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Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide directed against SERPINA1 mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues for the treatment of congenital alpha-1 antitrypsin deficiency

On 16 December 2019, orphan designation EU/3/19/2235 was granted by the European Commission to Dicerna Ireland Limited, Ireland, for synthetic double-stranded siRNA oligonucleotide directed against *SERPINA1* mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues (also known as DCR S1459) for the treatment of congenital alpha-1 antitrypsin deficiency.

What is congenital alpha-1 antitrypsin deficiency?

Congenital alpha-1 antitrypsin deficiency is an inherited disease characterised by a lack of normal forms of a protein called 'alpha-1 proteinase inhibitor' or 'alpha-1 antitrypsin' (AAT).

The liver makes AAT. One of the functions of AAT is to protect the lungs from an enzyme called neutrophil elastase. Neutrophil elastase attacks bacteria and other pathogens, and is also involved in breaking down damaged lung tissue. In patients lacking AAT, excessive neutrophil elastase activity can damage lung tissue and results in emphysema, which causes shortness of breath, coughing and wheezing. Sometimes, AAT deficiency can lead to a build-up of defective forms of AAT in liver cells, which can cause severe liver cirrhosis (scarring) often requiring liver transplantation.

Congenital AAT deficiency is a debilitating disease that is long lasting and can be life threatening due to worsening lung function and lung infections as well as liver injury.

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

At the time of designation, congenital alpha-1 antitrypsin deficiency affected approximately 2.4 in 10,000 people in the European Union (EU). This was equivalent to a total of around 124,000 people*, and is below the ceiling for orphan designation, which is 5 people in 10,000. This is based on the

*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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information provided by the sponsor and the knowledge of the Committee for Orphan Medicinal Products (COMP).

What treatments are available?

At the time of orphan drug designation, the medicine Respreeza (human alpha1-proteinase inhibitor) was authorised in the EU for slowing down the worsening of emphysema caused by congenital AAT deficiency and worked by replacing the missing enzyme. Patients were also given other medicines to manage the symptoms of obstructive lung disease and help prevent infections of the lungs and the airways. Some patients who developed liver disease were given liver transplantation.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with congenital alpha-1 antitrypsin deficiency because laboratory studies suggest that unlike current medicines, this medicine could treat patients with AAT disease affecting the liver.

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?

Patients with congenital AAT deficiency have a mutation (change) in the *SERPINA1* gene which causes the production of a defective AAT protein that builds up in the liver.

The medicine is made of a small strand of synthetic genetic material, called 'small interfering RNA' (siRNA), that interferes with the function of the gene *SERPINA1* and blocks the production of the defective protein. The medicine has been designed to allow it to enter the liver cells in order to reach the areas where the defective protein is assembled. This is expected to reduce the build-up of defective proteins and the damage to the liver.

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 congenital alpha-1 antitrypsin deficiency were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of congenital alpha-1 antitrypsin deficiency 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 7 November 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	Synthetic double-stranded siRNA oligonucleotide directed against SERPINA1 mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues	Treatment of congenital alpha-1 antitrypsin deficiency
Bulgarian	Синтетичен двойно-верижен siRNA олигонуклеотид, насочен срещу SERPINA1 иРНК, съдържащ четири модифицирани нуклеозиди, формиращи лиганден кластер от четири N-ацетилгалактозаминови остатъка	Лечение на вроден алфа-1 антитрипсинов дефицит
Croatian	Sintetički dvolančani siRNA oligonukleotid usmjeren protiv mRNA SERPINA1 i koji sadrži četiri modificirana nukleozida koji tvore ligandnu skupinu od četiri N-acetilgalaktozamin ostataka	Liječenje prirođenog manjka alfa-1-antitripsina
Czech	Syntetický dvouvláknový siRNA oligonukleotid namířený proti SERPINA1 mRNA a obsahující čtyři modifikované nukleosidy, které tvoří klastr ligandů čtyř N-acetylgalaktosoaminových reziduí	Léčba vrozeném deficitu alfa-1 antitrypsinu
Danish	Syntetisk dobbelt-strenget siRNA oligonucleotid rettet mod SERPINA1 mRNA, indeholdende fire modificerede nucleosider, som danner en ligand cluster af fire N-acetylgalactosaminenheder	Behandling af medfødt alfa-1 antitrypsinmangel
Dutch	Synthetisch dubbel-strengig siRNA oligonucleotide gericht tegen SERPINA1 mRNA en met vier gemodificeerde nucleosiden bevattend welke een ligand cluster vormen van vier N-acetylgalactosamineresiduen	Behandeling van aangeboren alfa-1 antitrypsine deficiëntie
Estonian	Sünteetiline kaheahelaline siRNA oligonukleotiid, mis on suunatud SERPINA1 mRNA vastu ja mis sisaldab nelja N-atsetüülgalaktoosamiini jäägiga ligandiklastrit moodustavat nelja modifitseeritud nukleosiidi	Kaasasündinud alfa-1 antitrüpsiini puudulikkuse ravi
Finnish	Synteettinen, kaksoiskierteinen siRNA oligonukleotidi, jonka kohteena on SERPINA1:n mRNA ja joka sisältää neljä muokattua nukleosidiä, jotka muodostavat neljä N-asetyyligalaktosamiini-jäämää sisältävän ligandi klusterin	Synnynnäisen alfa-1 antitrypsiinin puutteen hoito
French	Oligonucléotide d'ARNsi double-hélice ciblant l'ARNm SERPINA1 et contenant quatre nucléosides modifiés formant un sous-ensemble de quatre résidus de N-acetylgalactosamine	Traitement du déficit congénital en alpha-1 antitrypsine

