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Public summary of opinion on orphan designation

Combination of three adeno-associated viral vectors of serotype 8 containing the 5'-, the body- and the 3'- coding sequences of human *CEP290* fused to inteins for the treatment of inherited retinal dystrophies

On 28 February 2020, orphan designation EU/3/20/2254 was granted by the European Commission to Fondazione Telethon, Italy, for combination of three adeno-associated viral vectors of serotype 8 containing the 5'-, the body- and the 3'- coding sequences of human *CEP290* fused to inteins for the treatment of inherited retinal dystrophies.

What are inherited retinal dystrophies?

Inherited retinal dystrophies are a group of hereditary diseases of the eye that lead to progressive loss of sight. In patients with inherited retinal dystrophies, cells in the retina (the light-sensitive surface at the back of the eye) become damaged and eventually die.

Inherited retinal dystrophies are long-term debilitating diseases because they cause the patient's sight to get worse, eventually leading to blindness.

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

At the time of designation, inherited retinal dystrophies affected less than 3 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 156,000 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 orphan designation, the medicine Luxturna was authorised in the EU for the treatment of a form of inherited retinal dystrophy caused by mutations (changes) in the gene *RPE65*.

The sponsor has provided sufficient information to show that the medicine might be of significant benefit for patients with inherited retinal dystrophies. This is because early laboratory data have shown

[*]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 519,200,000 (Eurostat 2020).

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that this medicine can be used in patients with a form of the disease caused by mutations in a different gene, *CEP290*, for which no treatments are currently authorised. 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?

Some forms of inherited retinal dystrophy are caused by mutations in the *CEP290* gene, which is responsible for the production of a protein called centrosomal protein 290, that is necessary for the normal functioning of retinal cells. In patients with this form of the disease, this protein is lacking or does not function properly.

The medicine contains three viruses, each containing a different portion of a normal *CEP290* gene. When injected into the eye, under the retina, it is expected that the viruses carry the *CEP290* gene portions into the retinal cells, enabling them to produce a functioning CEP290 protein. This is then expected to help the cells in the retina to work better, reducing symptoms of the condition.

The type of virus used in this medicine (adeno-associated virus) does not cause disease in humans.

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 of the application for orphan designation, no clinical trials with the medicine in patients with inherited retinal dystrophies had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for the treatment of inherited retinal dystrophies 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 22 January 2020, 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	Combination of three adeno-associated viral vectors of serotype 8 containing the 5'-, the body- and the 3'- coding sequences of human CEP290 fused to inteins	Treatment of inherited retinal dystrophies
Bulgarian	Комбинация от три адено-асоциирани вирусни вектора на серотип 8, съдържащи 5', тяло и 3' кодиращи последователности на човешки CEP290, съединени с интеини	Лечение на наследствени ретинални дистрофии
Croatian	Kombinacija triju adeno-povezanih virusnih vektora serotipa 8 koji sadrže 5 ', tijelo' i 3’ kodirajuće sekvence ljudskog CEP290 spojene u inteine	Liječenje nasljednih distrofija mrežnice
Czech	Kombinace tří adeno-asociovaných virových vektorů sérotypu 8 obsahujících 5'-, body- a 3'-fragmenty kódující sekvence lidského CEP290 fúzované s inteiny	Léčba dědičných retinálních dystrofií
Danish	Kombination af tre adeno-associerede virale vektorer af serotype 8 indeholdende 5'-, krops- og 3'-fragmenterne af humane CEP290-kodende sekvenser fusioneret til inteiner	Behandling af arvelige nethinde dystrofier
Dutch	Combinatie van drie adeno-geassocieerde virale vectoren van serotype 8 die de 5'-, lichaams- en de 3'-fragmenten bevatten van menselijke CEP290 coderende sequenties gefuseerd aan inteïnen	Behandeling van erfelijke retinale dystrofieën
Estonian	Kolme adeno-assotsieerunud viirusvektori serotüüp 8 kombinatsioon, mis sisaldab inteiinidega liidetud inimese CEP290 kodeerivate järjestuste 5'-, keha- ja 3'-fragmente	Pärilike reetina düstroofiate ravi
Finnish	Yhdistelmä kolmesta serotyypin 8 adeno-assosioituneesta virusvektorista, joka sisältää ihmisen CEP290:tä koodaavien sekvenssien 5'-, runko- ja 3'-fragmentit fuusioituneena inteiineihin	Perinnöllisten verkkokalvorappeumien hoito
French	Combinaison de trois vecteurs viraux adéno-associés de sérotype 8 contenant les fragments 5 ’, corporel et 3’ des séquences codantes du CEP290 humain fusionnées à des entines	Traitement des dystrophies rétiniennes héréditaires

