31 March 2021
EMA/OD/0000033719
EMADOC-360526170-701918
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Sogroya (somapacitan)
Treatment of growth hormone deficiency
EU/3/18/2068

Sponsor: Novo Nordisk A/S

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Product and administrative information

Product	
Designated active substance(s)	Somapacitan
Other name(s)	-
International Non-Proprietary Name	Somapacitan
Tradename	Sogroya
Orphan condition	Treatment of growth hormone deficiency
Sponsor's details:	Novo Nordisk A/S Novo Alle 1 2880 Bagsvaerd Hovedstaden Denmark
Orphan medicinal product designation procedural history	
Sponsor/applicant	Novo Nordisk A/S
COMP opinion date	27 July 2018
EC decision date	28 August 2018
EC registration number	EU/3/18/2068
Marketing authorisation procedural history	
Rapporteur / Co-rapporteur	J. L. Hillege / J. M. Race
Applicant	Novo Nordisk A/S
Application submission date	11 September 2019
Procedure start date	3 October 2019
Procedure number	EMEA/H/C/005030/0000
Invented name	Sogroya
Proposed therapeutic indication	Sogroya is indicated for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD). Further information on Sogroya can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/medicines/human/EPAR/Sogroya
CHMP opinion date	28 January 2021
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	E. J. Rook / Z. Gyula
Sponsor's report submission	21 April 2020
COMP discussion and adoption of list of questions	3-5 November 2020
Oral explanation	17 February 2021
COMP opinion	18 February 2021

2. Grounds for the COMP opinion

Orphan medicinal product designation

The COMP opinion that was the basis for the initial orphan medicinal product in 2018 designation was based on the following grounds:

The sponsor Novo Nordisk A/S submitted on 21 March 2018 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing somapacitan 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 somapacitan was considered justified based on preliminary clinical data showing IGF-I response upon treatment;
- the condition is life-threatening and chronically debilitating due to the psychosocial impact, the cardiovascular risk, and risk of decreased bone mass and fractures;
- the condition was estimated to be affecting approximately 4.7 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 somapacitan will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting that treatment with the proposed long-acting growth hormone product was more convenient for patients compared to patients receiving currently authorised growth hormone products. The Committee considered that the reported patient centred outcomes could potentially translate into a major contribution to patient care.

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 somapacitan, as an orphan medicinal product for the orphan indication: 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 approved therapeutic indication "replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD)" falls within the scope of the designated orphan condition "Treatment of growth hormone deficiency".

The designated condition included both, paediatric and adult forms of growth hormone deficiencies (GHD).

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).

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

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. No new treatments were authorised for the condition since the orphan designation stage.

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 overall prevalence of GHD (children and adults combined) used as basis for obtaining the orphan drug designation has been recalculated to reflect the sponsor's prevalence estimation as of March 2020 and is estimated to be 4.9 per 10,000 persons. The recalculated estimate has not significantly changed since the time of orphan designation.

Epidemiological studies of GHD in children included by the sponsor were: Audi et al 2002, Thomas et al 2004, Migliaretti et al 2006, Stochholm et al 2006, Schweizer et al 2010. The GHD prevalence

estimates in the identified studies vary from 1.75 to 9.44 per 10.000 children (in only one study the prevalence estimate was above the criteria for orphan drug designation; Migliaretti et al 2006). Epidemiological studies of AGHD included by the sponsor were: Regal et al 2001 and Stochholm et al 2006. Two sensitivity calculations considering a potentially longer disease duration were done. The overall prevalence of AGHD based on the sensitivity analysis applying a disease duration of 17.4 and 25 years corresponds to 3.1 and 5.1 in 10,000 persons, respectively. The overall weighted prevalence estimates of GHD in children and adults based on the most conservative scenario (sensitivity analysis) are assessed to be 4.1 and 5.1 in 10,000 persons, respectively.

To provide a consolidated estimate of the prevalence of GHD in the EU population, the most recent numbers (2019) describing the demographics in the EU were taken from the EuroStat database (http://ec.europa.eu/eurostat/data/database. This corresponds to an overall GHD prevalence of approximately 4.9 in 10,000 persons.

Although the proposed prevalence of 4.9 is close to the threshold of 5 in 10,000, the estimate is considered valid and on the conservative side. The COMP accepted the prevalence to be less than 4.9.

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. No long-acting GH product with have been approved in the EU since the designation of the orphan medicinal product.

Significant benefit

The sponsor compared somapacitan primarily to daily GH (Norditropin) as evaluated in the clinical development trials. No protocol assistance has been sought.

Since the proposed therapeutic indication of this initial marketing authorisation relates to adult GHD only, and no paediatric data were part of the dossier for the marketing authorisation application, paediatric patient studies were not considered in the evaluation of significant benefit.

