid génterápiás régiójával	Béta-talasszémia intermedia és major kezelése
Italian	Cellule staminali ematopoietiche autologhe CD34+ con una regione enhancer eritroide del gene *BCL11A* modificata con CRISPR	Trattamento della beta-talassemia intermedia e major

[1] At the time of designation

Language	Active ingredient	Indication
Latvian	Autologas CD34+ hematopoētiskās cilmes šūnas ar CRISPR-modificētu *BCL11A* gēna eritroīda pastiprinātāja reģionu	Vidēji izteiktas un izteiktas bēta talasēmijas ārstēšana
Lithuanian	Autologinės CD34+ hematopoetinės kamieninės ląstelės su CRISPR-redaguota *BCL11A* geno eritroidų stipriklio sritimi	Vidutinio sunkumo ir sunkios β-talasemijos gydymas
Maltese	Ċelluli staminali CD34+ ematopojetiċi awtologi b'reġjun li jsaħħaħ l-eritrojde editjat b'CRISPR tal-ġene *BCL11A*	Kura tal-beta talassemija intermedja u maġġuri
Polish	Autologiczne krwiotwórcze komórki macierzyste o fenotypie CD34+ z wyłączonym techniką CRISPR rejonem erytroidalnym wzmacniającym ekspresję genu *BCL11A*	Leczenie talasemii beta- intermedia i major
Portuguese	Células estaminais hematopoiéticas autólogas CD34+ com uma região intensificadora de células eritroides do gene *BCL11A* editadas por CRISPR	Tratamento da beta talassémia intermédia e major
Romanian	Celule stem hematopoietice CD34+ autologe cu regiune de potențare eritroidă modificată la nivelul CRISPR a genei *BCL11A*	Tratamentul beta talasemiei intermediare şi majore
Slovak	Autológne CD34+ hematopoetické kmeňové bunky s erytroidným enhancerom génu *BCL11A* upraveným CRISPR	Liečba stredne závažnej a závažnej beta talasémie
Slovenian	Avtologne CD34+ hematopoetske matične celice s CRISPR spremenjeno eritroidno okrepljeno regijo gena *BCL11A*	Zdravljenje srednje in velike talasemije beta
Spanish	Células madre hematopoyéticas CD34+ autólogas con una región eritroide potenciadora editada mediante CRISPR del gen *BCL11A*	Tratamiento de la beta talasemia intermedia y mayor
Swedish	Autologa hematopoetiska CD34+-stamceller med en CRISPR-redigerad erytroid förstärkningsregion i *BCL11A*-genen	Behandling av beta-thalassaemia intermedia och major
Norwegian	Autologe CD34+ hematopoietiske stamceller med en CRISPR-redigert erytroid forsterkerregion for *BCL11A*-genet	Behandling av beta-thalassemia intermedia og beta-thalassemia major
Icelandic	Samgena blóðmyndandi CD34+ stofnfrumur með CRISPR-genaleiðréttu rauðfrumueflandi svæði *BCL11A* gensins	Meðferð á beta-Miðjarðarhafsblóðleysi intermedia og beta-Miðjarðarhafsblóðleysi major