14 February 2022
EMADOC-360526170-921331
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Ngenla (somatrogon)
Treatment of growth hormone deficiency
EU/3/12/1087
Sponsor: Pfizer Europe MA EEIG

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	Recombinant modified human growth hormone
Other name(s)	--
International Non-Proprietary Name	Somatrogon
Tradename	Ngenla
Initial orphan condition	Treatment of growth hormone deficiency
Sponsor's details:	Pfizer Europe MA EEIG Boulevard De La Plaine 17 1050 Brussels Brussels-Capital Region Belgium
Orphan medicinal product designation procedural history	
Sponsor/applicant	Richardson Associates Regulatory Affairs Ltd, United Kingdom
COMP opinion	6 December 2012
EC decision	24 January 2013
EC registration number	EU/3/12/1087
Post-designation procedural history	
Transfer of sponsorship	Transfer from Richardson Associates Regulatory Affairs Ltd, United Kingdom, to Richardson Associates Regulatory Affairs Ltd, Ireland, – EC decision of 14 December 2018
Transfer of sponsorship	Transfer from Richardson Associates Regulatory Affairs Ltd, Ireland, to Pfizer Europe MA EEIG – EC decision of 14 April 2020
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	Peter Kiely / Martina Weise
Applicant	Pfizer Europe MA EEIG
Application submission	3 February 2021
Procedure start	25 February 2021
Procedure number	EMA/H/C/005633/0000
Invented name	Ngenla
Proposed therapeutic indication	Ngenla is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone. Further information on Ngenla can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Ngenla
CHMP opinion	16 December 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Vallo Tillmann / Geraldine O'Dea

Sponsor's report submission	10 September 2021
COMP discussion	07-09 December 2021
COMP opinion (adoption via written procedure)	21 December 2021

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2013 was based on the following grounds:

- the intention to treat the proposed condition appears justified on the grounds of preliminary clinical data with patients affected by the condition showing normalisation of IGF-1 levels.
- the condition was estimated to be affecting approximately 4 in 10,000 persons in the European Union, at the time the application was made;
- the sponsor has provided satisfactory argumentation to establish that the condition is chronically debilitating and life-threatening due to the psychosocial impact, the cardiovascular risk, and risk of decreased bone mass and fractures;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that recombinant modified human growth hormone may be of significant benefit to those affected by the condition. This appears justified on the grounds of improved pharmacokinetic properties that may allow for a less frequent administration compared to currently authorised products. This would constitute a major contribution to patient care, and is supported by preliminary clinical data that show a once-weekly administration potential.

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 "Ngenla is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone" 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.

Clinical efficacy of somatrogon investigated in support of the treatment in paediatric patients with growth hormone deficiency (GHD) was evaluated in one Phase 2 dose-finding study (CP-4-004 + OLE), a pivotal Phase 3 study (CP-4-006 +OLE) and an additional phase 3 patient preference study C0311002).

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

The sponsor contracted with an external company to replicate the literature search conducted for the original orphan designation application (ODA), and identify any new published literature since that application or any prior published literature that was not included with the original ODA.

The literature search review on the incidence and/or prevalence of GHD identified 2 additional studies published since the ODA was submitted in August 2012. The literature search also identified 3 studies published prior to the ODA in 2012 that had the potential to be included, however only 2 of the 3 studies were included. The study from Audi et al, 2002, was excluded as it included aetiologies that, according to the sponsor, were not proven as validated GHD.

The point prevalence estimate at the end of the study period was 3.75 per 10,000 among all hypopituitary cases in the Fernandez-Rodriguez, 2013 article. As only a subset (~60%) had GH deficiency, the sponsor re-calculated the prevalence to include all 126 cases of GHD as the numerator among the 405,208 subjects reported at risk in the study denominator, which results in a prevalence of 3.11 per 10,000.

For the database review at the Children's Hospital at Helsinki University in Finland during 2015–2020 (Karkinen et al, 2020) the prevalence of GHD was not reported directly. Therefore, assumptions were

made in order to calculate a prevalence estimate based on the available data in the study and that of the population of Finland. The conclusion was 0.74 per 10,000, which is line with the range of estimates from other childhood GHD studies.

With regards to the Migliaretti et al, 2006 article a prevalence of a treated prevalence rate of 9.44 per 10,000, was reported. However, in order to sum the childhood and adult GHD prevalence estimates, the population at risk for this study was required to be re-calculated based on the total population of area of investigation (Piedmont, Italy) during the study period. Re-calculating the treated prevalence based on the new denominator, the treated prevalence was estimated as 598 GHD cases per 4,271,733 persons, or 1.40 per 10,000 for this study. The sponsor still considers this figure an outlier but could be due to the case definition and diagnostic criteria used for GHD in Italy at the time of the study.