[1] At the time of designation

Language	Active ingredient	Indication
German	Synthetisches doopelstraengiges siRNA Oligonucleotid, gerichtet gegen SERPINA1 mRNA, das vier modifizierte Nucleoside enthaelt, die einen Liganden-Cluster aus vier N- Acetylgalactosamin-Resten formen	Behandlung von erblichem Alpha-1 Antitrypsinmangel
Greek	Συνθετικό δίκλωνο siRNA ολιγονουκλεοτίδιο κατευθυνόμενο έναντι του mRNA του SERPINA1 και περιέχοντος τέσσερα τροποποιημένα νουκλεοσίδια που αποτελούν ένα σύμπλοκο συνδέτη από τέσσερα υπολείματα N-ακετυλγαλακτοσαμίνης	Θεραπεία της συγγενούς ανεπάρκειας άλφα-1 αντιθρυψίνης
Hungarian	Négy N-acetilgalaktózamin maradvány ligand klaszterét formázó négy módosított nukleozidot tartalmazó SERPINA1 mRNS elleni szintetikus duplaszálú siRNS oligonukleotid	Kongenitális alfa-1 antitripszin hiány kezelése
Italian	Oligonucleotide sintetico di siRNA a doppia elica diretto contro il RNA di SERPINA1, contenente quattro nucleosidi modificati che formano un insieme di ligandi di quattro residui di N-acetilgalattosamina.	Trattamento del deficit congenito di alfa-1 antitripsina
Latvian	Sintētisks divpavedienu siRNS oligonukleotīds, kas vērsts pret ERPINA1 mRNS and satur četrus modificētus nokleozīdus, kas veido četru N-scetilgalaktozamīna atlikumu ligandu klasteri	Iedzimta alfa -1 antitripsīna deficīta ārstēšana
Lithuanian	Sintetinis dvigrandis siRNR oligonukleotidas prieš SERPINA1 mRNR, turintis keturis modifikuotus nukleozidus, formuojančius ligandų klasterį iš keturių N-acetilgalaktozamino liekanų	Įgimtas alfa-1 antitripsino deficito gydymas
Maltese	Oligonukleotid sintetiku ta’ siRNA b'katina doppja dirett kontra SERPINA1 mRNA u li fih erba' nukleosidi modifikati li jiffurmaw ġabra ta' ligand ta' erba' residwi N-aċetilgalattosamina	Kura tan-nuqqas konġenitu ta’ l-alpha-1 antitrypsin
Polish	Syntetyczny dwuniciowy oligonukleotyd siRNA skierowany przeciw mRNA genu SERPINA1 oraz zawierający cztery zmodyfikowane nukleozydy, które tworzą klaster ligandu złożony z czterech reszt N-acetylgalaktozaminy	Leczenie wrodzonego niedoboru alfa-1 antytrypsyny
Portuguese	Oligonucleotídeo sintético siRNA de cadeia dupla dirigido contra o mRNA de SERPINA1 e contendo quatro nucleosídeos modificados que formam um aglomerado de ligantes de quatro resíduos de N-acetilgalactosamina	Tratamento da deficiência congénita em antitripsina alfa-1
Romanian	Oligonucleotid sintetic dublu catenar siARN îndreptat împotriva ARNm SERPINA1, ce conţine patru nucleozide modificate ce formează un cluster de legătură alcătuit din patru resturi de N-acetilgalactozamină	Tratamentul deficitului congenital de alfa-1 antitripsină

Language	Active ingredient	Indication
Slovak	Syntetická dvojvláknová siRNA oligonukleotidu namierenému proti SERPINA1 mRNA a obsahujucého štyri modifikované nukleozidy, ktoré vytvárajú zoskupenie ligandov so štyrmi N-acetylgalaktozamín zvyškami	Liečba deficitu alfa-1 antitrypsínu
Slovenian	Sintetični nukleotid dvoverižne siRNK usmerjen proti SERPINA1 mRNK, in vsebujoč 4 modificirane nukleozide, ki sestavljajo klasterski ligand štirih nukleozidov N-acetilcisteamina	Zdravljenje kongenitalnega pomanjkanja alfa-1 antitripsina
Spanish	Oligonucleotide de doble cadena siARN sintetico dirigia contra ARNm SERPINA1 que contiene cuatro nucleotides modificadas que forman un cluster de cuatroresiduos de N-acetilgalactosamina	Tratamiento del déficit congénito de alfa-1 antitripsina
Swedish	Syntetiskt dubbelsträngad siRNA oligonukleotid riktad mot SERPINA1 mRNA och innehållande fyra modifierade nukleosider vilka formar ett liganklusters av fyra N-acetylgalactosaminformer	Behandling av kongenital alpha-1 antitrypsin brist
Norwegian	Syntetisk dobbeltrådet siRNA oligonukleotid rettet mot SERPINA1 mRNA og som inneholder fire modifiserte nukleosider som danner et ligandkluster med fire enheter av N-acetylgalaktosamin	Behandling av alfa-1 antitrypsinmangel
Icelandic	Efnasmíðað tvíþátta siRNA fákirni miðað gegn SERPINA1 mRNA og með fjórum breyttum núkleósíðum sem mynda bindil-klasa úr fjórum N-acetýlgalaktósamín leifum	Meðferð á meðfæddum alfa-1 andtrýpsínskorti