11 January 2022
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Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Lonapegsomatropin Ascendis Pharma (lonapegsomatropin)
Treatment of growth hormone deficiency
EU/3/19/2213

Sponsor: Ascendis Pharma Endocrinology Division A/S

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)	Lonapegsomatropin
Other name(s)	Lonapegsomatropin Ascendis Pharma
International Non-Proprietary Name	Lonapegsomatropin
Tradename	Lonapegsomatropin Ascendis Pharma
Orphan condition	Treatment of growth hormone deficiency
Sponsor's details:	Ascendis Pharma Endocrinology Division A/S Tuborg Boulevard 12 2900 Hellerup Hovedstaden Denmark
Orphan medicinal product designation procedural history	
Sponsor/applicant	Ascendis Pharma Endocrinology Division A/S
COMP opinion	12 September 2019
EC decision	17 October 2019
EC registration number	EU/3/19/2213
Post-designation procedural history	
Sponsor's change of address	20 April 2021
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Johann Lodewijk Hillege / Jean-Michel Race
Applicant	Ascendis Pharma Endocrinology Division A/S
Application submission	8 September 2020
Procedure start	1 October 2020
Procedure number	EMA/H/C/5367/0000
Invented name	Lonapegsomatropin
Proposed therapeutic indication	Treatment of growth hormone deficiency Further information on Lonapegsomatropin Ascendis Pharma can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/lonapegsomatropin-ascendis-pharma
CHMP opinion	11 November 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Elisabeth Johanne Rook / Vallo Tillmann
Sponsor's report submission	9 April 2021
COMP discussion	7-9 September 2021
COMP opinion (adoption via written procedure)	15 November 2021

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2019 designation was based on the following grounds:

The sponsor Ascendis Pharma Endocrinology Division A/S submitted on 26 June 2019 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing lonapegsomatropin for treatment of growth hormone deficiency (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the application, the COMP considered that the sponsor has established the following:

- the intention to treat the condition with the medicinal product containing lonapegsomatropin was considered justified based on clinical data showing a significant effect on growth velocity in children affected by the condition;
- the condition is chronically debilitating due to delayed puberty and deficits in facial, dental and genital development, associated with reduced bone mass with increased risk of developing osteopenia, osteoporosis, and bone fractures. Patients also experience severe psychosocial problems linked to the very short stature;
- the condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made;

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing lonapegsomatropin will be of significant benefit to those affected by the condition. The sponsor has provided clinical data showing significantly increased growth velocity in children affected by the condition compared with the currently authorized standard of care growth hormone treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concludes that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled. The COMP therefore recommends the designation of this medicinal product, containing lonapegsomatropin as an orphan medicinal product for the orphan condition: treatment of growth hormone deficiency.

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

The designated condition included both paediatric and adult forms of growth hormone deficiencies (GHD) and is still acceptable as an orphan condition.

GHD is a consequence of deficient or insufficient growth hormone secretion that is generally associated with defects in the pituitary gland or the hypothalamus. In the paediatric population, GHD is primarily idiopathic, whereas in the adult population GHD more often is caused by tumours in the central nervous system, cranial irradiation, head trauma or organic causes. GHD in children is characterised by a diminished growth velocity and a markedly reduced final adult height compared to that predicted (Rosenfeld et al, 2001). In addition to profound growth failure, children with GHD develop the same physiological and cognitive abnormalities as the adult population. GHD may be present already at birth but is generally first discovered within the first years of childhood.

Adult growth hormone deficiency (AGHD) is characterised by several clinical features that comprises general health and quality of life. If left untreated, AGHD is associated with increased body fat, decreased lean body mass, reduced bone mineral density, disturbed lipoprotein metabolism, reduced exercise capacity, increased risk of cardiovascular morbidity and mortality, and decreased cognition and psychological well-being (Alexopoulou et al, 2010; Molitch et al, 2011).

The approved therapeutic indication "Growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency [GHD])." falls within the scope of the designated orphan condition "Treatment of growth hormone deficiency".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP, based on the pivotal study CT-301.