GH replacement therapy with daily injections has been available for decades and is shown to be a safe and effective treatment for growth restoring and improving body composition in children and adults with GHD, respectively. However, daily injections can be inconvenient, painful and distressing for some patients. The aim of developing a long-acting formulation of GH was to lessen the treatment burden of daily injections and to promote adherence.

The main study (n= 300) was a randomised placebo-controlled trial, primarily designed to compare in a 34-week double-blind setting the efficacy and safety of once-weekly dosing of somapacitan with once-weekly dosing of placebo in AGHD patients who were growth hormone treatment-naïve prior to randomization. In a third study arm, the clinical effects of open-label daily treatment with somatropin product Norditropin (daily doses) were evaluated. After completion of this main treatment phase, study

patients could enrol into a 53-week open-label extension period in which they were re-randomized to receive somapacitan or somatropin.
In addition, two open-label supportive studies were conducted in AGHD patients who have been treated previously with growth hormone (studies 4244 (n= 62) and 4043 (n= 92)). Participants were randomized to receive weekly somapacitan or daily somatropin.

In the main Study 4054, superiority of once weekly somapacitan vs placebo for the primary endpoint truncal fat % after 34 weeks of replacement therapy in AGHD patients was confirmed.
This primary endpoint was supported by secondary outcomes for somapacitan such as a decrease in visceral fat, an increase in lean body mass as well as appendicular skeletal muscle mass. However, the primary endpoint changes from baseline in truncal fat % and some other fat distribution endpoints was lower than with Norditropin (daily injections of growth hormone somatropin), the active control arm. Nevertheless, the totality of the observed effects of somapacitan compared to placebo is considered clinically relevant. Post-hoc simulations indicate that the titration schedule in the pivotal trial of somapacitan had been suboptimal for some patients and that an extended titration schedule may lead to more optimal results for these patients, and in a post-authorisation safety study, the extended titration schedule will be further explored.

The reduction in visceral fat and the increases in total lean body mass and appendicular skeletal muscle mass with somapacitan were maintained during the 86 weeks of treatment.

Adherence rates on treatment with once weekly somapacitan and daily Norditropin were numerically better after treatment with somapacitan than Norditropin in patients with AGHD (Figure 1) in all three studies.

Figure 1. Adherence to Somapacitan and Norditropin in the main and supportive studies.

	Somapacitan	Norditropin
Trial 4054, main part (n=300)	**95.5%**	**90.6%**
Trial 4244 (n=62)	**98.7%**	**92.2%**
Trial 4043 (n=92)	**93.1%**	**90.4%**

In clinical practice, adherence to once-weekly somapacitan is assumed to be higher than the adherence to once-daily GH replacement. In support of this notion, once-weekly dosing was associated with better adherence levels and greater odds of being adherent compared with daily dosing in patients with osteoporosis (Iglay *et al.*, 2015). Similarly, in patients with diabetes, convenience of once-weekly vs once-daily treatment administration was associated with better adherence in real-world studies involving GLP-1 (Giorgino *et al,* 2018). According to published literature (Rosenfeld RG and Bakker B, Endocr Pract. 2008;14(2):143-154) in real world around 35% of patients with AGHD are non-compliant and another 30% are occasionally non-compliant. In adults with GHD, 4 months of discontinuation of GH replacement therapy resulted in increased abdominal fat accumulation and a deterioration in lipid status and systemic inflammation (Filipsson et al, 2012).

The COMP found extrapolation from the literature regarding adherence in other conditions questionable but acknowledged that an improvement in adherence would be clinically relevant in this setting.

The COMP scrutinised also the impact of missing a dose in case of once weekly vs. once daily growth hormone. The sponsor provided a simulation of pharmacokinetics of somapacitan vs. daily growth hormone, to support the notion that missing a dose of somapacitan is not more detrimental than missing several doses of the daily growth hormone. In addition, compensation of a forgotten dose was foreseen in the product information, allowing for taking the missed dose up to 3 days post scheduled date. The impact of occasional non-compliance was therefore seen as comparable between both medicines.

The Treatment Satisfaction Questionnaire for Medication (TSQM-9) was applied across all clinical randomised trials in AGHD (4054, 4244 and 4043) to evaluate aspects of treatment satisfaction (convenience, effectiveness and global satisfaction domains). Treatment satisfaction refers to the individual patient's appraisal of his or her experience with treatment and is thus a subjective benefit-risk trade off with therapy which the sponsor considered a partial proxy for adherence to therapy in clinical practice.

