25 May 2023
EMA/268297/2023
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report on extension of marketing authorisation and an extension of indication variation

Sogroya

International non-proprietary name: somapacitan

Procedure No. EMEA/H/C/005030/X/0006/G

Note

Assessment report as adopted by the CHMP 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

Administrative information

Name of the medicinal product:	Sogroya
MAH:	Novo Nordisk A/S Novo Alle 2880 Bagsvaerd DENMARK
Active substance:	Somapacitan
International Non-proprietary Name/Common Name:	somapacitan
Pharmaco-therapeutic group (ATC Code):	anterior pituitary lobe hormones and analogues, somatropin and somatropin agonists (H01AC07)
Therapeutic indication(s):	Sogroya is indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD).
Pharmaceutical form(s):	Solution for injection
Strength(s):	5 mg/1.5 ml, 10 mg/1.5 ml and 15 mg/1.5 ml
Route(s) of administration:	Subcutaneous use
Packaging:	cartridge (glass) in pre-filled pen
Package size(s):	1 pre-filled pen and 5 (5 x 1) pre-filled pens (multipack)

Table of contents

List of abbreviations

AE	adverse event
AGHD	adult growth hormone deficiency
AME	absorption, metabolism and excretion
ANCOVA	analysis of covariance
AUC0−xh	area under the concentration-time curve from time 0 (dosing) to x hours after dosing
BID	twice daily
BMI	body mass index
Cavg	average concentration
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CL	clearance
CLCR	creatinine clearance
C_{max}	maximum concentration
CV	coefficient of variation
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
EMA	European Medicines Agency
EOT	end-of-text
ETD	estimated treatment difference
FAS	full analysis set
FDA	US Food and Drug Administration
FHD	first human dose
eGFR	estimated glomerular filtration rate
GCP	Good Clinical Practise
GFR	glomerular filtration rate
GH	growth hormone
HDL	high density lipoprotein
hsCRP	high-sensitivity C-reactive protein
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IGF-1IGF-I	insulin-like growth factor I
IGFBP	insulin-like growth factor binding protein
IL-6	interleukin 6
LDL	low density lipoprotein
MAR	missing at random
MD	multiple dose
OD	once daily
PD	pharmacodynamics
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	patient reported outcomes
PYE	patient years of exposure
QTc	corrected QT interval
QTcF	Fridericia heart rate corrected QT interval
R_{acc}	accumulation ratio
s.c.	subcutaneous
SD	single dose or standard deviation (in a statistical context)
SF-36	36-Item Short Form Survey
$t_{½}$	terminal half-life
TID	three times daily
TRIM-AGHD	Treatment Related Impact Measure - Adult Growth Hormone Deficiency
t_{max}	time to maximum observed concentration
TSQM-9	Treatment Satisfaction Questionnaire for Medication
V/F	volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

Novo Nordisk A/S submitted on 23 June 2022 a group of variation(s) consisting of an extension of the marketing authorisation and the following variation(s):

Variation(s) requested		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	II

The MAH applied for an extension application to add a new strength of 15 mg/1.5 mL solution for injection in pre-filled pen grouped with a type II variation C.I.6 to add a new indication 'Replacement of endogenous growth hormone (GH) in children and adolescents with growth failure due to growth hormone deficiency (GHD)', based on results from the completed main 52-week period of the confirmatory phase 3 trial (4263), supported with long-term data from the phase 2 trial (4172), up to week 208 completed. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the SmPC have been updated and the Package Leaflet has been updated accordingly. A revised RMP version 3.0 was provided as part of the application.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

Sogroya was designated as an orphan medicinal product EU/3/18/2068 on 06 April 2021 in the following condition: treatment of growth hormone deficiency.

The new indication, which is the subject of this application, falls within the above-mentioned orphan designation.