Chronically debilitating and/or life-threatening nature

No change in the chronically debilitating and/or life-threatening nature of the condition has been reported since the designation of the orphan medicinal product.

The condition is associated with a wide range of neuropsychiatric, cognitive, cardiac, metabolic, muscular, and bone symptoms. GHD in children is characterised by a diminished growth velocity and a markedly reduced final adult height compared to that predicted (Rosenfeld et al, 2001). In addition to profound growth failure, children with GHD develop the same physiological and cognitive abnormalities as the adult population. If left untreated, AGHD is associated with increased body fat, decreased lean body mass, reduced bone mineral density, disturbed lipoprotein metabolism, reduced exercise

capacity, increased risk of cardiovascular morbidity and mortality, and decreased cognition and psychological well-being (Alexopoulou et al, 2010; Molitch et al, 2011).

Number of people affected or at risk

Since GHD manifests differently in children and adults due to a shift in roles of GH between these age groups, childhood and adult GHD populations are typically reported separately in most epidemiological assessments. There is only one report mentioned in this evaluation, which discusses estimates for both childhood and adult GHD (Stochholm 2006).

The sponsor noted that while national registries (e.g. Dutch National Registry of GH Treatment in Adults) , Sponsor's registries (e.g. Pfizer International Growth Database [KIGS]) and international registries such as Genetics and Neuroendocrinology of Short Stature International Study [GeNeSIS], Hypopituitary Control and Complications Study [HypoCCS], National Cooperative Growth Study [NCGS], NordiNet® International Outcome Study [IOS]) have been established, these databases are not accessible for public review. Therefore, the sponsor relied on published literature for the prevalence estimation.

A systematic literature search was conducted, and twelve papers were identified that complied with the predefined criteria. Seven papers reported on childhood prevalence or incidence: Vimpani 1977, Hilken 2001, Audí 2002, Thomas 2004, Migliaretti 2006, Stochholm 2006 and Schweizer 2010. Five studies reported on adult prevalence or incidence: Sassolas 1999, Regal 2001, Stochholm 2006, van Bunderen 2011 and van Nieuwpoort 2011.

The sponsor reviewed all these articles and conducted a meta-analysis based on the prevalence (or incidence) figures published. A separate meta-analysis was done for childhood GHD (Figure 1) and adult GHD (Figure 2). Based on these analyses, which included the higher, more conservative estimates from the sensitivity analyses, the best prevalence estimate for childhood GHD in the EU was 3.8 per 10,000 children (95% CI: 2.7-.9 per 10,000) and for adult GHD in the EU was 2.5 per 10,000 adults (95% CI: 1.0-4.0 per 10,000).

For the purposes of this application, the highest estimates (upper 95% CI) are used for the overall prevalence of GHD in the EU. This corresponds to 4.9 per 10,000 children and 4 per 10,000 adults.

