4 July 2018
EMA/275373/2018

Public summary of opinion on orphan designation

Synthetic double-stranded siRNA oligonucleotide targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N-acetylgalactosamine residues for the treatment of transthyretin-mediated amyloidosis (ATTR amyloidosis)

On 25 May 2018, orphan designation (EU/3/18/2026) was granted by the European Commission to Alnylam UK Limited, United Kingdom, for synthetic double-stranded siRNA oligonucleotide targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N-acetylgalactosamine residues (also known as ALN-TTRSC02) for the treatment of transthyretin-mediated amyloidosis (ATTR amyloidosis).

What is transthyretin-mediated amyloidosis (ATTR amyloidosis)?

Transthyretin-mediated 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 build up mainly in the heart and the nervous system. Patients with this condition usually have 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.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

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

At the time of designation, ATTR amyloidosis affected less than 0.2 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 10,000 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). Vyndaqel was authorised to delay nerve damage caused by ATTR amyloidosis in patients with the early stage of nerve disease. The only other treatment option was liver transplantation.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with all forms of ATTR amyloidosis. Early studies indicated that the way the medicine works could make it effective in a broader patient group than current 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 of a small strand of synthetic genetic material, called 'small interfering RNA' (siRNA), that stops the gene for transthyretin from working and thereby blocks the production of transthyretin in the liver. This is expected to reduce transthyretin deposits in the tissues and thus relieve the symptoms of the disease.

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 ATTR amyloidosis had been started.

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 19 April 2018 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;

*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).

- 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 medicine's rare disease designations page.

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 targeted against transthyretin mRNA, with six phosphorothioate linkages in the backbone, and nine 2'-fluoro and thirty-five 2'-O-methyl nucleoside residues in the sequence, which is covalently linked via a phosphodiester group to a ligand containing three N-acetylgalactosamine residues	Treatment of transthyretin-mediated amyloidosis
Bulgarian	Синтетичен двойноверижен siРНК олигонуклеотид, насочен срещу транстиретинова иРНК с шест фосфоротиоатни връзки в основната верига и девет 2'-флуоро и тридесет и пет 2'-О-метил нуклеозидни остатъци в последователността, който е ковалентно свързан чрез фосфодиестерна група с лиганд, съдържащ три-N-ацетилгалактозаминови остатъци	Лечение на транстиретин-медиирана амилоидоза
Croatian	Sintetički oligonukleotid dvolančane siRNK usmjeren protiv mRNK transtiretina, sa šest fosforotioatnih veza u okosnici molekule i devet 2'-fluoro i trideset-pet 2'-O-metil nukleozidnih ostataka u sekvenci, fosfodiesterskom vezom kovalentno vezan za ligand koji sadrži tri ostatka N-acetilgalaktozamina	Liječenje transtiretinske amiloidoze
Czech	Syntetický dvouvláknový oligonukleotid siRNA nasměrovaný proti mRNA transthyretinu, s šesti substituenty fosforothioátu v páteřní struktuře, devíti 2'-fluor a třiceti pěti nukleosidovými rezidui 2'-O-methyl v sekvenci, který je kovalentně spojený prostřednictvím fosfodiesterové skupiny s ligandem obsahujícím tři rezidua N-acetylgalaktosaminu	Léčba transthyretinové amyloidózy
Danish	Syntetisk dobbeltstrenget siRNA-oligonukleotid rettet mod transthyretin-mRNA med seks thiophosphatbindinger i rygraden og ni 2'-fluor-og femogtredive 2'-O-methylnukleosidenheder i sekvensen, kovalent bundet via en phosphodiestergruppe til en ligand indeholdende tre N-acetylgalactosaminenheder	Behandling af transthyretin medieret amyloidose
Dutch	Synthetisch dubbelstrengig siRNA oligonucleotide, gericht tegen transthyretine mRNA, met zes fosforothioaatverbindingen in de ruggengraat, en negen 2'-fluor en vijfendertig 2'-O-methylnucleoside residuen in de sequentie, dat covalent gebonden is via een fosfodiëstergroep aan een ligand dat drie N-acetylgalactosamine residuen bevat	Behandeling van transthyretine-gemedieerde amyloïdose

