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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Skysona (elivaldogene autotemcel, autologous haematopoietic stem cells transduced with lentiviral vector Lenti-D encoding the human *ABCD1 cDNA*)
Treatment of adrenoleukodystrophy
EU/3/12/1003

Sponsor: bluebird bio (Netherlands) B.V.

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Autologous haematopoietic stem cells transduced with lentiviral vector Lenti-D encoding the human *ABCD1 cDNA*
Other name(s)	Skysona, Autologous haematopoietic stem cells transduced with lentiviral vector Lenti-D encoding the human ABCD1 cDNA,
International Non-Proprietary Name	Elivaldogene autotemcel
Tradename	Skysona
Orphan condition	Treatment of adrenoleukodystrophy
Sponsor's details:	bluebird bio (Netherlands) B.V. Stadsplateau 7 3521 AZ Utrecht Netherlands
Orphan medicinal product designation procedural history	
Sponsor/applicant	Bluebird bio France
COMP opinion	12 April 2012
EC decision	6 June 2012
EC registration number	EU/3/12/1003
Post-designation procedural history	
Transfer of sponsorship	- Transfer from bluebird bio France to bluebird bio (Germany) GmbH – EC decision of 25 Jul 2018 - 2nd Transfer from bluebird bio (Germany) GmbH to bluebird bio (Netherlands) B.V. – EC decision of 21 Feb 2019
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	L. Barkholt / A. Pastoft
Applicant	bluebird bio (Netherlands) B.V.
Application submission	10 September 2020
Procedure start	1 October 2020
Procedure number	EMA/H/C/003690
Invented name	Skysona
Proposed therapeutic indication	Treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age, with an ABCD1 genetic mutation, and for whom a human leukocyte antigen (HLA) matched sibling haematopoietic stem cell donor is not available. Further information on Skysona can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/skysona
CHMP opinion	18-20 May 2021

COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	D. Matusevicius / A. Magrelli
Sponsor's report submission	13 November 2020
COMP opinion (adoption via written procedure)	26 May 2021

2. Grounds for the COMP opinion

2.1. Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2012 designation was based on the following grounds:

The sponsor, bluebird bio France, submitted on 30 January 2012 an application for designation of a medicinal product containing autologous haematopoietic stem cells transduced with lentiviral vector Lenti-D encoding the human ABCD1 cDNA as an orphan medicinal product for treatment of adrenoleukodystrophy.

Whereas, the Committee for Orphan Medicinal Products (COMP), having examined the application, concluded:

- adrenoleukodystrophy (hereinafter referred to as "the condition") was estimated to be affecting not more than 0.4 in 10,000 persons in the European Union, at the time the application was made; the sponsor has sourced data from the European Leukodystrophy Association and a literature search of peer reviewed journals; this is not more than 5 in 10,000 persons as established in Article 3(1) (a) of Regulation (EC) 141/2000;
- the sponsor has established that the condition is chronically debilitating and life threatening. Three phenotypes of adrenoleukodystrophy result in different degrees of severity. The most severe, childhood cerebral adrenoleukodystrophy, affects only males in childhood and is associated with behavioural abnormalities, including inattention, hyperactivity, and emotional lability. The course is progressive with seizures, spastic tetraplegia, and dementia developing within months of onset. Once the neurologic manifestations appear, progression of the illness is usually rapid with death occurring between the ages of 5 and 10 years. In the second form, adrenomyeloneuropathy (AMN), symptoms appear between 20 and 30 years of age. Patients present with stiffness and clumsiness in their legs and gait disturbance becomes severe within 10 to 15 years, requiring the use of a cane or a wheelchair. AMN patients die within 20 years of onset. The mildest form affects seventy percent of adrenoleukodystrophy patients and presents with primary adrenocortical insufficiency but, nearly all patients with this phenotype develop AMN later in adulthood;
- there is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