1.3. Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included the EMA Decision(s) P/0068/2017 and P/0178/2018 on the granting of a (product-specific) waiver.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.5. Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

CHMP Peer reviewer(s): N/A

The Rapporteur appointed by the PRAC was:

PRAC Rapporteur: Martin Huber

The application was received by the EMA on	23 June 2022
The procedure started on	14 July 2022
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	3 October 2022
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	11 October 2022
The CHMP Co-Rapporteur's Critique was circulated to all CHMP and PRAC members on	17 October 2022
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	27 October 2022
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	10 November 2022
The MAH submitted the responses to the CHMP consolidated List of Questions on	13 February 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	3 March 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	16 March 2023
The CHMP Rapporteur's updated Assessment Report was circulated to all CHMP and PRAC members on	23 March 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the MAH on	30 March 2023
The MAH submitted the responses to the CHMP List of Outstanding Issues on	24 April 2023

The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	12 May 2023
The CHMP Rapporteurs circulated the updated Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	17 May 2023
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Sogroya on	25 May 2023
The CHMP adopted a report on similarity of Sogroya with name of the authorised orphan medicinal product(s) on (see Appendix on similarity)	25 May 2023

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Sogroya is indicated for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD).

In the current variation procedure, it is proposed to extend the indication to endogenous growth hormone (GH) in children and adolescents with growth failure due to growth hormone deficiency (GHD).

The initially proposed indication in this variation procedure is (added text: underlined):

Replacement of endogenous GH *in children and adolescents with growth failure due to growth hormone deficiency (paediatric GHD)* and in adults with growth hormone deficiency (adult GHD).

Growth hormone deficiency (GHD) is characterised by too low systemic levels of growth hormone. Growth hormone (GH) is produced by the somatotroph cells of the anterior pituitary gland. The secretion of growth hormone from the pituitary gland is stimulated by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin, both of which are produced by the hypothalamus. Growth hormone deficiency (GHD) is often associated with defects arising in the pituitary gland or the hypothalamus.

The typical symptom of GHD in children is growth failure. Growth failure is suspected if the growth of paediatric subjects develops at a slower rate than would be expected based on the growth chart of the local geographic area. In this case, further diagnostic evaluations can be considered to find the cause of growth failure.[1]

2.1.2. Epidemiology

The incidence of short stature associated with GHD has been estimated to be approximately 1:4000 to 1:10,000[2,3] . GHD may be isolated or may be associated with deficiencies of other pituitary hormones.

Growth hormone deficiency is the primary indication for growth hormone treatment in childhood, which presently requires daily subcutaneous injections for the patient except for the recently registered Skytrofa and Ngenla, which are also administered once weekly.

2.1.3. Aetiology and pathogenesis

There are different causes of growth hormone deficiency, which can be categorized in different categories, namely:

- Congenital (organic causes such as pituitary aplasia, primary empty sella syndrome etc. or genetic causes including various mutations)
- Acquired (tumours of the hypothalamic-pituitary region, most commonly craniopharyngioma, head trauma, infection etc.)
- Idiopathic (no clear aetiology)

The aetiology of childhood GHD is usually hypothalamic in origin with impaired GHRH secretion, with the most common diagnosis being isolated idiopathic GHD (Cook 2009).

[1] Collett-Solberg et al. Diagnostics, genetics and therapy of short stature in children: a growth hormone research society international perspective. Horm Res Paediatr 2019; 92:1-14.
[2] Rona RJ, Tanner JM. Aetiology of idiopathic growth hormone deficiency in England and Wales. Arch Dis Child. 1977 Mar;52(3):197-208.
[3] Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. Arch Dis Child. 2016 Jan; 101(1):96-100. Epub 2015 Jul 7.

2.1.4. Clinical presentation and diagnosis

In neonates, clinical presentations of congenital pituitary GHD include profound hypoglycemia, hypoglycemic seizures, prolonged jaundice, and microphallus and cryptorchidism in boys. The patients diagnosed at younger ages generally have more severe GHD, are more likely to suffer from multiple pituitary hormone deficiencies and tend to have more complications at birth. A substantial reduction in growth rate may become apparent within the first few months of life (Huet 1999, Ogilvy-Stuart 2003, Ranke 2003). This is sometimes associated with a delay in fontanelle closure.

