23 September 2014
EMA/COMP/432877/2014
Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Vector based on an adeno-associated virus serotype 2 backbone, pseudo-serotyped with a type 8 capsid, which carries the coding sequence of the human *TYMP* gene under the control of the human thyroxine binding globulin promoter for the treatment of mitochondrial neurogastrointestinal encephalomyopathy

On 22 August 2014, orphan designation (EU/3/14/1326) was granted by the European Commission to Vall d'Hebron Institute of Research, Spain, for vector based on an adeno-associated virus serotype 2 backbone, pseudo-serotyped with a type 8 capsid, which carries the coding sequence of the human *TYMP* gene under the control of the human thyroxine binding globulin promoter for the treatment of mitochondrial neurogastrointestinal encephalomyopathy.

What is mitochondrial neurogastrointestinal encephalomyopathy?

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is an inherited disease caused by mutations (defects) in the *TYMP* gene, which is responsible for the production of an enzyme called 'thymidine phosphorylase'. This enzyme controls the amount of certain compounds in the cells, such as thymidine.

Patients with the disease do not have enough of the thymidine phosphorylase enzyme and therefore are unable to break down thymidine, causing it to build up in the cells, where it damages the DNA contained in mitochondria, which are important organelles of the cell. Damaged mitochondrial DNA leads to the symptoms of the disease, although the exact way in which this happens is not clear.

The disease affects many parts of the body, particularly the digestive system, where it causes problems such as nausea (feeling sick), stomach ache, bloating, diarrhoea and weight loss, and the nervous system, where it causes symptoms such as weakness, numbness and tingling sensations mostly in the hands and feet. Symptoms can appear at any time from birth but usually start during the second decade of life, and worsen with time.

MNGIE is a debilitating disease that is long lasting and life threatening due to its effects on the gut and on the nervous system.

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

At the time of designation, MNGIE affected less than 0.01 in 10,000 people in the European Union (EU). This was equivalent to a total of fewer than 500 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 the treatment of MNGIE. Patients were given treatments to help alleviate their symptoms and genetic counselling (discussion of the risks of passing the condition on to children). In some patients, allogeneic stem-cell transplantation was used. This is a complex procedure where the patient receives stem cells from a matched donor to help restore the bone marrow.

How is this medicine expected to work?

This medicine is made of a virus that contains a normal copy of the *TYMP* gene, which produces the thymidine phosphorylase enzyme, attached to a liver-specific promoter (a genetic 'switch' which only allows it to work inside liver cells). When the medicine is given to the patient, the virus is expected to carry the *TYMP* gene into the liver cells where it produces thymidine phosphorylase. It is expected that thymidine phosphorylase will then break down the thymidine that enters the liver via the bloodstream, thus avoiding its build-up in cells and improving the symptoms of the disease.

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?

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 MNGIE had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for MNGIE 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 10 July 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. This represents a population of 511,100,000 (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	Vector based on an adeno-associated virus serotype 2 backbone, pseudo-serotyped with a type 8 capsid, which carries the coding sequence of the human *TYMP* gene under the control of the human thyroxine binding globulin promoter	Treatment of mitochondrial neurogastrointestinal encephalomyopathy
Bulgarian	Вектор на базиран на структурата на адено-асоцииран вирус 2, псевдо-серотипиран с капсид от тип 8, който носи кодиращата последователност на човешкият *TYMP* ген под контрола на човешкият тироксин-регулиран глобулинов промотор	Лечение на митохондриална неврогастроинтестинална енцефаломиопатия
Croatian	Adeno-povezani virusni vektor okosnice serotipa 2, pseudo-serotipiziran kapsidom tipa 8, koji sadrži kodirajuće sljedove ljudskog gena za *TYMP* pod kontrolom promotora ljudskog globulina koji veže tiroksin	Liječenje mitohondrijske neurogastrointestinalne encefalomiopatije
Czech	Vektor založený na kostře odvozené z adeno-asociovaného viru sérotypu 2, pseudo-sérotypizovaný kapsidem typu 8, nesoucí kódující sekvenci pro lidský gen *TYMP* pod kontrolou promotoru pro lidský tyroxin-vázající globulin	Léčba mitochondriální neurogastrointestinální encefalomyopatie
Danish	Vektor baseret på adeno-associeret virus serotype 2 backbone, pseudo-serotypet med en type 8 kapsid, som bærer den kodende sekvens for det humane *TYMP* gen under kontrol af den humane thyroxine bindende globulin promotor	Behandling af mitokondriel neurogastrointestinal encefalomyopati
Dutch	Vector gebaseerd op een adeno-geassocieeerd virus serotype 2 backbone, pseudo-serotyped met een type 8 capsid, dat een coderende sequentie heeft voor het humane *TYMP* gen onder controle van de humane thyroxine-bindende globuline promotor	Behandeling van mitochondriale neurogastrointestinale encephalomyopathie
Estonian	Vektor, mis põhineb adenoga assotsieerunud viiruse 2. serotüübi põhistruktuuril, mida on pseudo-serotüpiseeritud kapsiidi 8. tüübiga, mis kannab inimese *TYMP* geeni kodeerivat järjestust ja mis on inimese türoksiini siduva globuliini promootori kontrolli all	Mitokondriaalse neurogastrointestinaalse entsefalomüopaatia ravi