The sponsor applied pooled mean estimates by GHD subpopulation which was then summed to obtain the total GHD prevalence. For estimates of prevalence derived from incidence, a treatment duration of 10 years was used for conversion to prevalence for childhood GDA prevalence estimates, and a treatment duration of 25 years was used for conversion to prevalence for adult GDA prevalence estimates.

Table 1. Summary of Measured and Calculated Prevalence of Adult and Childhood GHD from Published Sources (Main analysis)

GHD Population	Reference	Region	Prevalence	Mean Prevalence
Childhood GHD	Vimpani et al., 1977	Scotland	0.94 / 10,000	**0.74 / 10,000**
	Lindsay et al., 1994	United States	0.47 / 10,000	
	Thomas et al., 2004	Belgium	0.38 / 10,000	
	Stochholm et al., 2006	Denmark	0.47 / 10,000*	
	Migliaretti et al., 2006	Italy	1.40 / 10,000	
	Schweizer et al., 2010	Germany	0.76 / 10,000*	
	Karkinen et al., 2020	Finland	0.74 / 10,000	
Adult GHD	Regal et al., 2001	Spain	1.77/ 10,000	**2.98 / 10,000**
			2.78/ 10,000	
	Stochholm et al., 2006	Denmark	4.23/ 10,000*^	
	Sassolas et al., 1999	France		
			3.00 / 10,000*^	
	Fernandez-Rodriguez et al., 2013	Spain	3.11/ 10,000	
Total GHD				**3.72 / 10,000**

* calculated from annual incidence; ^ adjusted to include 25% childhood onset GHD.

The sponsor also performed a sensitivity analysis varying the treatment duration time.

Table 2. Summary of Measured and Calculated Prevalence of Adult and Childhood GHD from Published Sources, Using a Maximum 10 Year Treatment Duration for Childhood GHD and 40 Year Treatment Duration for Adult GHD (Sensitivity analysis: Upper bound estimate)		
GHD Population	Reference	Prevalence per 10,000
Childhood GHD	Vimpani et al., 1977	0.94
	Lindsay et al., 1994	0.47
	Thomas et al., 2004	0.38
	Stochholm et al., 2006	0.47*
	Migliaretti et al., 2006	1.40
	Schweizer et al., 2010	0.76*
	Karkinen et al., 2020	0.74
	Mean of 10 year treatment duration assumption	**0.74**
Adult GHD	Regal et al., 2001	1.77
		2.78
	Stochholm et al., 2006	6.77*^
	Sassolas et al., 1999	4.8*^
	Fernandez-Rodriguez et al., 2013	3.11
	Mean of 40 year treatment duration assumption	**3.85**
Total GHD (Upper bound estimate)		**4.58**

* calculated from annual incidence; ^ adjusted to include 25% childhood onset GHD

The sponsor concludes on a prevalence of 4.6 in 10,000. This is slightly less than what has been used in recent designations and marketing authorisations, however the difference is due to adjusted figures in order to reflect only the GHD patients reported in the studies as well as a correction with regards to the general population in the area the study was made. This results in somewhat lower figures. It cannot be ascertained that the adjustments the sponsor has done are entirely correct, but they seem plausible and therefore the adjustment could be warranted and therefore the COMP accepted the proposed prevalence of 4.6 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

The standard treatment for patients with GHD (children and adults) in the EU is daily, s.c. injection with recombinant hGH (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 somatropin Sogroya (somapacitan) which is approved for "replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD)".

Lonapegsomatropin Ascendis Pharma recently received a positive CHMP opinion for the treatment of 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]). However, this product has not yet received the EC decision and is therefore not considered authorised.