Figure 1: Meta-Analysis of Prevalence of Childhood GHD

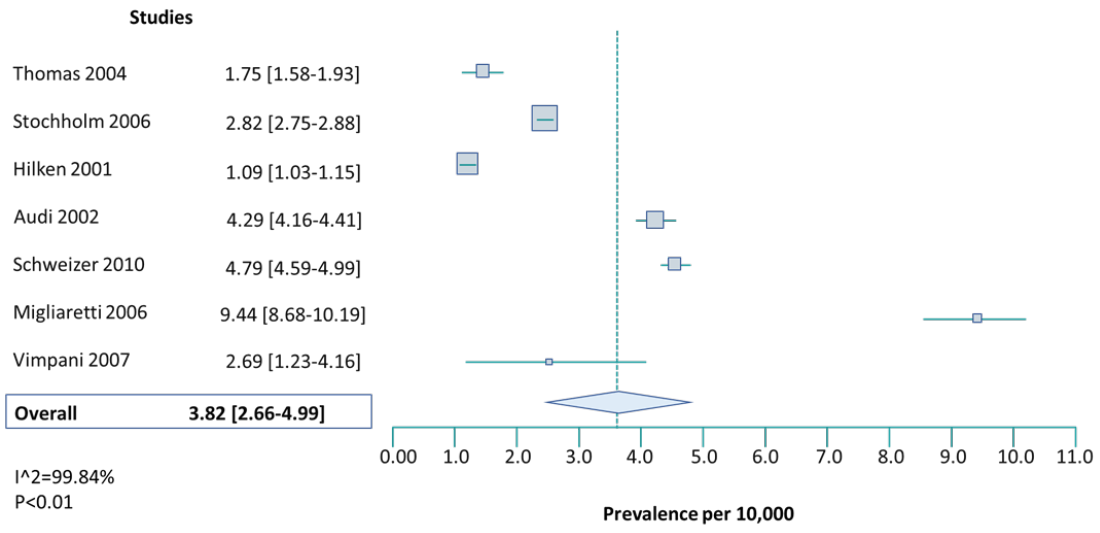
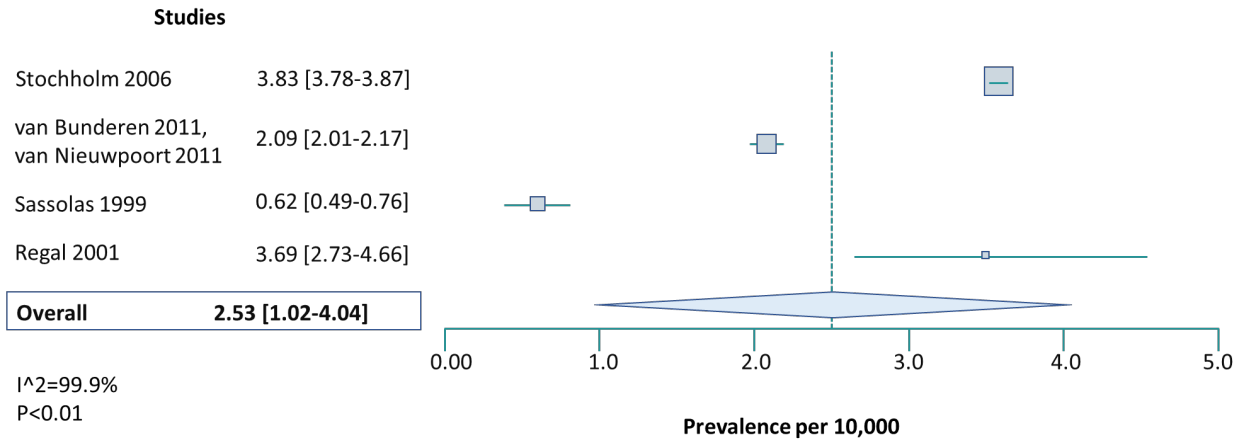


Figure 2: Meta-Analysis of Prevalence of Adult GHD



Some childhood studies reported prevalence in only a subset of children; therefore, assumptions were made regarding the prevalence in the entire 0-18-year-old population. Expanding the prevalence to the 0-18-year-old age group is considerably conservative as few children are diagnosed with GHD at ages less than 2 and greater than 13 years.

The overall weighted prevalence of GHD in children and adults is based on the most conservative scenario (upper 95% confidence interval) from each meta-analysis, estimated to be 4.9 per 10,000 and 4.0 per 10,000, respectively, for children and adults. To provide an overall estimate of GHD in Europe, the most recent estimates of the European population have been used. Based on 2020 data (https://ec.europa.eu/eurostat/data/database), the total population of Europe (27 countries) was 447,319,916. The population aged 0-18 years was 86,511,672 and the population aged >18 years was 360,808,244.

Applying the estimated prevalence of childhood GHD and adult AHD to the European population, the total prevalence of GHD in Europe is calculated by: $((4.9 \times 10^{-4} \times 86{,}511{,}672) + (4.0 \times 10^{-4} \times 360{,}808{,}244)) / 447{,}319{,}916$. This gives an overall prevalence estimate of 4.17 per 10,000 general population.