[1] At the time of designation

Language	Active ingredient	Indication
Finnish	Vektori, jossa on ihmisen *TYMP*-geeniä koodaava sekvenssi, ja sitä säätelee thyroxine-binding globulin -geenin promoottori. Vektori on adenovirus serotyyppi 2-pohjainen ja pseudoserotyypitetty tyypin 8 kapsidilla	Mitokondriaalisen neurogastrointestinaalisen enkefalomyopatian hoito
French	Vecteur basé sur la structure d'un virus adéno-associé de sérotype 2, pseudo-sérotypé avec une capside de type 8, portant la séquence codante du gène humain de la *TYMP* sous le contrôle du promoteur humain de la globuline liant la thyroxine	Traitement des encéphalomyopathies neurogastrointestinales mitochondriales
German	Auf einem Adeno-assoziierten Virus serotyp 2 Plasmid basierender Vektor mit pseudo-serotyp Typ 8 Kapsid, der unter der Kontrolle des menschlichen Thyroxin-bindenden Globulin Promoters fuer das menschliche *TYMP* Gen kodiert	Behandlung der Mitochondrialen Neurogastrointestinalen Enzephalopathie
Greek	Φορέας βασισμένος σε αδενο-σχετιζόμενο ιό οροτύπου 2, ψευδο-οροτυποποιημένου με καψίδιο τύπου 8, που φέρει την κωδικοποιούσα αλληλουχία του ανθρώπινου *TYMP* γονιδίου, υπό τον έλεγχο του υποκινητή της ανθρώπινης σφαιρίνης που συνδέεται με την θυροξίνη	Θεραπεία της μιτοχονδριακής νευρογαστροεντερικής εγκεφαλομυοπάθειας
Hungarian	2-es szerotípusú adeno-asszociált vírus vázra alapozott, a humán tiroxinkötő globulin promoter által szabályozott humán *TYMP* gén kódoló szekvenciáját hordozó 8-as típusú kapsziddal pszeudo-szerotipizált vektor	Mitokondriális neurogasztrointesztinális enkefalomyopáthia kezelésére
Italian	Vettore basato sulla struttura di un virus adeno-associato sierotipo 2, pseudo-sierotipizzato con un capside di tipo 8, contenente la sequenza codificante del gene umano *TYMP* controllato dal promotore umano di globulina che lega la tiroxina	Trattamento della encefalomiopatia mitocondriale neurogastrointestinale
Latvian	Uz adeno-saistītā vīrusa 2. serotipa bāzes veidots vektors, kas pseido-serotipēts ar 8. tipa kapsīdu un kas katur cilvēka *TYMP* gēna kodējošo sekvenci, ko kontrolē cilvēka tiroksīna saistošā globulīna promoters	Mitohondriālās neirogastrointestinālās encefalomiopātijas ārstēšana
Lithuanian	Vektorius, sudarytas remiantis su adeno virusu susijusio serotipo 2 karkasu, pseudoserotipuojamas su 8 tipo kapside, kurioje pernešama žmogaus *TYMP* geno koduojanti seka, kontroliuojama žmogaus tiroksiną surišančio globulino aktyvatoriaus	Mioneurogastrointestininės encefalopatijos (mitochondriopatijos) gydymas