[1] At the time of designation

Language	Active ingredient	Indication
German	Kombination von drei Adeno-assoziierten viralen Vektoren des Serotyps 8, die die 5'-, Körper- und 3'-Fragmente von humanen CEP290-Kodierungssequenzen enthalten, die an Inteine fusioniert sind	Behandlung von hereditären Netzhautdystrophien
Greek	Συνδυασμός τριών αδενο-συσχετιζόμενων ιικών φορέων ορότυπου 8, που περιέχουν τα τμήματα 5'-άκρου, σώματος και 3'-άκρου της κωδικοποιητικής αλληλουχίας του ανθρώπινου CEP290 συζευγμένων με ιντεΐνες	Θεραπεία των κληρονομικών δυστροφιών του αμφιβληστροειδούς
Hungarian	A humán CEP290 kódoló szekvenciák 5'-, test- és 3'-fragmenseit tartalmazó, a 8. szerotípus három adeno-asszociált vírusvektorának kombinációja, inteinekhez kapcsolva	Örökletes retina-disztrófiák kezelése
Italian	Miscela di tre vettori virali adeno-associati di sierotipo 8, contenenti le le sequenze 5’, centrale, e 3’ del gene ABCA4 fuse ad inteine	Trattamento della distrofia ereditaria della retina
Latvian	Trīs adeno-asociētu 8. seroptipa vīrusu vektoru, kas satur ar ineīniem sapludinātas cilvēka CEP290 5'-, ķermeņa- un 3'- kodējošās secības, kombinācija	Iedzimtu tīklenes distrofiju ārstēšana
Lithuanian	Trijų su adeno virusu susijusių 8 serotipo vektorių junginys, turintis 5’-, pagrindo- ir 3’-koduojančias žmogaus CEP290 sekas, sujungtas su inteinais	Paveldimų tinklainės distrofijų gydymas
Maltese	Kombinazzjoni ta' tliet vetturi virali adeno-assoċjati ta' serotip 8 li fiha l-5’-, il-ġisem- u t-3’- sekwenzi ta' kodifikazzjoni ta’ CEP290 tal-bniedem imdewba ma' intejini	Kura ta’ distrofiji retinali ereditarji
Polish	Kombinacja trzech powiązanych z adenowirusami wektorów wirusowych serotypu 8 zawierających fragmenty 5 ', ciało i 3' ludzkich sekwencji kodujących CEP290 połączonych z inteinami	Leczenie dziedzicznych dystrofii siatkówki
Portuguese	Combinação de três vetores virais adeno-associados de serotipo 8 contendo os fragmentos 5 ', corpo e 3' das sequências de codificação CEP290 humanas fundidas à inteína	Tratamento de distrofias retinianas congénitas
Romanian	Combinație a trei vectori virali adeno-asociați de serotipul 8 ce conține fragmentele 5’, corp și 3’ ale secvențelor de codificare a CEP290 umane, fuzionate la inteine	Tratamentul distrofiei retiniene congenitale
Slovak	Kombinácia troch adeno-asociovaných vírusových vektorov sérotypu 8 obsahujúcich 5', telové a 3'-sekvencie kódujúce humánne CEP290 fúzované k inteínom	Liečba vrodených retinálnych dystrofií

Language	Active ingredient	Indication
Slovenian	Kombinacija treh adeno-povezanih virusnih vektorjev serotipa 8, ki vsebujejo 5-, telesne in 3’-fragmente humane CEP290 kodirne sekvence, spojene v inteine	Zdravljenje prirojenih distrofij mrežnice
Spanish	Combinación de tres vectores virales adenoasociados del serotipo 8 que contienen los fragmentos 5 ', cuerpo y 3' de la secuencia codificante de CEP290 humano fusionadas a las inteínas	Tratamiento de distrofias retinianas hereditarias.
Swedish	Kombination av tre adenoassocierade virala vektorer av serotyp 8 innehållande 5'-, kropps- och 3'-fragmenten av humana CEP290-kodande sekvenser smälta till inteiner	Behandling av ärftliga retinala dystrofier
Norwegian	Kombinasjon av tre adenoassosierte virusvektorer av serotype 8 som inneholder de 5'-, kropps- og 3'-kodende sekvenser av humant CEP290 koblet til inteiner	Behandling av arvelige netthinnedystrofier
Icelandic	Samsetning þriggja adenótengdra veirugenaferja af sermisgerð 8 sem innihalda 5'-, body- og 3'-táknraðirnar af manna CEP290 tengdar inteinum	Meðferð við arfgengum sjónukyrkingi