Table 1. TSQM-9 domain scores at week 34 - Trial 4054

	Estimated score at week 34			ETD [95% CI] at week 34	ETD [95% CI] at week 34
	Soma	PBO	Nordi	Soma – PBO	Soma - Nordi
Effectiveness	57.13	50.52	67.86	6.60 [-0.47; 13.67]	-10.74 [-16.49; -4.98]
Convenience	77.84	74.98	73.84	2.86 [-2.54; 8.27]	4.00 [-0.40; 8.39]
Global satisfaction	63.77	55.32	69.22	8.45 [0.66; 16.24]	-5.45 [-11.80; 0.89]

Notes: Since patients were GHD-treatment naïve TSQM-9 data could not be collected at baseline. ETDs are based on week 34 scores and MMRM. Scale is 0 – 100 with higher values representing better outcomes. **Abbreviations:** ETD = estimated treatment difference; PBO = placebo; MMRM = mixed model for repeated measures; Nordi = Norditropin; Soma = somapacitan.

Table 2. TSQM-9 domain scores – Trials 4043 and 4244

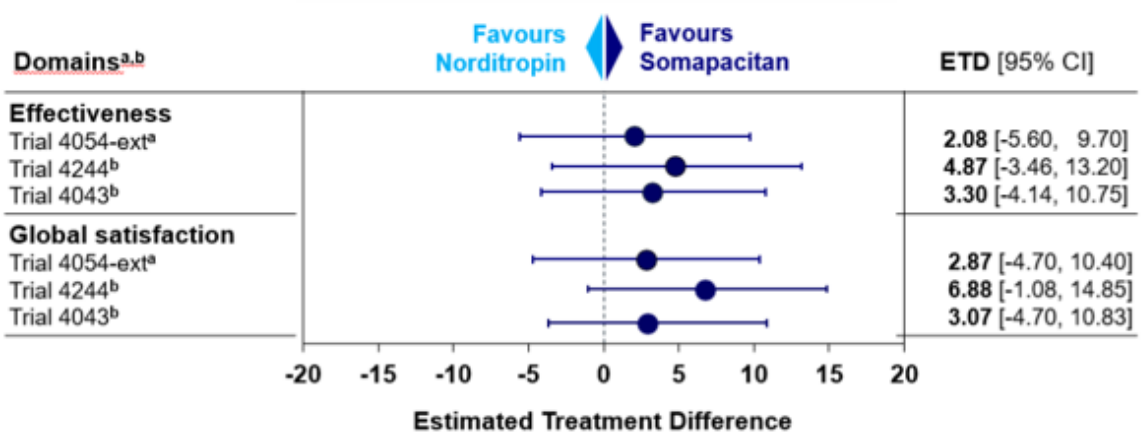
	Trial 4043			Trial 4244		
	Estimated change from baseline to week 26		ETD [95% CI] at week 26	Estimated change from baseline to week 52		ETD [95% CI] at week 52
	Soma	Nordi	Soma - Nordi	Soma	Nordi	Soma - Nordi
Effectiveness	9.7	3.8	3.30 [-4.14; 10.75]	7.99	3.12	4.87 [-3.46;13.20]
Convenience	15.3	3.0	8.22 [1.51; 14.93]	14.01	7.22	6.79 [-1.04;14.61]
Global satisfaction	5.4	-1.2	3.07 [-4.70; 10.83]	10.07	3.18	6.88 [-1.08;14.85]

Notes: ETDs are based change from baseline to week 26 (trial 4043), to week 52 (trial 4244) and MMRM. Scale is 0 – 100 with higher values representing better outcomes. **Abbreviations:** ETD = estimated treatment difference; MMRM = mixed model for repeated measures; Nordi = Norditropin; Soma = somapacitan; TSQM-9 = Treatment Satisfaction Questionnaire for Medication – 9.

The sponsor argued that the differences in global satisfaction in the main study may have been biased due to the fact that the somatropin (Norditropin) study arm was open-label, and patients were thus aware that they got an effective treatment. In contrast, the assignment to somapacitan was blinded. The post-hoc analyses of patients switching from Norditropin to somapacitan, in the open-label

extension phase of the study, showed that the effectiveness and global satisfaction scores were more similar after switching. Notably, across all studies, the convenience score was in favour of somapacitan.

Figure 2. TSQM-9 global satisfaction and effectiveness domains in the phase 3 trials in AGHD



Scale range is 0-100, higher score is better.