Although the most obvious feature of GHD may be short stature, the disease has broad health implications. Children with GHD may have a small midface, hands, and feet, excess subcutaneous truncal fat, reduced muscle mass, thin hair and nails, a high-pitched voice, delayed skeletal and dental maturation, and delayed puberty (Albanese 1994, Levy 1996). In addition, GHD can influence cognitive functions and the overall sense of well-being. When accompanied by other pituitary deficiencies, further clinical manifestations may be present.

2.1.5. Management

The typical symptom of GHD in children is growth failure, and consequently, the aim of treatment is to normalize the growth rate during childhood and attainment of normal adult height.

With current treatment algorithms, paediatric recombinant human growth hormone doses are based on the body weight of the growing child. IGF-I plasma concentrations should be maintained in the normal age and sex-adjusted range for safety reasons. Periodic checks of IGF-I levels are required because they may change over time, even if the growth hormone dosage does not change.

While daily human growth hormone is safe and effective, its frequency of administration can be burdensome for both children and their caregivers. Although children with GHD treated with daily growth hormone replacement can achieve normal adult height, real-world outcomes have not matched expectations. Due to nonadherence rates ranging from 5 to 82% (Fisher 2013), most GHD patients do not reach their target genetic height (Guyda 1999, Lustig 2004), leaving an opportunity to improve treatment outcomes in paediatric GHD.

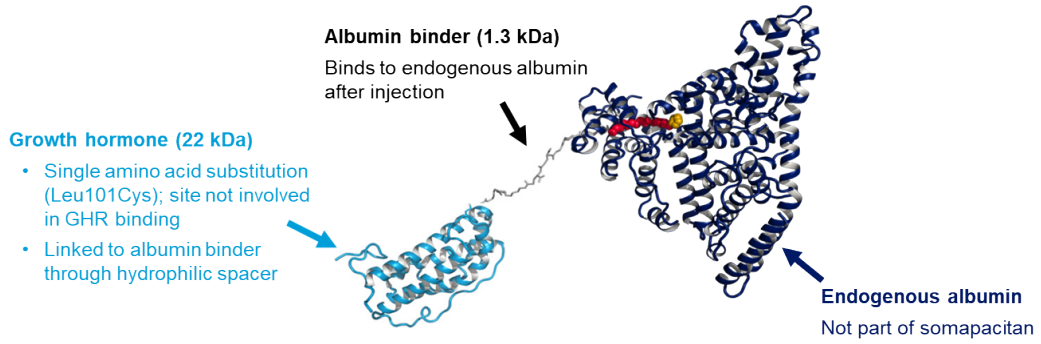
While there are multiple therapeutic goals of human growth hormone therapy in treating GHD, including achievement of normal growth patterns, lean/fat body composition, bone mass, glucose homeostasis, cognition and improved quality of life, the most readily measured indicator of efficacy is growth. Therefore, a therapy that results in improved growth outcomes at the end of 52 weeks of treatment is expected to result in better clinical effects with long-term therapy.

For paediatric GHD patients, medicinal products for daily (e.g. Omnitrope (EU/1/06/332), Nutropin Aq (EU/1/00/164)) or weekly (e.g. Ngenla (EU/1/21/1617), Skytrofa (EU/1/21/1607)) growth hormone supplementation are available.

2.2. About the product

Somapacitan is a long-acting recombinant human growth hormone derivative with a single substitution in the peptide backbone (leucine [L] at position 101 substituted with cysteine [C]) to which an albumin binding moiety has been attached. The albumin binding moiety (side-chain) consists of a C16 fatty acid moiety and a hydrophilic spacer attached to position 101 of the protein by chemical conjugation. The non-covalent, reversible binding to endogenous albumin delays the elimination of somapacitan and prolongs the in vivo half-life (t½ and duration of action). Similar techniques have previously been used

to prolong the half-life of insulin and GLP-1 molecules, such as Levemir, Victoza and Ozempic.



Somapacitan bound to albumin

The pharmacological effects of somapacitan are like those of human growth hormone. These include stimulation of somatic growth, especially skeletal and muscle growth and maintenance. In addition, human growth hormone has many other effects on the body including increasing lipolysis, protein synthesis, muscle mass, and gluconeogenesis in the liver, and reducing glucose uptake in the liver. As for human GH, the mechanism of action of somapacitan is either direct via the growth hormone receptor or indirect via stimulation of IGF-I expression and release.