[1] At the time of designation

Language	Active ingredient	Indication
Estonian	Transtüretiini mRNA vastu suunatud sünteetiline kaheahelaline siRNA oligonukleotiid, millel on põhiahelas kuus fosforotioaadi sidet ja järjestuses üheksa 2'-fluoro- ja 35 2'-O-metüülnukleosiidjääki ning mis on fosfodiesterrühma kaudu kovalentselt seotud kolme N-atsetüülgalaktoosamiini jääki sisaldava ligandiga	Transtüretiiniga seotud amüloidoosi ravi
Finnish	Transtyretiini-mRNA:ta vastaan kohdistettu synteettinen kaksijuosteinen siRNA-oligonukleotidi, jonka runko-osassa on kuusi fosforotioaattisidosta ja sekvenssissä yhdeksän 2'-fluoronukleosiditähdettä sekä kolmekymmentäviisi 2'-O-metyylinukleosiditähdettä ja joka on kovalenttisesti sidottu fosfodiesteriryhmän välityksellä kolme N-asetyyligalaktosamiinitähdettä sisältävään ligandiin	Transtyretiinivälitteisen amyloidoosin hoito
French	Oligonucléotide de pARNi double brin de synthèse ciblant l'ARNm de la transthyrétine, comprenant six liaisons phosphorothioate dans le squelette et neuf résidus nucléosidiques 2'-fluoro et trente-cinq résidus nucléosidiques 2'-O-méthyle dans la séquence, lié de manière covalente par un groupement phosphodiester à un ligand contenant trois résidus N-acétylgalactosamine	Traitement de l'amylose à transthyrétine
German	Synthetisches doppelsträngiges siRNA-Oligonukleotid, das gezielt gegen Transthyretin-mRNA gerichtet ist, mit sechs Phosphorothioat-Bindungen im Rückgrat sowie neun 2'-Fluor- und fünfunddreißig 2'-O-Methyl-Nukleosid-Resten in der Sequenz, das über eine Phosphodiester-Gruppe kovalent an einen Liganden mit drei N-Acetylgalactosamin-Resten gebunden ist	Behandlung der Transthyretin-vermittelten Amyloidose
Greek	Συνθετικό δίκλωνο ολιγονουκλεοτίδιο siRNA στοχευμένο έναντι του mRNA τρανσθυρετίνης, με έξι δεσμούς θειοφωσφορικού εστέρα στον πεπτιδικό σκελετό και εννιά 2'-φθορο και τριάντα πέντε 2'-O-μεθυλο νουκλεοσιδικά υπολείμματα στην αλληλουχία, το οποίο συνδέεται ομοιοπολικά μέσω φωσφοδιεστερικής ομάδας με συνδέτη που περιέχει τρία υπολείμματα N-ακετυλογαλακτοσαμίνης	Θεραπεία της σχετιζόμενης με την τρανσθυρετίνη αμυλοείδωσης
Hungarian	A transztiretin mRNS ellen irányuló, fő láncán hat foszfortioát kötést és szekvenciájában kilenc 2'-fluor-és harmincöt 2'-O-metil-nukleozid-maradványt tartalmazó szintetikus kétszálú siRNS oligonukleotid, amely egy foszfodiészter-csoporton keresztül kovalens kötéssel kapcsolódik a három N-acetil-galaktózamin maradványt tartalmazó ligandumhoz	Transztiretin-mediált amyloidosis kezelése

Language	Active ingredient	Indication
Italian	Oligonucleotide siRNA sintetico a doppio filamento mirato all'mRNA della transtiretina, con sei legami di tipo fosforotioato nella catena principale e nove residui nucleosidici 2'-fluoro e trentacinque 2'-O-metile nella sequenza, legato covalentemente tramite un gruppo fosfodiesterico con un legante contenente tre residui di N-acetilgalattosamina	Trattamento dell'amiloidosi da accumulo di transtiretina
Latvian	Sintētisks divpavedienu siRNS oligonukleotīds, kas mērķēts pret transtiretīna mRNS un kas satur sešas fosfortioāta saites pamatķēdē un deviņus 2'-fluor un trīsdesmit piecus 2'-O-metilnukleozīdu atlikumus sekvencē, kas ar fosfodiesteru grupu ir kovalenti piesaistīta ligandam, kas satur trīs N-acetilgalaktozamīna atlikumus	Transtiretīna mediētas amiloidozes ārstēšana
Lithuanian	Sintetinis dvigrandis siRNR oligonukleotidas, nukreiptas prieš transtiretino iRNR, su šešiomis fosforotioato jungtimis pagrinde, ir devyniomis 2'-fluoro ir trisdešimt penkiomis 2'-O-metil nukleotidų liekanomis sekoje, kuris kovalentiškai prisijungęs per fosfodiesterinę grupę prie ligando, turinčio tris N-acetilgalaktozamino liekanas	Transtiretino medijuotos amiloidozės gydymas
Maltese	Oligonukleotida siRNA sintetika b'żewġ filamenti, immirata kontra transtiretin mRNA, b'sitt rabtiet fosforotiat fis-sinsla, u disa' 2'-fluworo u ħamsa u tletin 2'-O-metil residwi ta' nukleosid fis-sekwenza, li hija marbuta b'mod kovalenti permezz ta' grupp ta' fosfodiester ma' ligand li fih tliet residwi ta' N-aċetilgalattosamina	Kura ta' amilojdożi medjata minn transthyretin
Polish	Syntetyczny dwuniciowy oligonukleotyd siRNA skierowany przeciwko mRNA transtyretyny, z sześcioma wiązaniami fosforotionianowymi w łańcuchu głównym oraz dziewięcioma resztami 2'-fluoro-nukleozydu i trzydziestoma pięcioma resztami 2'-O-metylo-nukleozydu w sekwencji, połączony kowalencyjnie poprzez grupę fosfodiestrową z ligandem zawierającym trzy reszty N-acetylogalaktozaminy	Leczenie amyloidozy transtyretynowej
Portuguese	Oligonucleótido sintético siRNA de cadeia dupla dirigido contra o mRNA da transtirretina, com seis ligações fosforotioato no esqueleto e nove resíduos nucleósidos 2'-fluoro e trinta e cinco resíduos 2'-O-metilados na sequência, o qual está ligado covalentemente através de um grupo fosfodiéster a um ligante contendo três resíduos de N-acetilgalactosamina	Tratamento da amiloidose associada à transtirretina