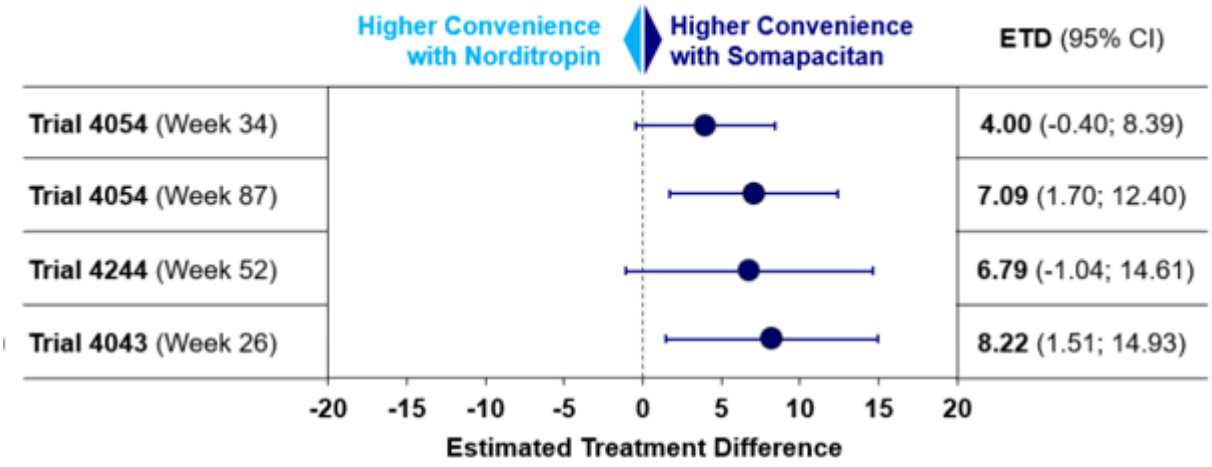
[a]Trial 4054: *post hoc* analysis. Data represents change from week 34 (end of main) to week 87 (end of extension) (Norditropin®/somapacitan – Norditropin®/Norditropin®)

[b]Trials 4244 and 4043: Data represents change from baseline (somapacitan – Norditropin®).

Trial 4054: n=103 (combined in the two relevant treatment groups); Trial 4244: n=62, Trial 4043; n=92

Abbreviations: ETD = estimated treatment difference; CI = confidence interval

Figure 3. TSQM-9 convenience scores in phase 3 trials in AGHD



Note that since the TSQM-9 assesses perception of treatment, patients need to be on treatment for some time before the questionnaire can be applied. Therefore, the depicted values from trial 4054 (treatment-naïve patients) are based solely on the week 34 and week 87 assessments (and not change from baseline). For trial 4054 (week 87), the treatment groups used in the analysis are patients on somapacitan or Norditropin® throughout the trial. For trials 4244 and 4043 (previously treated patients), scores are change from baseline.

Trial 4054 (main): n=300; Trial 4244: n=62, Trial 4043; n=92

Abbreviations: ETD = estimated treatment difference; n = number of patients in the trial

Both, the sponsor and the COMP, involved patient experts whose testimonies helped clarify the importance of the convenience for improving the adherence to treatment. The need to refrigerate most

daily growth hormone products was mentioned as impacting the ability to travel or decisions on skipping medication. The sponsor also further discussed the small difference (albeit consistent across 3 clinical trials) in adherence, in favour of somapacitan.

The true real-world compliance with somapacitan is impossible to assess at this point. Therefore, the data on treatment convenience and adherence were considered with caution. However, taking into consideration the totality of evidence presented by the sponsor and the testimonies of both patient experts, the COMP considered that the assumption of significant benefit of somapacitan on basis of major contribution to patient care still holds.

4. COMP position adopted on 18 February 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 in to be less than 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 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. Adult growth hormone deficiency is associated with abdominal obesity, decreased lean body mass, reduced muscle strength and exercise capacity. Patients also experience severe psychosocial problems linked to the very short stature;
- although satisfactory methods for the treatment of the condition have been authorised in the European Union, the assumption that Sogroya 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 Sogroya (once weekly growth hormone) and Norditropin (once daily growth hormone) are of comparable effectiveness. However, convenience scores were improved for Sogroya as compared to the Norditropin control. In addition, treatment adherence was marginally better in the Sogroya treatment arm, which is expected to be more pronounced in the real-life setting. The totality of evidence presented was accepted as supporting the argument of the 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 Sogroya, somapacitan for treatment of growth hormone deficiency (EU/3/18/2068) is not removed from the Community Register of Orphan Medicinal Products.

APPENDIX 1

Divergent position expressed by some members of the COMP

Although it is acknowledged that the once weekly dosing schedule of somapacitan may be perceived as more convenient for some adult GHD patients compared to the regular growth hormone preparations that have to be administered daily, this is overall not considered sufficient as an argumentation for significant benefit. The assumption of better compliance is challenged, because patients did not perceive a benefit regarding effectiveness and global treatment satisfaction as compared to daily growth hormone. In addition, there is no data confirming better compliance or better efficacy in real world daily practice. There are concerns that lack of adherence to the posology might have more detrimental effect clinically for a weekly dose, versus a daily dose.

COMP members expressing divergent position:

Elisabeth Penninga (Denmark)

Elisabeth Rook (Netherlands)

Michel Hoffmann (Luxembourg)