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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Antisense oligonucleotide complementary to the exonic splicer enhancer sequence at intron 26 of the centrosomal protein 290 pre-mRNA for the treatment of Leber's congenital amaurosis

On 28 April 2016, orphan designation (EU/3/16/1641) was granted by the European Commission to ProQR Therapeutics IV BV, the Netherlands, for antisense oligonucleotide complementary to the exonic splicer enhancer sequence at intron 26 of the centrosomal protein 290 pre-mRNA (also known as QR-110) for the treatment of Leber's congenital amaurosis.

What is Leber's congenital amaurosis?

Leber's congenital amaurosis is an inherited disease characterised by loss of sight at birth or soon after birth. The disease is linked to a number of genetic mutations (changes), which affect the normal development of the light-sensitive cells in the eye.

Leber's congenital amaurosis is a long-term debilitating disease due to progressive loss of vision.

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

At the time of designation, Leber's congenital amaurosis affected approximately 0.4 in 10,000 people in the European Union (EU). This was equivalent to a total of around 21,000 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, no satisfactory methods were authorised in the EU for treating Leber's congenital amaurosis. Patients with the condition usually received regular medical follow up, vision aids and genetic counselling on the risks of passing the condition on to their children.

*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 513,700,000 (Eurostat 2016).

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How is this medicine expected to work?

Mutations (changes) in the *CEP290* gene are the most common mutations that cause Leber's congenital amaurosis. As a result of these mutations, patients produce a 'short' CEP290 protein which cannot work properly. CEP290 has an important role in the development of the light-sensitive cells in the eye.

This medicine is an 'antisense oligonucleotide', a short piece of genetic material that is expected to make the *CEP290* gene produce adequate levels of the CEP290 protein of normal length. It is expected to do so by allowing the correct cutting ('splicing') of *CEP290* that serves as the 'template' for the CEP290 protein. This is expected to lead to an increased production of the normal-length CEP290 protein, thus allowing the light sensitive cells in the eye to develop properly.

What is the stage of development of this medicine?

At the time of submission of the application for orphan designation, the evaluation of the effects of the medicine in experimental models was ongoing.

At the time of submission, no clinical trials with the medicine in patients with Leber's congenital amaurosis had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for Leber's congenital amaurosis 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 23 March 2016 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 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	Antisense oligonucleotide complementary to the exonic splicer enhancer sequence at intron 26 of the centrosomal protein 290 pre-mRNA	Treatment of Leber's congenital amaurosis
Bulgarian	Антисенс олигонуклеотид, комплементарен на секвенцията на екзонен сплайсинг усилвател при интрон 26 на центрозомен протеин 290 пре-иРНК	Лечение на вродена амавроза на Лебер
Croatian	Protusmisleni oligonukleotid komplementaran slijedu egzonskih pojačivača izrezivanja na intronu 26 centrosomalnog proteina 290 pre-mRNK	Liječenje Leberove kongenitalne amauroze
Czech	Antisense oligonukleotid komplementární k sekvenci exonického sestřihového enhanceru na intronu 26 S centrozomálního proteinu 290 pre-mRNA	Léčba Leberovy vrozené slepoty e
Danish	Komplementært antisense-oligonukleotid til enhancersekvensen for exonic splejsning på intron 26 på det centrosomale protein 290 pre-mRNA	Behandling af Lebers kongenitte amaurose
Dutch	Antisense oligonucleotide complementair aan de exon transcriptieverhogersequentie ter hoogte van het intron 26 van het pre-mRNA voor het centrosomale eiwit 290	Behandeling van amaurosis congenita van Leber
Estonian	Eksoni splaisseri-võimendaja järjestust täiendav antisense-oligonukleotiid tsentrosomaalse valgu 290 pre-mRNA intronis 26	Leberi tüüpi kaasasündinud amauroosi ravi
Finnish	Antisense-oligonukleotidi, joka on komplementaarinen eksonin silmukointia parantavalle sekvenssille, joka sijaitsee sentrosomiproteiini 290:n esi-mRNA:n intronissa 26	Leberin synnynnäisen amauroosin (sokeus) hoito
French	Oligonucléotide antisens complémentaire à la séquence activatrice de l'épissage exonique au niveau de l'intron 26 du pré-ARNm de la protéine centrosomique 290	Traitement de l'amaurose congénitale de Leber
German	Antisense-Oligonukleotid komplementär zur exonischen Splicing-Verstärkersequenz im Intron 26 der prä-mRNA des zentrosomalen Proteins 290	Behandlung der Leberschen Kongenitalen Amaurose
Greek	Αντινοηματικό ολιγονουκλεοτίδιο συμπληρωματικό στην αλληλουχία εξονικού ενισχυτή ματίσματος στο ιντρόνιο 26 του πρόδρομου mRNA κεντροσωματικής Πρωτεΐνης 290	Θεραπεία τής συγγενους αμαύρωσης του Leber
Hungarian	Az exon splice fokozó szekvenciát kiegészítő antisens oligonukleotid a centroszómális fehérje 290 pre-mRNS-ének 26-os intronjánál	Leber-féle hereditaer opticus atrophia kezelése
Italian	Oligonucleotide antisenso complementare alla sequenza enhancer di splicing esonica relativa all'introne 26 del pre-mRNA della proteina centrosomica 290	Trattamento dell'amaurosi congenita di Leber
Latvian	Antisenss oligonukleotīds, kas papildina eksona splaisinga uzlabošanas sekvenci pie 290. centrosomālā proteīna pre-mRNS 26. introna	Iedzimta Lēbera akluma ārstēšana