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

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

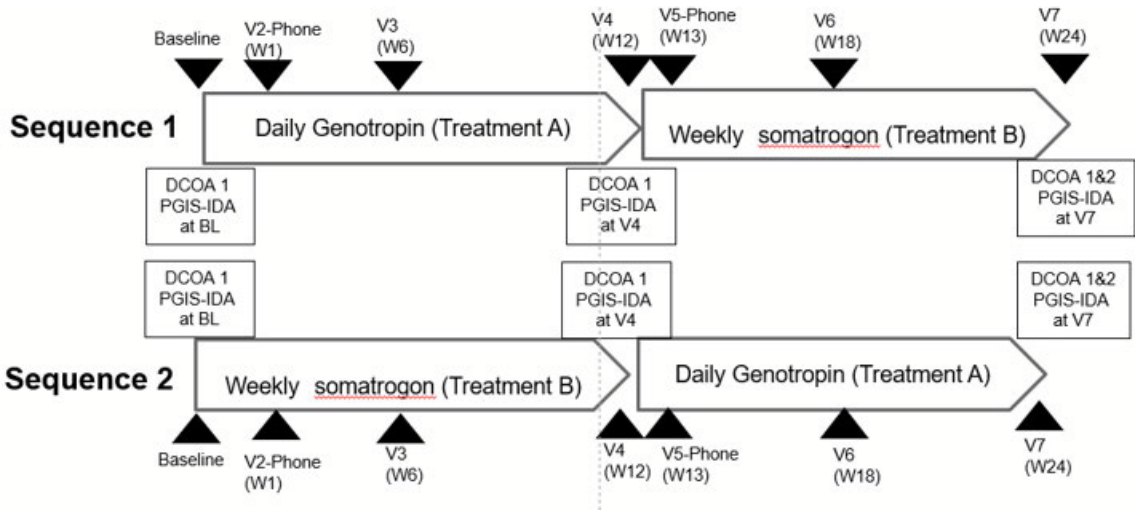
The original sponsor of the orphan designation asked for scientific advice in 2016 in relation to the clinical development as well as the study designed to evaluate the patient preferences. The sponsor seems to have implemented the advice in the study design.

As somatrogon is non-inferior to Genotropin in the treatment of paediatric GHD patients who have or have not received prior growth hormone treatment, the sponsor bases the justification of significant benefit on a major contribution to patient care.

Following receipt of the above advice, a new clinical outcome assessment tool called the Dyad Clinical Outcome Assessment (DCOA) was developed by Pfizer (also referred to as the Life Interference Questionnaire for Growth Hormone Deficiency [LIQ-GHD] (Turner-Bowker et al, 2020). Briefly, the DCOA contains several modules, intended to be completed by the patient, the caregiver, or the patient and caregiver together (as a "dyad"). The content is organized into 2 main sections, referred as DCOA 1 and DCOA 2.

C0311002 was a randomized, open-label, multi-center, 2-period crossover study in children 3 to <18 years of age with GHD. Subjects had been on stable treatment with an rhGH injection administered once daily (ie, either Genotropin® Pen® or Genotropin® GoQuick Pen,® HumatroPen®, or Omnitrope® Pen) for at least 3 months prior to enrollment. Subjects were randomized in a 1:1 ratio to one of 2 sequences, either 12 weeks of treatment with daily Genotropin followed by 12 weeks of treatment with once weekly Somatrogon (Sequence 1), or 12 weeks of treatment with once weekly somatrogon followed by 12 weeks of treatment with daily Genotropin (Sequence 2), for a total treatment duration of 24 weeks.

Figure 1. C0311002 Study Design



The primary endpoint in Study C0311002, treatment burden, was assessed as the difference in mean Overall Life Interference total scores between the weekly injection schedule and daily injection schedule as assessed by the Patient Life Interference Questionnaire. Of the 87 participants that were randomized, 43 were randomized to the Genotropin then somatrogon sequence and 44 were randomized to the somatrogon then Genotropin sequence.

The study met its primary endpoint and the treatment burden as assessed by the Overall Life Interference total score was lower for the once weekly somatrogon injection schedule than for the once daily Genotropin injection schedule. See table 5 from sponsors application.

Table 5. Primary Endpoint (Treatment Burden): Overall Life Interference Total Scores, Treatment Comparison - Primary Analysis : All Subject Questionnaires - Full Analysis Set (Protocol C0311002)

	During Genotropin Treatment (N=86)	During Somatrogon Treatment (N=87)
Overall (drug received during any period)		
N[a]	85	82
Mean (SD)	24.1 (20.0)	8.4 (11.0)
Median (Min, Max)	21.4 (0.0, 82.1)	3.6 (0.0, 50.0)
Model-based mean (95% CI)[b]	24.13 (20.61, 27.65)	8.63 (5.05, 12.22)
Somatrogon vs Genotropin		
Difference in overall scores (95% CI)[b]	-15.49 (-19.71, -11.27)	

