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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of ATTR amyloidosis

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Disclaimer

Please note that revisions to the Public Summary of Opinion are purely administrative updates. Therefore, the scientific content of the document reflects the outcome of the Committee for Orphan Medicinal Products (COMP) at the time of designation and is not updated after first publication.

On 29 April 2014, orphan designation (EU/3/14/1267) was granted by the European Commission to Voisin Consulting S.A.R.L., France, for synthetic double-stranded siRNA oligonucleotide directed against transthyretin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues for the treatment of ATTR amyloidosis.

The sponsorship was transferred to Alnylam UK Limited, United Kingdom, in November 2014.

What is ATTR amyloidosis?

ATTR amyloidosis belongs to a group of diseases called systemic amyloidosis in which deposits of proteins (called amyloids) accumulate and cause damage in body organs. In ATTR amyloidosis the amyloids are made up of transthyretin, a protein produced in the liver that transports various substances in the blood.

In patients with ATTR amyloidosis, transthyretin deposits accumulate mainly in the heart and the nervous system causing heart problems and symptoms such as muscle weakness in the limbs and, at later stages, inability to walk, problems affecting the stomach and the gut (leading to malnutrition), and bladder dysfunction.

ATTR amyloidosis is a long-term debilitating disease due to the progressive worsening of nervous system symptoms. It is also life threatening because amyloid deposits in the heart can cause fatal heart conditions.

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

At the time of designation, ATTR amyloidosis affected approximately 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 5,000 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).

What treatments are available?

At the time of designation, the only medicine authorised in the EU to treat ATTR amyloidosis was Vyndaqel (tafamidis). The only other treatment option was liver transplantation.

The sponsor has provided sufficient information to show that this medicine might be of significant benefit for patients with ATTR amyloidosis because it works in a different way to existing treatment and early studies show that it might lead to significant reductions in amyloid levels. 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?

This medicine is a very short piece of synthetic RNA (a type of genetic material) which has been designed to attach to the part of the genetic material of cells that is responsible for producing the transthyretin protein, and prevent it from working. This reduces transthyretin production, thereby reducing the formation of amyloid deposits and relieving the symptoms of ATTR amyloidosis. The synthetic RNA is attached to another substance (a ligand) that allows the medicine to be taken up by the cells in the liver that are mainly responsible for producing transthyretin.

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 healthy volunteers were ongoing.

At the time of submission, the medicine was not authorised anywhere in the EU for ATTR amyloidosis 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 12 March 2014 recommending the granting of this designation.

[*]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.
At the time of designation, this represented a population of 512,900,000 (Eurostat 2014).

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:

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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 transthyretin mRNA and covalently linked to a ligand containing three N-acetylgalactosamine residues	Treatment of ATTR amyloidosis
Bulgarian	Синтетичен двойноверижен siRNA олигонуклеорид, насочен към транстиретинова mRNA, която е ковалентно свързана с лиганд съдържащи три-N-ацетилгалактозамин утайки	Лечение на транстиретинова амилоидоза
Croatian	Sintetički dvolančani oligonukleotid siRNK usmjeren protiv mRNK transtiretina, kovalentno vezan za ligand koji sadrži tri N-acetilgalaktozamin skupine	Liječenje ATTR amiloidoze
Czech	Syntetický dvouvláknový oligonukleotid siRNA proti mRNA transtyretinu, který je kovalentně spojen s ligandem obsahujícím tři rezidua N-acetylgalaktosaminu	Léčba ATTR amyloidózy
Danish	Syntetisk dobbelt-strenget siRNA oligonukleotid rettet imod transthyretin mRNA, ogkovalent bundet til en ligand indeholdende tre N-acetylgalaktosamin -rester	Behandling af familiær ATTR amyloidose
Dutch	Synthetisch dubbelstrengig siRNA oligonucleotide, gericht tegen transthyretine mRNA dat covalent gebonden is aan een ligand dat drie N-acetylgalactosamine residuen bevat	Behandeling van ATTR amyloïdose
Estonian	Sünteetiline kahekihiline siRNA oligonukleotiid, mis on suunatud transtüretiin mRNA vastu, mis on kovalentselt seotud ligandiga, mis sisaldab kolme N-atsetüülgalaktoosamiini jääki	Transtüretiiniga seotud amülodoosi (ATTR) ravi
Finnish	Synteettinen kaksoisjuosteinen siRNA oligonukleotidi, joka on kohdistettu transtyretiini mRNA:ta vastaan, joka on kovalenttisesti sidottu kolme N-asetyyligalaktosamiini -jäämää sisältävään ligandiin.	Suvuittain esiintyvän amyloidipolyneuropatian hoito
French	Petit ARN interférent - oligonucléotide double brin de synthèse - dirigé contre l'ARNm de la transthyrétine, lié de manière covalente à un ligand contenant 3 résidus N-acétylgalactosamine	Traitement de l'amyloïdose ATTR
German	Synthetisches doppelsträngiges siRNA-Oligonukleotid, das gegen die Transthyretin-mRNA gerichtet und kovalent an einen Liganden aus drei N-Acetylgalactosamin-Resten gebunden ist	Behandlung der ATTR Amyloidose