Language	Active ingredient	Indication
Romanian	Oligonucleotid sintetic dublu-catenar de siARN, îndreptat împotriva mARN al transtiretinei , cu șase legături fosforotioat la nivelul lanțului principal și nouă reziduuri de 2'-fluoro și treizeci și cinci de 2'-O-metil nucleozide în secvență, care este legat covalent, prin intermediul unei grupări fosfodiesterice, de un ligand care conține trei reziduuri N-acetil-galactozaminice	Tratamentul amiloidozei cu transtiretină
Slovak	Syntetický dvojvláknový oligonukleotid siRNA nasmerovaný proti transtyretínovej mRNA, so šiestimi skupinami fosfortioátu v backbone, deviatimi 2'-fluór a tridsiatimipiatimi nukleozidovými reziduami 2'-O-metyl v sekvencii, ktorá je kovalentne spojená prostredníctvom fosfodiesterovej skupiny s ligandom obsahujúcim tri rezíduá N-acetylgalaktozamínu	Liečba transtyretínovej amyloidózy
Slovenian	Sintetični oligonukleotid dvoverižne siRNK, usmerjen proti mRNK transtiretina, s šestimi fosforotioatnimi vezmi v ogrodju in devetimi 2'-fluoro ter petintridesetimi 2'-O-metil nukleozidnimi ostanki v zaporedju, ki je prek fosfodiestrske skupine kovalentno vezan na ligand, ki vsebuje tri ostanke N-acetilgalaktozamina	Zdravljenje transtiretinske amiloidoze
Spanish	Oligonucleótido sintético de ARNip bicatenario dirigido al ARNm de la transtiretina, con seis enlaces fosforotioato en el esqueleto y nueve residuos nucleosídicos de 2'-fluoro y treinta y cinco de 2'-O-metil, que está unido mediante enlace covalente a través de un grupo fosfodiéster a un ligando que contiene tres residuos de N-acetilgalactosamina	Tratamiento de la amiloidosis asociada a latranstiretina
Swedish	Syntetiskt dubbelsträngad siRNA-oligonukleotid inriktad mot transtyretin-mRNA, med sex fosforotioratbindningar i stamkedjan, och nio rester av 2'-fluoro och trettiofem rester av 2'-O-metylnukleosid, som är kovalent länkade via en fosfodiestergrupp till en ligand innehållande tre rester av N-acetylgalaktosamin	Behandling av transtyretin-amyloidos
Norwegian	Syntetisk dobbelttrådet siRNA oligonukleotid rettet mot transtyretin mRNA, med seks fosfortiolatbindinger i skjelettet og ni 2'-fluoro- og trettifem 2'-O-metylnukleosidenheter i sekvensen, som er kovalent bundet via en fosfodiestergruppe til en ligand som inneholder tre N-acetylgalaktosaminenheter	Behandling av transtyretinmediert amyloidose
Icelandic	Tilbúið tvíþátta siRNA-fákirni sem beinist gegn transtýretín mRNA, með sex fosfórtíóat tengingum í uppistöðunni og níu 2'-flúor og þrjátíu og fimm 2'-O-metýl kirnisleifum í röðinni, sem er tengd með samgiltu tengi með hópi fosfódíestera við bindil sem inniheldur þrjár N-asetýlgalaktósamín efnaleifar	Meðferð við transtýretín-miðluðu mýlildi