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# Public summary of opinion on orphan designation

## 2'-O-(2-Methoxyethyl)-d-ribose antisense oligonucleotide targeting glial fibrillary acidic protein messenger ribonucleic acid for the treatment of Alexander disease

On 17 October 2019, orphan designation EU/3/19/2206 was granted by the European Commission to Ionis Development (Ireland) Limited, Ireland, for 2'-O-(2-methoxyethyl)-d-ribose antisense oligonucleotide targeting glial fibrillary acidic protein messenger ribonucleic acid (also known as ION-1166998) for the treatment of Alexander disease.

### What is Alexander disease?

Alexander disease is a genetic disorder of brain cells called astrocytes in the so-called white matter of the brain. It is caused by a mutation (change) in a gene that makes the protein GFAP (glial fibrillary acidic protein), which is needed for the growth and function of these cells. The change results in too much of the protein being made, interfering with normal function.

The disorder usually begins in infancy and causes the gradual loss of bodily and mental functions; symptoms can include seizures, spasticity, developmental disorders, enlargement of the head, and problems with speech and movement (including abnormal eye and facial movement and difficulty swallowing). Another form begins later in life and causes difficulty swallowing and speaking, and problems with coordination and movement.

Alexander disease is a severe, progressive and debilitating condition that can eventually result in death due to loss of control over automatic functions like breathing. Infants and young children who develop the condition rarely survive beyond the teenage years or young adulthood.

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

At the time of designation, Alexander disease affected approximately 0.01 in 10,000 people in the European Union (EU). This was equivalent to a total of around 500 people*, and is below the ceiling for

*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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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, no satisfactory methods were authorised in the EU for the treatment of Alexander disease. Patients received supportive treatment to manage the symptoms of the condition, including medicines to manage seizures.

## How is this medicine expected to work?

The medicine is an 'antisense oligonucleotide', a small strand of synthetic genetic material. It has been designed to stop the altered gene from working and producing so much GFAP protein. By reducing the excessive production of GFAP in patients with Alexander disease, the medicine is expected to help control 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 Alexander disease had been started.

At the time of submission, this medicine was not authorised anywhere in the EU for the treatment of Alexander disease 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.

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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.

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 | 2'-O-(2-methoxyethyl)-D-ribose antisense oligonucleotide targeting glial fibrillary acidic protein messenger ribonucleic acid | Treatment of Alexander disease |
| Bulgarian | 2'-O-(2-метоксиетил) модифициран антисенс олигонуклеотид, насочен срещу пре мРНК за глиален фибрилерен кисел протеин | Лечение на болест на Александър |
| Croatian | 2'-O-(2-metoksietil)- D-riboza protusmjerni oligonukleotid usmjeren na mRNA za glijalni fibrilarni kiseli protein | Liječenje Alexanderove bolesti |
| Czech | 2'-O-(2-methoxyethyl)-D-ribosa antisense oligonukleotid zacílený na messengerovou ribonukleovou kyselinu gliálního fibrilárního kyselého proteinu | Léčba Alexandrovy choroby |
| Danish | 2'-O-(2-methoxyethyl)-D-ribose antisense-oligonukleotid rettet mod mRNA for glial fibrillær syre protein | Behandling af Alexander sygdom |
| Dutch | 2'-O-(2-methoxyethyl) gemodificeerd antisense oligonucleotide gericht op gliaal fibrillair zuur eiwit pre-mRNA | Behandeling van de ziekte van Alexander |
| Estonian | Gliia fibrillaarse happelise valgu mRNA vastu suunatud 2'-O-(2 metoksüetüül)-D-riboos antisenss-oligonukleotiid | Alexanderi tõve ravi |
| Finnish | 2'-O-(2-metoksietyyli)-D-riboosi antisense-oligonukleotidi, joka kohdistuu Glial Fibrillary Acidic -proteiinin mRNA:han | Alexanderin taudin hoito |
| French | Oligonucléotide antisens modifié par un groupe 2'-O-(2-méthoxyéthyle) ciblant le pré-ARNm de la protéine acide fibrillaire gliale | Traitement de la maladie d'Alexander |
| German | 2'-O-(2-methoxyethyl-)modifiziertes Antisense-Oligonukleotid, das auf die mRNA des sauren Gliafaserproteins abzielt | Behandlung der Alexander-Krankheit |
| Greek | 2'-O-(2-μεθοξυαιθυλ) τροποποιημένο αντιπληροφοριακό ολιγονουκλεοτίδιο που στοχεύει το προ mRNA γλοιακής ινιδικής όξινης πρωτεΐνης | Θεραπεία της νόσου Alexander |
| Hungarian | Gliális fibrilláris savas fehérje mRNS elleni 2'-O-(2-metoxietil)-D-ribóz antiszensz oligonukleotid | Alexander-betegség kezelése |

[1] At the time of designation

| Language | Active ingredient | Indication |
|---|---|---|
| Italian | Oligonucleotide antisenso modificato 2'-O-(2-metossietil) contro il pre-mRNA della proteina acida fibrillare gliale | Trattamento della malattia di Alexander |
| Latvian | 2'-O-(2-metoksietil)-D-ribozes antisensa oligonukleotīds, kas vērsts pret glijas fibrillārā skābā proteīna matricas ribonukleīnskābi | Aleksandera slimības ārstēšana |
| Lithuanian | 2'-O-(2-metoksietil) – D – ribozės priešprasmis oligonukleotidas, nukreiptas į glijos fibrilinio rūgštinio baltymo informacinę ribonukleorūgštį | Alexander ligos gydymas |
| Maltese | Oligonukleotide antisense modifikat permezz ta'-2'-O-(2-methoxyethyl) li jimmira l-proteina glijali fibrillari aċidika pre-mRNA | Trattament tal-marda ta' Alexander |
| Polish | Zmodyfikowany 2'-O-(2-metoksyetylem) antysensowny oligonukleotyd skierowany przeciw pre-mRNA kwaśnego białka włókienkowego gleju | Leczenie choroby Alexandra |
| Portuguese | Oligonucleótido anti-sentido 2'-O-(2-metoxietil) dirigido ao pré-ARNm da proteína ácida glial fibrilar | Tratamento da doença de Alexander |
| Romanian | Oligonucleotid antisens modificat cu 2'-O-(2-metoxietil) care ţinteşte pre-ARNm al proteinei acide fibrilare gliale | Tratamentul bolii Alexander |
| Slovak | 2'-O-(2-metoxyetyl) modifikovaný antisense oligonukleotid cielený proti pre-mRNA gliálneho fibrilárneho kyslého proteínu | Liečba Alexandrovej choroby |
| Slovenian | 2'-O-(2-metoksietil)-modificiran protusmerni oligonukleotid usmerjen na pre mRNA za glijalni fibrilarni kisli protein | Zdravljenje Aleksandrove bolezni |
| Spanish | Oligonucleótido antisentido modificado con 2'-O-(2-metoxietil) dirigido a pre mRNA de la proteína ácida fibrilar glial | Tratamiento de la enfermedad de Alexander |
| Swedish | 2'-O-(2-metoxietyl)-D-ribos antisense-oligonukleotid riktad mot surt gliafilamentprotein mRNA | Behandling av Alexanders sjukdom |
| Norwegian | 2'-O-(2-metoksyetyl)-D-ribose antisense oligonukleotid rettet mot gliafibrillært surt protein budbringer-ribonukleinsyre | Behandling av Alexanders sykdom |
| Icelandic | 2'-O-(2-metoxýetýl) aðlagað andþætt fákirni gegn for mRNA taugatróðs-súrþráðlupróteini | Meðferð við Alexander-sjúkdómi |