[1] At the time of designation

Language	Active ingredient	Indication
Greek	Συνθετικό δίκλωνο ολιγονουκλεοτίδιο siRNA κατευθυνόμενο έναντι του mRNA της τρανσθυρετίνης το οποίο συνδέεται ομοιοπολικά με συνδέτη που περιέχει τρία υπολείμματα N-ακετυλογαλακτοσαμίνης	Θεραπεία της ATTR αμυλοείδωσης
Hungarian	mRNS transztiretin ellenes, három N-acetil-galaktózamin rezidumot tartalmazó ligandumhoz kovalens kötéssel kapcsolódó szintetikus kétszálú siRMS oligonukleotid	ATTR típusú amyloidosis kezelése
Italian	Oligonucleotide siRNA sintetico a doppio filamento diretto contro il mRNA della transtiretina avente legame covalente con un legante contenente tre residui di N-acetilgalattosamina	Trattamento della Amiloidosi familiare (ATTR)
Latvian	Pret transtiretīna mRNS vērsts sintētisks dubultspirāles siRNS oligonukleotīds, kas ir kovalenti saistīts ar trīs N-acetilgalaktozamīna atliekas saturošu ligandu	ATTR amiloidozes ārstēšana
Lithuanian	Sintetinis dvigrandis siRNR oligonukleotidas, nukreiptas prieš transtiretino mRNR ir prisijungęs kovalentiniu ryšiu, turinčiu tris N-acetilgalaktozamino liekanas	ATTR amiloidozės gydymas
Maltese	Oligonukleotide sintetiku tas-siRNA b'katina doppja immirat kontra transthyretin mRNA u marbut b'mod kovalenti ma' ligand li fih tliet residwi ta' N-acetylgalactosamine	Kura tal-amilojdosi assoċjata mat-*transthyretin* (ATTR)
Polish	Syntetyczny dwuniciowy oligonukleotyd siRNA skierowany przeciwko mRNA transtyretyny kowalentnie połączony z ligandem zawierającym trzy reszty N-acetylogalaktozaminy	Leczenie amyloidozy wrodzonej typu ATTR
Portuguese	Oligonucleótido sintético do siRNA de cadeia dupla dirigido contra o mRNA da transtirretina e ligado covalentemente a um ligante contendo três resíduos de N-acetilgalactosamina	Tratamento da amiloidose associada à transtirretina
Romanian	Oligonucleotide de sintezătice dublu catenare siARN, îndreptate împotriva ARNm pentru transtiretinăei mARN care este legateă covalent de un ligand care conţine trei reziduuri de N-acetil-galactozamină	Tratamentul amiloidozei cu transtiretina (ATTR)
Slovak	Syntetický dvojvláknový oligonukleotid siRNA nasmerovaný proti transtyretínovej mRNA, ktorý je kovalentne spojený s ligandom obsahujúcim tri rezíduá N-acetylgalaktosamínu	Liečba ATTR amyloidózy
Slovenian	Sintetični oligonukleotid dvoverižne siRNK, usmerjen proti mRNK transtiretina, kovalentno vezan na ligand, ki vsebuje tri ostanke N-acetilgalaktozamina	Zdravljenje ATTR amiloidoze

Language	Active ingredient	Indication
Spanish	Oligonucleótido sintético de ARNip bicatenario dirigido al ARNm de la transtiretina unido mediante enlace covalente a un ligando que contiene tres residuos de N-acetilgalactosamina	Tratamiento de amiloidose associada a la transtirretina
Swedish	Syntetisk dubbelsträngad siRNA-oligonukleotid riktad mot transthyretin-mRNA kovalent bunden till en ligand som innehåller tre N-acetylgalaktosamin-rester	Behandling av ATTR amyloidos
Norwegian	Syntetisk dobbelttrådet siRNA oligonukleotid rettet mot transtyretin mRNA som er kovalent bundet til en ligand som inneholder tre N-acetylgalaktosamin rester	Behandling av ATTR amyloidose
Icelandic	Tilbúið tvíþátta siRNA-fákirni beint gegn transtýretín mRNA sem er samgilt tengt við bindil sem inniheldur þrjár N-acetýlgalaktósamín efnaleifar	Meðferð við ATTR mýlildisfjöltaugakvilla