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Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide directed against *TMPRSS6* mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of beta-thalassaemia intermedia and major

On 11 January 2019, orphan designation (EU/3/18/2132) was granted by the European Commission to Silence Therapeutics GmbH, Germany, for synthetic double-stranded siRNA oligonucleotide directed against *TMPRSS6* mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues 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 iron-rich protein found in red blood cells that carries 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 0.3 in 10,000 people in the European Union (EU). This was equivalent to a total of around 16,000 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 517,400,000 (Eurostat 2018).

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' - high iron levels in the body caused by repeated 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 laboratory studies have shown that it might reduce iron levels in the blood and improve the anaemia. 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?

In patients with beta thalassaemia intermedia or major, excess iron can build up in the body damaging organs such as the heart and liver and reducing the formation of red blood cells.

This medicine is made of a small strand of synthetic genetic material, called 'small interfering RNA', which is expected to block the production of the TMPRSS6 protein. This protein controls the production of another protein, hepcidin, which regulates the levels of iron in the body. Hepcidin reduces the amount of iron in the blood by blocking absorption of iron from food and stopping the release of iron from iron-storage cells.

By reducing TMPRSS6 more hepcidin is produced. This is expected to improve iron regulation and to decrease the damaging effect of iron on the formation of red blood cells, thus improving anaemia and the symptoms of the condition.

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, no clinical trials with the medicine in patients with beta-thalassaemia intermedia and major had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for beta-thalassaemia intermedia and major or designated as an orphan medicinal product elsewhere for this condition.

In accordance with Regulation (EC) No 141/2000 of 16 December 1999, the COMP adopted a positive opinion on 6 December 2018 recommending the granting of this designation.

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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, on the 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 orphan condition in all official EU languages[1], Norwegian and Icelandic

Language	Active ingredient	Indication
English	Synthetic double-stranded siRNA oligonucleotide directed against *TMPRSS6* mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues	Treatment of beta-thalassaemia intermedia and major
Bulgarian	Синтетичен, двойно-спирален siRNA олигонуклеотид, насочен срещу *TMPRSS6* mRNA, ковалентно свързан с лиганд, съдържащ три остатъка на N-ацетил галактозамин	Лечение на бета таласемия интермедия и майор
Croatian	Sintetički oligonukleotid siRNK s dvostrukim lancem usmjeren protiv mRNK za *TMPRSS6*, kovaletno vezan za ligand koji sadržava tri N-acetilgalaktozaminske skupine	Liječenje beta-talasemije intermedije i major
Czech	Oligonukleotid syntetické dvouvláknové siRNA namířený proti mRNA *TMPRSS6*, který je kovalentně spojen s ligandem obsahujícím tři rezidua N-acetylgalaktosaminu	Léčení beta-thalasémie intermedia a major
Danish	Syntetisk dobbeltstrenget siRNA-oligonukleotid rettet mod *TMPRSS6*-mRNA og kovalent bundet til en ligand indeholdende tre N-acetylgalactosamin-rester	Behandling af beta-thalassæmia intermedia og major
Dutch	Synthetisch dubbelstrengig siRNA oligonucleotide gericht tegen *TMPRSS6* mRNA dat covalent gebonden is aan een ligand dat drie N-acetylgalactosamine residuen bevat.	Behandeling van bètathalassemie intermedia en major
Estonian	*TMPRSS6* mRNA vastu suunatud sünteetiline kaheahelaline siRNA oligonukleotiid, millega on kovalentselt seotud kolme N-atsetüülgalaktoosamiini jääki sisaldav ligand	Keskmise ja raske beetatalasseemia ravi