2.3. Type of Application and aspects on development

On 31 March 2021, Sogroya was approved by the European Commission for the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD).

On 25 April 2022, the European Commission has approved an extension application to add a new strength of 5 mg/1.5 mL (3.3 mg/mL), for which a bioequivalence study was submitted.

The current application for Sogroya is an extension of the Marketing Authorisation to add a new strength of 15 mg/1.5 mL solution for injection in pre-filled pen, grouped with a type II variation for adding a therapeutic indication in paediatric patients, starting from 3 years of age.

2.4. Quality aspects

2.4.1. Introduction

Sogroya is a long-acting recombinant human growth hormone (hGH) derivative based on the active substance Somapacitan. It is intended for once-weekly subcutaneous injection by patients, caregivers and/or healthcare professionals.

The finished product is presented as a solution for injection containing somapacitan as active substance. Other ingredients are: histidine, mannitol, poloxamer 188, phenol, water for injections, hydrochloric acid (for pH adjustment) and sodium hydroxide (for pH adjustment).

The product is available in 1.5 mL glass cartridge (Type I colourless glass) with a plunger made of chlorobutyl rubber and a stopper made of bromobutyl/isoprene rubber sealed with an aluminium cap. The cartridge is contained in a multidose disposable pen made of polypropylene, polyacetal,

polycarbonate and acrylonitrile butadiene styrene and in addition two metal springs. The cartridge is permanently sealed in a pen-injector. The finished product is available in pack sizes of 1 pre-filled pen and multipack of 5 (5 packs of 1) pre-filled pens.

The product is currently approved in 5 mg/1.5 mL (3.3 mg/mL) and 10 mg/1.5 mL (6.7 mg/mL) strengths with an in-use time of up to 6 weeks. This application is an extension of the marketing authorisation for Sogroya with the scope of introducing a new strength 15 mg/1.5 mL (10 mg/mL) solution for injection, (packsizes of 1 and 5 prefilled pens), grouped with a variation to add a new indication for the treatment of GHD in children and adolescents.

2.4.2. Active Substance

Changes to the active substance manufacture and control are not proposed in this application. CTD section 3.2.S.4. Control of Drug Substance, has been updated to include the updated validation reports of analytical methods common to active substance and finished product for the 15 mg strength.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and Pharmaceutical Development

The MAH has updated this section to include the new 15 mg strength. The content of active ingredient is the only difference in composition (see Table 1) between the different strengths of the finished product. This is clearly stated in the updated document, and acceptable.

Table 1 Finished product composition

Component	**Function**	**Reference to standards**
Active substance		
Somapacitan	Active ingredient	Novo Nordisk A/S
Excipients		
Histidine	Buffering agent	Ph. Eur., USP, JP
Mannitol	Tonicity agent	Ph. Eur., USP, JP
Poloxamer 188	Stabiliser	Ph. Eur., USP, JPE
Phenol	Preservative	Ph. Eur., USP, JP
Hydrochloric acid	pH adjustment	Ph. Eur., USP, JP
Sodium hydroxide	pH adjustment	Ph. Eur., USP, JP
Water for injections	Solvent	Ph. Eur., USP, JP

All changes in the composition have been implemented prior to phase 3 clinical trials.

The formulation development work for the original MAA procedure of Sogroya was already performed with somapacitan finished product in a matrix covering finished product strengths from 5 mg to 15 mg

in a 1.5 ml cartridge. With regard to application of Sogroya for the paediatric population, the formulation is not changed and no direct safety issues are foreseen from the excipients used.

For the medical device (see figure 1-3 below) the description, comparison to other pens, test report for device performance requirements and shelf life data according to ISO are updated to encompass the 15 mg strength. The associated Notified Body report is provided and assessed under regional Information. No changes are proposed for the primary container closure system.