The COMP recommends the designation of this medicinal product, containing autologous haematopoietic stem cells transduced with lentiviral vector Lenti-D encoding the human *ABCD1* cDNA, as an orphan medicinal product for the orphan indication: treatment of adrenoleukodystrophy.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Adrenoleukodystrophy (ALD), also referred to as X-linked adrenoleukodystrophy, (X-ALD) is a recessively inherited neurometabolic disorder characterized by a progressive central inflammatory demyelination in the brain and slowly progressing axonal degeneration of the corticospinal tracts, resulting in spastic paraparesis and adrenal insufficiency. It is caused by mutations in the ABCD1 gene (located in Xq28), which encodes the ATP-binding cassette transporter, an integral peroxisomal membrane protein. Loss of function results in an impaired import of very long-chain fatty acids (VLCFA) into peroxisomes and their accumulation in the target organs and in plasma.

The condition can present with many different phenotypes, including childhood cerebral ALD (CALD), pure cerebral ALD in adulthood, adrenomyeloneuropathy (AMN), adrenal insufficiency only, and even as a carrier state (Moser at al. JAMA 2005; 294:3131).

The approved therapeutic indication "Skysona is indicated for the treatment of early cerebral adrenoleukodystrophy in patients less than 18 years of age, with an ABCD1 genetic mutation, and for whom a human leukocyte antigen (HLA)-matched sibling haematopoietic stem cell (HSC) donor is not available (see section 5.1)." falls within the scope of the designated orphan condition "treatment of adrenoleukodystrophy".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, see EPAR.

Chronically debilitating and/or life-threatening nature

There has been no change to the chronically debilitating and life-threatening nature of the condition since the initial orphan designation.

ALD is considered a progressive metabolic disease. It appears that all patients with ALD are born pre-symptomatic. The condition is life-threatening and chronically debilitating taking into consideration the two main phenotypes with which the condition presents. Cerebral adrenoleukodystrophy is associated with seizures, spastic tetraplegia, behavioural abnormalities and cognitive decline and patients usually die within several years after the onset of symptoms. Adrenomyeloneuropathy is associated with primary adrenocortical insufficiency as well as progressive stiffness and gait disturbance, with patients dying within 20 years after the onset of symptoms.

Number of people affected or at risk

The sponsor reports that in the EU and the US, the incidence of ALD has been estimated at between 1/16,800 and 1/20,000 births, including hemizygotes and heterozygous women. Using the highest

incidence reported to date 1/10,000 (from the North Carolina pilot study; (Taylor and Lee 2019) and the 2018 EUROSTAT - Demographic Report) the number of new X-ALD gene carriers born in one year in the EU can be estimated at approximately 424 new-borns/year. Only a few new publications on the prevalence of the condition in Europe have been published and therefore the variability across Member States cannot be established.

The sponsor proposes two methodological approaches.

Methodological approach 1:

The sponsor only identified one article with prevalence estimate (only for X-ALD hemizygote males). This article (van Geel et al., 1994) reported an estimated prevalence of 1/200,000 male inhabitants in the Netherlands.

In this publication, out of 7.5 million males (all ages) living in the country, 38 males were known to have X-ALD. This led the authors to conclude the prevalence of X-ALD in males was 1/200,000, which is equivalent to 0.05 per 10,000 male inhabitants. Estimating that the total population of the Netherlands was around 15 million at the time, they estimate that this figure is equivalent to 0.025 per 10,000 inhabitants https://countryeconomy.com/demography/population/netherlands?year=1993 (accessed 19 August 2020).

Bezman et al., 2001 used standard population genetics arguments to estimate the ratio of female heterozygotes to hemizygous males under modified Hardy-Weinberg conditions as a ratio of about 1.5. Using this figure and the Netherlands hemizygous prevalence number, the sponsor proposes an estimate for the total prevalence of X-ALD in the EU to be 0.0625 per 10,000 inhabitants.

Methodological approach 2:

The sponsor has estimated an incidence of X-ALD cases in the EU is 424 cases per year (male and female). Out of these 424 cases, it is assumed that the ratio between the female cases and the male cases is estimated at 1.5. Thus, it is proposed that the estimate out of these yearly incident 424 cases, 142 are males and 282 are females.