Considering that the orphan condition of growth hormone deficiency includes both adults and children the COMP decided that the highest prevalence estimate of 4.9 per 10,000 would be the most appropriate and sufficiently conservative estimate. This estimate is also in line with the one from the recently adopted medicinal product Sogroya, in the same condition.

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

The standard treatment for patients with GHD (children and adults) in the EU is daily, s.c. injection with recombinant human GH (somatropin). The sponsor provided a list of current approved products for daily administration in the EU for treatment of GHD in children and adults, all of which contain

somatropin as active ingredient. They also include the recently authorised long acting growth hormone Sogroya which is approved for "replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD)".

The daily administered somatropin products are generally authorised for children which is the target patient population for Lonapegsomatropin. Therefore, they are considered as satisfactory methods and a significant benefit will have to be justified versus somatropin for daily use.

Sogroya, on the other hand is only approved for adults and therefore Sogroya is not considered a satisfactory method for treatment of children with GHD.

Significant benefit

The sponsor argues a clinically relevant advantage based on the outcome of the pivotal study (**CT-301),** which demonstrated non-inferiority and, additionally, statistical superiority for lonapegsomatropin in 105 patients compared to daily somatropin therapy (Genotropin, 56 patients) on the primary endpoint of Annualized Height Velocity (AHV) at 52 weeks. In an ANCOVA analysis of the ITT population, lonapegsomatropin resulted in a statistically greater AHV of 11.2 cm/year compared to 10.3 cm/year for Genotropin (P=0.0088). Although statistical significance was reached, the CHMP concluded that there is insufficient evidence to conclude therapeutic superiority of lonapegsomatropin over daily somatropin, as the difference in the treatment effect was less than the non-inferiority margin of 2 cm/year which was defined prior to the study. Therefore, a significant benefit based on a clinically relevant advantage regarding efficacy cannot be established.

The sponsor also argues a major contribution to patient care based on improved treatment burden, convenience, and satisfaction with the once weekly injection as opposed to the daily injections.

Treatment burden among children and their parents was assessed with the Child Sheehan Disability Score (CSDS; 1). This decrease in CSDS scores occurred even though children may have used a pen or other device for their prior daily somatropin treatment versus syringe/needle for once-weekly lonapegsomatropin during the clinical trials.

In CT-302, an 26 weeks open-label study in 146 paediatric GHD patients aged 6 months up to 18 years where the vast majority of patients was treated before with daily somatropin, the CSDS summary score decreased from baseline (reflecting prior daily somatropin therapy) to the end of the trial, indicating that treatment burden was alleviated with the switch from daily somatropin to once-weekly lonapegsomatropin treatment. Similarly, CSDS scores decreased for children (and their parents) who switched from daily Genotropin in CT-301 to once-weekly lonapegsomatropin in CT-301EXT. the extension phase of the pivotal trial. The data are summarised in Table 1.

Table 1: CT-302 and CT-301EXT: Child Sheehan Disability Summary Scores for Child and Parent

CT-302	CT-302 Baseline (reflects prior daily somatropin therapy)		CT-302 Week 26 (reflects lonapegsomatropin syringe/needle)	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Child (N=100)	100	2.5 (4.2)	98	1.4 (3.0)[a]
Parent (N=146)	143	5.7 (6.4)	143	1.9 (2.9)[b]
CT-301EXT: CT-301 Genotropin Group	**CT-301EXT Baseline** (reflects prior CT-301 Genotropin pen)		**CT-301EXT Week 13** (reflects lonapegsomatropin syringe/needle)	
	n	**Mean (SD)**	**n**	**Mean (SD)**
Child (N = 34)	33	1.4 (2.7)	33	0.6 (1.8)
Parent (N = 55)	53	2.0 (3.7)	52	1.1 (2.3)

[a] P = 0.0086 for comparison to CT-302 Baseline.
[b] P<0.0001 for comparison to CT-302 Baseline.