[1] At the time of designation

Finnish	*TMPRSS6* mRNA:ta vastaan kohdistettu synteettinen kaksoisjuosteinen siRNA-oligonukleotidi, joka on kovalenttisesti sidottu kolme N-asetyyligalaktosamiinitähdettä sisältävään ligandiin	Beetatalassemia intermedia - ja major-tyypin hoito
French	Petit ARN interférent (pARNi) oligonucléotidique synthétique double brin dirigé contre l'ARNm du gène *TMPRSS6*, lié de manière covalente à un ligand contenant trois résidus N-acétylgalactosamine	Traitement de la bêta-thalassémie intermédiaire et majeure
German	Synthetisches, doppelsträngiges siRNA Oligonukleotid, gerichtet gegen *TMPRSS6*-mRNA, das kovalent an einen Ligand mit drei N-Acetylgalactosamin-Restgruppen gebunden ist.	Behandlung der Beta-Thalassämie (Intermediäre und Major-Form)
Greek	Συνθετικό δίκλωνο siRNA ολι γονουκλεοτίδιο έναντι του *TMPRSS6*-mRNA, οποιοπολικά συνδεδεμένο με πρόσδεμα που περιέχει τρία υπολείμματα N-ακετυλογαλακτοζαμίνης.	Θεραπεία της β-μεσογειακής αναιμίας, ενδιάμεσης και μείζονος
Hungarian	A *TMPRSS6* mRNS-e elleni szintetikus kétszálú siRNS oligonukleotid, amely kovalens kötéssel kapcsolódik egy három N-acetil-galaktóztamin maradványt tartalmazó ligandumhoz	Béta-talasszémia intermedia és major kezelése
Italian	Oligonucleotide siRNA sintetico a doppio filamento diretto contro il mRNA del gene *TMPRSS6* legato in modo covalente ad un legante contenente tre residui di N-acetilgalattosamina	Trattamento della beta-talassemia intermedia e major
Latvian	Sintētisks dubultspirāles siRNA oligonukleotīds, kas vērsts pret *TMPRSS6* mRNS un ir kovalenti saistīts ar trīs N-acetilgalaktozamīna atliekas saturošu ligandu	Vidēji izteiktas un izteiktas bēta talasēmijas ārstēšana
Lithuanian	Sintetinis dvigrandis siRNR oligonukleotidas nukreiptas prieš *TMPRSS6* mRNR ir kovalentiškai sujungtas su trimis N-acetilgalaktozamino liekanomis	Vidutinio sunkumo ir sunkios β-talasemijos gydymas

Maltese	Oligonukleotid sintetiku tas-siRNA b'katina doppja dirett kontra *TMPRSS6* mRNA u magħqud b'mod kovalenti ma' ligand li fih tliet residwi ta' N-aċetilgalattosamina	Kura tal-beta talassemija intermedja u maġġuri
Polish	Syntetyczny dwuniciowy oligonukleotyd siRNA skierowany przeciwko mRNA *TMPRSS6* i połączony kowalencyjnie z ligandem zawierającym trzy reszty N-acetylogalaktozaminy	Leczenie talasemii beta- intermedia i major
Portuguese	Oligonucleótido sintético siRNA de cadeia dupla dirigido contra o mRNA do gene *TMPRSS6* e com ligação covalente a um ligante contendo três resíduos de N-acetilgalactosamina	Tratamento da beta talassémia intermédia e major
Romanian	Oligonucleotid sintetic siARN dublu catenar îndreptat împotriva ARNm *TMPRSS6* care este legat covalent de un ligand ce conține trei reziduuri de N-acetil-galactozamină	Tratamentul beta talasemiei intermediare şi majore
Slovak	Oligonukleotid syntetickej dvojvláknovej siRNA namierený proti mRNA *TMPRSS6* spojený kovalentnou väzbou s ligandom obsahujúcim tri reziduá N-acetylgalaktozamínu	Liečba stredne závažnej a závažnej beta talasémie
Slovenian	Sintetični dvoverižni oligonukleotid siRNA, usmerjen proti mRNA za *TMPRSS6*, ki je kovalentno vezan na ligand, ki vsebuje tri ostanke N-acetilgalaktozamina	Zdravljenje srednje in velike talasemije beta
Spanish	Oligonucleótido sintético con ARNip bicatenario dirigido contra el ARNm del gen *TMPRSS6* y unido covalentemente a un ligando que contiene tres residuos de N-acetilgalactosamina	Tratamiento de la beta talasemia intermedia y mayor
Swedish	Syntetisk dubbelsträngad siRNA-oligonukleotid riktad mot *TMPRSS6*-mRNA som är kovalent bunden till en ligand innehållande tre N-acetylgalaktosaminrester	Behandling av beta-thalassaemia intermedia och major
Norwegian	Syntetisk dobbelttrådet siRNA-oligonukleotid rettet mot *TMPRSS6* mRNA og kovalent bundet til en ligand som inneholder tre N-acetylgalaktosaminenheter	Behandling av beta-thalassemia intermedia og beta-thalassemia major

Icelandic	Tilbúið tvíþátta siRNA-ólígónúkleótíð sem beinist gegn *TMPRSS6* mRNA, tengt með samgildu tengi við bindil sem inniheldur þrenns konar leifar N-acetýlgalaktósamína	Meðferð á beta-Miðjarðarhafsblóðleysi intermedia og beta-Miðjarðarhafsblóðleysi major