The sponsor proposed that approximate that 40% of the X-ALD patients have CALD and 60% of the patients have AMN with 15 years and 70 years of life expectancy, respectively, and 100% of the females have "AMN" with 15- and 70-years life expectancy for CALD and AMN respectively. There is very little information available on the life expectancy of AMN patients. For "pure-AMN" patients (without cerebral lesions), the life expectancy is similar to healthy individuals. The estimated life expectancy of 15 years for untreated patients with cerebral lesions is highly overestimated as the majority of these patients die within 5 years of diagnosis of the cerebral form of the disease if left untreated. Similarly, assuming 70 years for AMN patients is conservative as we know a certain number of these patients will develop cerebral lesions and have a life expectancy of only a few years. Based on a report by Moser 1997) approximately 40% of the AMN patients have died within 25 years of onset.

Lastly, it is known from the published literature that approximately only 50% of heterozygous women will develop symptoms similar to AMN (Moser 2007), thus counting all heterozygous women in our prevalence calculation is an overestimate as it appears that only half of them develop X-ALD.

In 2018, the EU-27 population was estimated to be 513 million (EuroStat Newsrelease, July 2018).

The overall prevalence of ALD in the EU is therefore estimated 0.518 per 10,000 inhabitants.

As it is known that the condition is underdiagnosed the birth incidence figure of 1 in 10,000 births is potentially plausible. The sponsor stated that there do not seem to be state run screening programmes

in the European Union. The COMP however noted that there is a screening programme in the Netherlands which, while not comparable with the United States, can offer some insight. As underreporting is a plausibility the result of the first methodological approach would appear to be an under-estimate. Following this logic, the second methodological approach would appear to reflect more closely the current prevalence in Europe as it uses data involving the older phenotypic subgroups which recently appear to be superseded by the acceptance that there is a wide variability in penetrance, of course with the caveat that it is probably incomplete due to the scarcity of publicly available data.

In conclusion, based on consistency of estimates in published data, the sponsor concludes conservatively that the prevalence of X-ALD in the EU is approximately 0.518 per 10,000 inhabitants. This represents a slight increase from the original prevalence figure reported in the initial OMP application was 0.4 per 10,000. The COMP could accept the revised figure of 0.5 in 10,000 which is still well below the threshold of 5 in 10,000.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There are currently no authorized medicines for the treatment of the condition in Europe.

Treatment of ALD with glucocorticoid supplementation is similar to that of patients with other causes of primary adrenal insufficiency. As adrenal insufficiency can be the presenting symptom of ALD, endocrinologists should, therefore, test for VLCFA accumulation in boys and men when tests for adrenal cortex autoantibodies are negative, or when signs of myelopathy are present.

Haematopoietic stem cell transplantation (HSCT) remains the only therapeutic intervention for cerebral ALD.

Significant benefit

Not Applicable.

4. COMP position adopted on 26 May 2021

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan condition of the designated Orphan Medicinal Product.
- the prevalence of adrenoleukodystrophy (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 0.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is life-threatening and chronically debilitating taking into consideration the two main phenotypes with which the condition presents. Cerebral adrenoleukodystrophy is associated with seizures, spastictetraplegia, behavioural abnormalities and cognitive decline and patients usually die within several years after the onset of symptoms. Adrenomyeloneuropathy is associated with primary adrenocortical insufficiency as well as progressive stiffness and gait disturbance, with patients dying within 20 years after the onset of symptoms;
- there is, at present, no satisfactory method for the treatment of adrenoleukodystrophy that has been authorised in the European Union for patients affected by the condition.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Skysona, Autologous haematopoietic stem cells transduced with lentiviral vector Lenti-D encoding the human ABCD1 cDNA, elivaldogene autotemcel for treatment of adrenoleukodystrophy (EU/3/12/1003) is not removed from the Community Register of Orphan Medicinal Products.