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Committee for Orphan Medicinal Products

Public summary of opinion on orphan designation

Autologous CD34+ cells transduced with a lentiviral vector containing the human *RAG1* gene for the treatment of recombination-activating gene 1 deficient severe combined immunodeficiency

On 26 March 2014, orphan designation (EU/3/14/1257) was granted by the European Commission to Prof F.J.T. Staal, the Netherlands, for autologous CD34+ cells transduced with a lentiviral vector containing the human *RAG1* gene for the treatment of recombination-activating gene 1 deficient severe combined immunodeficiency.

What is recombination-activating gene 1 deficient severe combined immunodeficiency?

Recombination-activating gene 1 (RAG1) deficient severe combined immunodeficiency (SCID) is an inherited disorder where the patient is unable to fight infections due to the lack of a type of white blood cells called lymphocytes.

It is caused by defects in the gene called *RAG1*, which makes a protein essential for the development of lymphocytes. Patients with this defect do not produce enough lymphocytes to fight infections and are highly susceptible to bacterial, fungal and viral infections. The main symptoms usually occur in the first six months of life, and include pneumonia, diarrhoea and a failure to grow and develop normally.

RAG1-deficient SCID is a long-term debilitating and life-threatening condition due to repeated and long-lasting infections which can lead to various health problems in the longer term, including developmental disorders, hearing loss, skeletal dysplasia (dwarfism) and liver and kidney problems.

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

At the time of designation, RAG1-deficient SCID affected approximately 0.1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 5,000 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).

[*]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).

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What treatments are available?

At the time of designation, no satisfactory methods were authorised in the EU for the treatment of RAG1-deficient SCID. In some patients, allogeneic haematopoietic (blood) stem-cell transplantation was used. This is a complex procedure whereby 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 up of immature bone marrow cells (called CD34+ cells) that are taken from the patient. These cells are able to develop into different types of blood and immune cells. To make this medicine, the CD34+ cells are modified by a virus that contains a normal form of the *RAG1* gene, so that this gene is carried into the cells. When these modified cells are transplanted back into the patient, they are expected to grow and be able to produce the lymphocytes which are lacking in patients with RAG1-deficient SCID, and thereby help to relieve the symptoms of the disease.

The type of virus used in this medicine ('lentivirus') is modified in order not to 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 RAG1-deficient SCID had been started.

At the time of submission, the medicine was not authorised anywhere in the EU for RAG1-deficient SCID 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 6 February 2014 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

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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	Autologous CD34+ cells transduced with a lentiviral vector containing the human *RAG1* gene	Treatment of recombination-activating gene 1 deficient severe combined immunodeficiency
Bulgarian	Автоложни CD34+ клетки, трансдуцирани с лентивирусен вектор, съдържкащ човешки *RAG1* ген	Лечение на тежък комбиниран имунодефицит с недостатъчност на рекомбинация-активиращ ген 1
Czech	Autologní buňky CD34+ transdukované lentivirálním vektorem obsahujícím lidský gen *RAG1*	Léčba deficiru recombination activating gene 1 závážného kombinovaného imunodeficitu
Croatian	Autologne CD34+ stanice transducirane lentivirusnim vektorom koji sadrži ljudski gen RAG1	Liječenje teške kombinirane imunodeficijencije uzrokovane deficijencijom rekombinaze 1
Danish	Autologe CD34+ celler transduceret med en lentivirus vektor indeholdende det humane *RAG1*-gen	Behandling af svær kombineret immundefekt forårsaget af mangel på rekombination-aktiverende gen 1
Dutch	Autologe CD34+ cellen getransduceerd met een lentivirale vector die het humane *RAG1* gen bevat	Behandeling van recombinatie – activerend gen 1 deficiënte ernstige gecombineerde immunodeficiëntie
Estonian	Autoloogsed CD34+ rakud transdukteeritud lentiviraalse vektoriga, mis sisaldab inimese *RAG1*-geeni	*Recombination activating gene 1* defitsiidist tingitud raske kombineeritud immuunpuudulikkuse ravi
Finnish	Autologisia CD34+_soluja, jotka kuljetetaan ihmisen *RAG1*-geenin sisältävällä lentivirusvektorilla	Rekombinaatiota aktivoivan geeni 1:n puutteen, johon liittyy vakava immuunivajaus, hoito
French	Cellules CD34+ autologues transduites avec un vecteur lentiviral contenant le gene humain *RAG1*	Traitement de l'immunodéficience combinée sévère au gène 1 activant la recombinaison
German	Autologe CD34+ Zellen, transduziert mit einem lentiviralen Vektor, der das menschliche *RAG1*-Gen enthält	Behandlung der schweren kombinierten Immunschwäche, die durch den Mangel des RAG1-Gens (Rekombinationsaktivierendes Gen 1) hervorgerufen wird
Greek	Αυτόλογα κύτταρα CD34+ διαμολυσμένα με φορέα λεντι-ιού που περιέχει το ανθρώπινο γονίδιο *RAG1*	Θεραπεία της βαριάς συνδυασμένης ανοσοανεπάρκειας που οφείλεται στην ανεπάρκεια του γονιδίου ενεργοποίησης ανασυνδυασμού 1(RAG1)
Hungarian	Humán *RAG1* gént hordozó lentivirus vektorral transzdukált autológ CD34+ sejtek	Rekombináns aktivált gén-1(RAG1) hiány okozta súlyos kombinált immunhiány kezelése
Italian	Cellule CD34+ autologhe trasdotte con un vettore lentivirale contenente il gene umano *RAG1*	Trattamento della immunodeficienza grave combinata da deficit del recombination activating gene 1