The convenience and overall satisfaction domains of the Treatment Satisfaction Questionnaire for Medication (TSQM-9) were completed by all parents during CT-302 and by parents of children who were previously in the CT-301 Genotropin arm during CT-301EXT. Treatment satisfaction refers to the individual patient's appraisal of his or her experience with treatment. The summary scores range from 0 to 100, with higher scores indicating greater convenience or satisfaction.

While global satisfaction scores remained high across timepoints, the convenience score increased notably upon transition to lonapegsomatropin administration via the GH Auto-Injector from either lonapegsomatropin administered via syringe/needle (CT-302 or CT-301 lonapegsomatropin) or daily somatropin administered via a pen (CT-301 Genotropin). These results suggest that both frequency and mode of administration factor heavily into parent's assessment of convenience. Once-weekly lonapegsomatropin as administered with GH Auto-Injector was associated with relatively high convenience and satisfaction scores as assessed by parents.

Table 2: CT-301EXT: Convenience and Overall Satisfaction Domains of TSQM-9 for Subjects who Transitioned to the GH Auto-Injector, by Parent Trial Group – Completed by Parent

Summary Score	**CT-301EXT Baseline** (reflects lonapegsomatropin vial/syringe [CT-302, CT-301 lonapegsomatropin] or Genotropin pen [CT-301 Genotropin])	**Transition Week 6**[a] (reflects lonapegsomatropin via GH Auto-Injector)	**Transition Week 13**[a] (reflects lonapegsomatropin via GH Auto-Injector)
Convenience, Mean (SD)	(n=158) 73.8 (15.6)	(n=142) 86.1 (13.7)	(n=111) 87.0 (14.8)
Global Satisfaction, Mean (SD)	(n=157) 86.3 (14.5)	(n=142) 89.5 (12.6)	(n=111) 90.8 (12.5)

[a] Transition Week x means approximately x weeks after transition from lonapegsomatropin via syringe/needle to lonapegsomatropin via GH Auto-Injector.

The improved treatment burden, as assessed by the CSDS scores, confirms a statistically significant preference by both children and parents for the weekly treatment with Lonapegsomatropin. This is supported by the results from the TSQM-9 (Treatment Satisfaction Questionnaire for Medication version 9) convenience score which also indicate a higher convenience with Lonapegsomatropin as opposed to the comparator. In addition, a consistent preference for once-weekly lonapegsomatropin relative to daily somatropin treatment was reported by children and parents in studies CT-302 and CT-301EXT. The majority of patients preferred weekly (children 84%, parents 90%) over daily injection treatment (children 9%, parents 5%) after switching.

The COMP involved a paediatric patient representative and a carer whose testimonies supported the findings from the study. The prospect of a once weekly GH preparation was considered to alleviate the daily burden of injections. This was not only considered to reduce the physical burden of injections but to also grant patients and their families more freedom while away from home. This was considered to be a great benefit by the patient representatives as carrying along the daily GH preparations requires optimal cooling conditions and finding a suitable place and time to inject in privacy.

The assumption of significant benefit of lonapegsomatropin on basis of major contribution to patient care still holds.

4. COMP list of issues

Not applicable.

5. COMP position adopted on 15 November 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 growth hormone deficiency (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be 4.9 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to psychosocial problems linked to the short stature, abdominal obesity, reduced bone mass with increased risk of developing osteopenia, osteoporosis and bone fractures. In children, the condition can cause episodes of hypoglycaemia and delayed puberty. Adults are in addition affected by decreased lean body mass, reduced muscle strength and exercise capacity. The condition can be life-threatening with a twofold excess in overall mortality compared to the general population;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that lonapegsomatropin may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided global treatment satisfaction data from the pivotal clinical trial demonstrating that lonapegsomatropin (once weekly growth hormone) and somatropin (once daily growth hormone) are of comparable efficacy. However, the treatment burden for patients and the satisfaction scores were improved for lonapegsomatropin as compared to the somatropin control. This was considered acceptable in support of a major contribution to patient care.

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 Lonapegsomatropin Ascendis Pharma, lonapegsomatropin for treatment of growth hormone deficiency (EU/3/19/2213) is not removed from the Community Register of Orphan Medicinal Products.