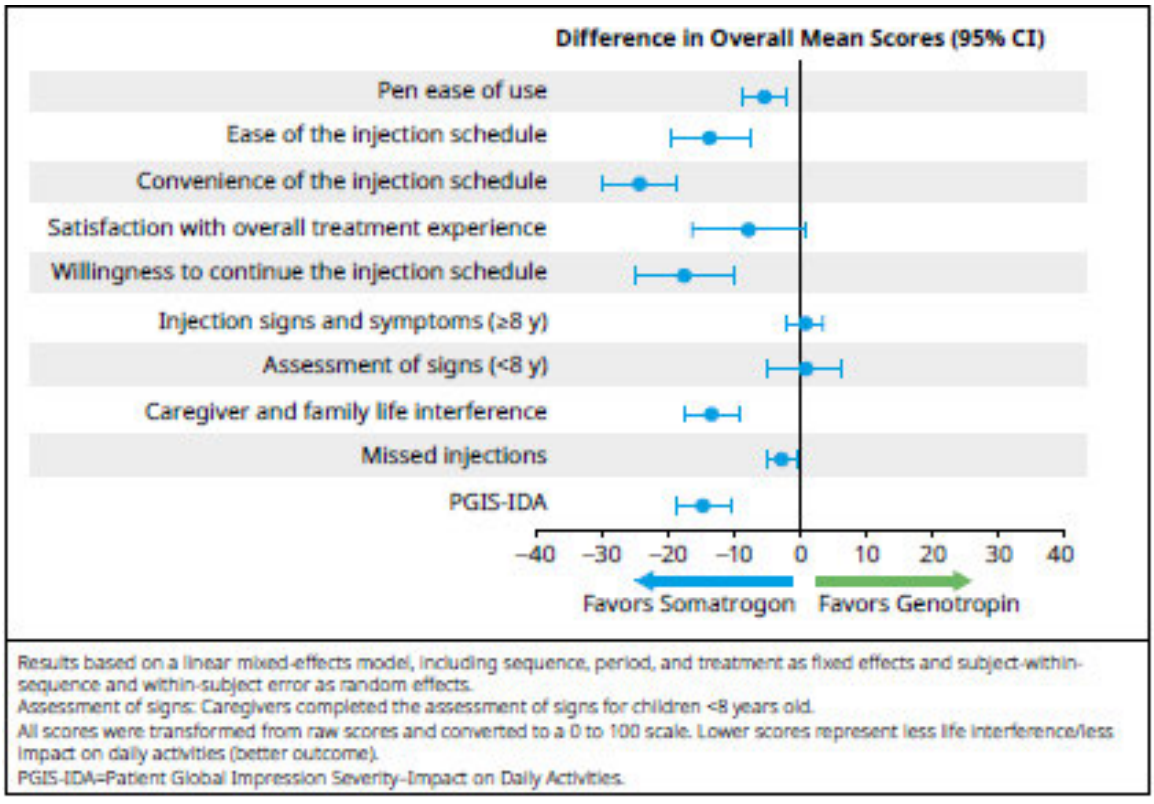
Table 5. Primary Endpoint (Treatment Burden): Overall Life Interference Total Scores, Treatment Comparison - Primary Analysis : All Subject Questionnaires - Full Analysis Set (Protocol C0311002)

	During Genotropin Treatment (N=86)	During Somatrogon Treatment (N=87)
p-value[b]	<0.0001	

a. Number of participants with non-missing values.
b. Results based on a linear mixed effects model including sequence, period, and treatment as fixed effects and subject within sequence and within-subject error as random effects.
All scores were transformed from raw scores and converted to a 0 to 100 scale. Lower scores represent less life interference (better outcome).
The analysis does not include data for Participant 10061006 because proper informed consent was not obtained.
PFIZER CONFIDENTIAL SDTM Creation: 28SEP2020 (02:18) Source Data: Table 16.2.6.1.1 Output File: ./C0311002/C0311002 CSR/t14 2 1 1 1 Date of Generation: 09OCT2020 (16:05)
Table 14.2.1.1.1 Somatrogon is for Pfizer internal use.

The secondary endpoints also favoured the weekly administration as opposed to the daily, as detailed in Fig 2 from the sponsors application.

Figure 2. Patient and Caregiver Assessments of Treatment Experience (DCOA 1 and PGIS-IDA)



Source: Maniatis et al. 2021, Figure 2.

The majority of participant/caregiver dyads preferred the once weekly somatrogon injection schedule compared with those who preferred the once daily Genotropin injection schedule or expressed no

difference/no preference between injection schedules for most variables within the DCOA 2 questionnaire.

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

4. COMP position adopted on 21 December 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 4.6 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 Ngenla may be of potential significant benefit to those affected by the orphan condition still holds. The sponsor provided data from clinical trials demonstrating that somatrogon (once weekly growth hormone) and somatropin (once daily growth hormone) are of comparable efficacy. In addition, treatment satisfaction data from a specifically designed study demonstrated that the treatment burden for patients and carers was reduced for somatrogon 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 Ngenla, recombinant modified human growth hormone, somatrogon for treatment of growth hormone deficiency (EU/3/12/1087) is not removed from the Community Register of Orphan Medicinal Products.