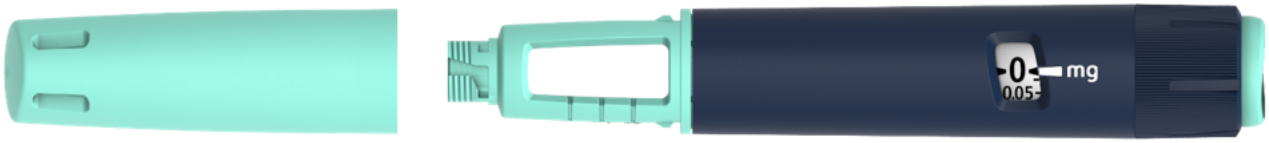


Figure 1 Somapacitan 5 mg in a 1.5 mL cartridge assembled in a PDS290 pen-injector

Figure 2 Somapacitan 10 mg in a 1.5 mL cartridge assembled in a PDS290 pen-injector

Figure 3 Somapacitan 15 mg in a 1.5 mL cartridge assembled in a PDS290 pen-injector

The pen-injectors are highly similar in all strengths, only differing in colour and dose delivered per dose step. The suitability of the 15 mg pen for the line extension is considered sufficiently justified. The suitability of the pens with regard to the new indication for the treatment of GHD in children was also sufficiently addressed.

The Summary of Human Factors validation has been updated to encompass the 15 mg strength and the inclusion of children in the evaluation of handling and differentiation.

2.4.3.2. Manufacture of the product and process controls

The existing description of the finished product manufacturing process is still adequate with the introduction of the 15 mg strength.

The assembly flowchart with IPCs for the pen-injector was resubmitted with editorial changes to adapt the text to the inclusion of the 15 mg strength.

While the process validation submitted with procedure EMEA/H/C/005030/X/0001/G (addition of the 5 mg strength) already included data on the 15 mg strength, the MAH has submitted a new document. The changes found are mainly editorial changes and some additional data on the 15 mg strength (Process time for bioburden and bacterial endotoxin). These new data do not give rise to concerns. Validation results of three 15mg full scale batches which were all used in clinical studies have been

submitted and results sufficiently support the commercial process for the new strength. The manufacturing process for the 15 mg strength is considered validated.

2.4.3.3. Product specification, analytical procedures, batch analysis

The finished product specification parameters and acceptance criteria are identical for the three strengths, except for the content that varies with finished product strength and related substances, for which the MAH has substantiated with data that the 15 mg strength has increased degradation over time and proposed a separate limit based on stability data at 5°C for up to 24 months.

Analytical procedures and reference standards

The suitability of the compendial procedures for Somapacitan 15 mg has been verified, and brief summaries of the validation of the non-pharmacopoeial analytical procedures have been provided. For non-pharmacopoeial analytical procedures used for somapacitan finished product only, brief summaries are provided. The information provided confirms suitability of the analytical methods for the new strength.

Reference standards are not changed through this application.

Batch analysis

An updated document on batch analyses is provided with mainly editorial changes. New data are added for “somapacitan 10 mg, batch no CLDP013, phase 2 specification”. These data do not give rise to concern. All data on the 15 mg strength, comprising a total of 8 commercial scale batches of which 3 produced at the current facility, were already submitted with procedure EMEA/H/C/005030/X/0001/G, but with Content reported ‘for information only’. In the current submission, the proposed acceptance criterium for content of the 15 mg strength is included. The data provided on the 15 mg strength confirm that the consistency of the product as shown for the 5 mg and 10 mg strength also applies to this new strength.

2.4.3.4. Stability of the product

The existing stability program as approved for the 5 mg and 10 mg strengths is extended to the 15 mg strength, which is acceptable. The stability commitment as provided for the 5 mg and 10 mg strength is updated to include three full scale (2x15 L and 1x 50L) batches of the 15 mg strength as well.

Sufficient representative batches of the 15 mg strength (four for primary stability studies, three for full scale manufacturing validation stability at FF, three for in-use stability, and one for photostability) have been included and the proposed shelf life is covered.

Data resulting from long term, accelerated, in use and photostability studies are submitted. For related substances, the results of 15 mg strength reveal slightly more increase in product related substances than those of the other strengths (of which the 5 mg is also slightly less degraded than the 10 mg strength. Thus, this parameter seems to increase with product strength). The other results are broadly equivalent between the strengths. The results for related substances for the 15 mg strength still remain within the shelf life acceptance criteria as approved for the already marketed strengths.