Language	Active ingredient	Indication
Maltese	Vettur ibbażat fuq sinsla ta' serotip 2 imnissel mill-adenovirus, psewdo-serotipat ma' kapsid tat-tip 8, li jġorr is-sekwenza li tikkodifika il-gene *TYMP* uman ikkontrollat mill-promotur tal-globulina umana li tingħaqad mat-tiroxina	Kura ta' enċefalomijopatija newrogastrointestinali mitokondrijali
Polish	Wektor oparty o AAV serotypu 2, pseudoserotypowany kapsydem typu 8, zawierający sekwencję kodującą ludzki gen *TYMP* pod kontrolą promotora dla ludzkiej globuliny wiążącej tyroksynę	Leczenie zespołu mitochondrialnej encefalomiopatii dotyczącej układu nerwowego, żołądka i jelit
Portuguese	Vector baseado na estrutura de um vírus adeno-associado de serotipo 2, pseudo-serotipado com uma cápside de tipo 8, que contém a sequência de codificação do gene humano *TYMP* sob o controlo do promotor humano da globulina de ligação a tiroxina	Tratamento da encefalomiopatia neurogastrointestinal mitocondrial
Romanian	Vector bazat pe structura unui virus adeno-asociat de serotip 2, pseudoserotipat cu o capsidă de tip 8, ce conţine secvenţa codantă a genei *TYMP* umane, sub controlul promotorului globulinei umane ce leagă tiroxina (thyroxine-binding globulin)	Tratamentul encefalomiopatiei neurogastrointestinale mitocondriale
Slovak	Vektor založený na kostre adeno-asociovaného vírusu sérotypu 2 pseudosérotypovaného s kapsidom typu 8, ktorý nesie kódujúcu sekvenciu ľudského *TYMP* génu pod kontrolou promótora pre ľudský thyroxín-viažuci globulín	Liečba mitochondriálnej neurogastrointestinálnej encefalomyopatie
Slovenian	Vektor, sestavljen na osnovi adeno-pridruženega virusa serotipa 2, psevdo-serotipiziran s kapsido tipa 8, ki prenaša zapis človeškega *TYMP* gena pod nadzorom promotorja za globulin, ki veže humani tiroksin	Zdravljenje mitohondrijske neurogastrointestinalne encefalomiopatije
Spanish	Vector basado en la estructura de un virus adeno-asociado serotipo 2, pseudo-serotipado con una cápside tipo 8, conteniendo la secuencia codificante del gen *TYMP* humano bajo el control del promotor humano de la globulina enlazante de tiroxina	Tratamiento de la encefalomiopatía neurogastrointestinal mitocondrial
Swedish	En vektor baserad på en ryggrad av adenoassocierat virus serotyp 2, pseudoserotypad med en typ 8 kapsid, som bär den kodande sekvensen för den humana *TYMP* genen under kontroll av den humana tyroxinbindande globulinpromotorn	Behandling av mitokondriell neurogastrointestinal encefalomyopati

Language	Active ingredient	Indication
Norwegian	Vektor basert på en adenoassosiert virus serotype 2 struktur, pseudo-serotypet med en type 8 kapsid, som inneholder den kodende sekvensen av det humane genet *TYMP* under kontroll av den humane tyroksinbindende globulin promotoren	Behandling av mitokondrie-neurogastrointestinal encefalomyopati
Icelandic	Ferja sem byggir á adenó-tengdri veiru sermisgerð 2 grunni með týpu 8 capsid sem flytur kóðunarröð manna *TYMP* gens undir stjórn manna thýroxín bindiglóbúlín örva	Meðferð á hvatbera taugameltingarfæra heila vöðvakvilla