[1] At the time of designation

Language	Active ingredient	Indication
Lithuanian	Priešprasminis oligonukleotidas, komplementarus egzonų sandūros sustiprinimo sekai ties 26-uoju centrosomos baltymo 290 pre-mRNR intronu	Įgimtos Lėberio amaurozės gydymas
Maltese	Oligonukleotide antisens komplimentari għas-sekwenza tal-*exonic splicer enhancer* fl-intron 26 tal-proteina ċentrosomali 290 pre-mRNA	Kura ta' l-amawrożi konġenitali ta' Leber
Polish	Oligonukleotyd antysensowny komplementarny do eksonowej sekwencji wzmacniającej składanie genu przy intronie 26 pre-mRNA białka centrosomalnego o masie 290 kDa	Leczenie wrodzonej ślepoty Lebera
Portuguese	Oligonucleótido anti-senso complementar da sequência promotora de splicing exónico no intrão 26 do pré-ARNm da proteína centrossomal 290	Tratamento do Amaurose Congénita de Leber
Romanian	Oligonucleotidă antinsens complementară secvenţei intensificatoare a episajului exonilor la intronul 26 al pre-ARNm al proteinei centrozomale 290	Tratamentul amaurozei congenitale Leber
Slovak	Protismerný oligonukleotid komplementárny k sekvencii exónového zosilňovača zostrihu pri intróne 26 pre pre-mRNA centrozomálneho proteínu 290	Liečba Leberovej vrodenej amaurózy
Slovenian	Protismerni oligonukleotid, ki je komplementaren zaporedju eksonskega ojačevalca izrezovanja pri intronu 26 centralnosomalnega proteina 290 prekurzorske mRNA	Zdravljenje Leberjeve vrojene amavroze
Spanish	Oligonucleótido antisentido complementario a la secuencia exónica que estimula el corte y empalme del intrón 26 del pre-ARNm de la proteína centrosómica 290	Tratamiento de la amaurosis congénita de Leber
Swedish	Antisense-oligonukleotid komplementär till den exona skarvningförstärkarsekvensen vid intron 26 på pre-mRNA:t för centrosomalt protein 290.	Behandling av Lebers kongenitala amauros
Norwegian	Antisense-oligonukleotid komplementært til den eksoniske splicerenhancer-sekvensen ved intron 26 av sentrosomalt protein 290 pre-mRNA	Behandling av Lebers kongenitale amaurose
Icelandic	Antisense-ólígónúkleótíð samfallandi við táknraðandi samskeytta eflirröð við innröð 26 geislaskautaðs próteins 290 pre-mRNA	Meðferð á Leber meðfæddri blindu