[1] At the time of designation

Language	Active ingredient	Indication
Latvian	Ar cilvēka *RAG1* gēnu saturošu lentivīrusa vektoru transducētas autologas CD34+ šūnas	Rekombinācijas aktivācijas 1 gēna deficīta izraisīta smaga kombinēta imūndeficīta ārstēšana
Lithuanian	Autologinės CD34+ ląstelės, pkeistos lentivirusiniu vektoriumi, turinčiu žmogaus *RAG1* geną	Rekombinantinio – aktyvinto geno 1 stokos sąlygoto sunkaus kombinuoto imunodeficito gydymas
Maltese	Ċelluli CD34+ awtologi trasformati b'vettur lentivirali li fih il-ġene *RAG1* uman	Kura ta' immunodefiċjenza magħquda severa minħabba nuqqas tal-ġene tat-tip 1 li jattiva ir-rikombinazzjoni
Polish	Autologiczne komórki CD34+ transfekowane wektorem lentiwirusowym zawierającym ludzki gen *RAG1*	Leczenie ciężkiego skojarzonego niedoboru odporności związanego z niedoborem genu 1 aktywującego rekombinację
Portuguese	Células CD34+ autólogas transduzidas com um vetor lentiviral que contém o gene *RAG1* humano	Tratamento da imunodeficiência combinada grave com défice de gene activador da recombinase 1
Romanian	Celule autologe CD34+ transduse cu un vector lentiviral conţinând gena umană *RAG1*	Tratamentul imunodeficienţei combinate severe produse de deficitul de recombination activating gene 1
Slovak	Autológne CD34+ bunky transfektované lentivírusovým vektorom, ktorý obsahuje ľudský *RAG1* gén	Liečba ťažkej kombinovanej imunodeficiencie spôsobenej deficitom génu RAG1
Slovenian	Avtologne CD34+ celice, transducirane s pomočjo lentivirusnega vektorja, ki vsebuje človeški *RAG1* gen	Zdravljenje hude kombinirane imunske pomanjkljivosti, povezane s pomanjkanjem recombinantnega activacijskega gena 1
Spanish	Células CD34+ autólogas transfectadas con un vector lentivírico que contiene el gene humano de la *RAG1*	Tratamiento de la inmunodeficiencia severa combinada del deficit del gene activadora recombinase 1
Swedish	Autologa CD34+ celler transducerade med en lentivirusvektor innehållande den mänskliga *RAG1*-genen	Behandling av svår kombinerad immunbrist beroende på recombination-activating gene 1 brist
Norwegian	Autologe CD34+ celler transdusert med lentiviral vektor som inneholder det humane *RAG1*-genet	Behandling av alvorlig kombinert immunsvikt som skyldes rekombineringsaktiverende gen 1-mangel
Icelandic	Samgena CD34+ frumur sem manna *RAG1*-gen hefur verið flutt í með lentiveiru genaferju	Meðferð á alvarlegum, blönduðum ónæmisbresti sem stafar af skorti á samtengingar-virkjunar geni 1