Based on the data, the shelf life of 24 months at 2-8 °C and in-use period of 6 weeks at 2-8 ºC including the possibility of storage at or below 30 ºC for a maximum of 72 hours (3 days) are justified and acceptable. It is also agreed that data from the photostability study show that all strengths of somapacitan finished product are photostable when stored in the pen-injector. Thus, the existing shelf life criteria can be maintained and extended to the new 15 mg strength.

2.4.3.5. Adventitious agents

There are no changes to previously submitted information in relation to adventitious agents.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Based on the data provided, the chemical, biological and pharmaceutical quality of Sogroya 15 mg strength is generally satisfactory and comparable to the approved 5 mg and 10 mg strengths. The formulation of the 15 mg strength is identical to the other strengths except for the concentration of the active substance somapacitan. The integrated medical device, i.e. the pen-injector used for administration is highly similar between all strengths, only differing in colour and dose delivered per dose step. Based on batch release and stability data, especially regarding product-related impurities, the three strengths can be considered comparable.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC.

2.5. Non-clinical aspects

No new non-clinical studies were conducted to support this line extension. Exposure multiples achieved in repeat dose toxicity studies remain sufficiently high to support the higher dose for this paediatric indication. Based on this, no new toxicological findings were noted that would be of clinical relevance.

2.5.1. Discussion on non-clinical aspects

The application is a line-extension grouped with an extension of indication and from a non-clinical point of view, the CHMP has considered that the pharmacology, safety pharmacology, pharmacokinetics and toxicological properties are considered known.

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, somapacitan is not expected to pose a risk to the environment.

2.5.2. Conclusion on the non-clinical aspects

Overall, the toxicology programme revealed no novel findings that would be of relevance for this application. All information has been adequately addressed in the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Table 2 Tabular overview of conducted clinical studies

Study ID	Study design	Study patients exposed	Dose regimens
NN8640-4042 (Phase 1)	Safety, tolerability, PK/PD of somapacitan Randomised, open-labelled, active-controlled, multinational, dose-escalation study Status: completed Trial duration: 28-35 days	32 non-naïve pre-pubertal children with GHD Country: Austria, Belgium, France, Israel, Macedonia, Slovenia, Spain and Sweden Female/Male: 9/23 Age: 6.0-11.0 years	Somapacitan single dose 0.02, 0.04, 0.08 and 0.16 mg/kg or somatropin 0.03 mg/kg/day for 7 days.
NN8640- 4172 (Phase 2)	Efficacy and safety Randomized, multinational, multi-centre, active-controlled (open-labelled), dose-finding (double-blinded), parallel group studya Status: ongoing Completed: 208 weeks Total study duration: 364 weeks (7 years) Status (cohort II and III): enrolment ongoing	Cohort Ib: 59 GH treatment naïve pre- pubertal children with GHD Age: 2.7-9.7 years Country: Globalc, including 12 children from Japan 2 children were not included in the FAS due to violation of inclusion/exclusion criteria Female/Male: 23/34d Cohort IIe: 1 child (age below 2.5	Week 0 to 52 (26-week main +26-week extension period) somapacitan 0.04, 0.08 or 0.16 mg/kg/week or somatropin 0.034 mg/kg/day (1:1:1:1) Week 52 to 156 (safety extension period) somapacitan 0.16 mg/kg/week or somatropin 0.034 mg/kg/day (3:1) Week 156 to 364 (long-term safety extension period) somapacitan 0.16 mg/kg/week (all children)

		years at enrolment) Cohort IIIe: 9 children (age 9-17 years (girls)/10-17 years (boys) at enrolment)	
NN8640- 4263 (Phase 3)	Efficacy and safety Randomized, multinational, multi-centre, open-labelled, active-controlled, parallel group study Status: ongoing Completed: 52 weeks Total trial duration: 208 weeks (4 years)	200 GH treatment naïve pre- pubertal children with GHD Country: GlobalF, including 30 children from Japan Female/Male: 51/149 Age: 2.5-11.0 years	Week 0 to 52 (main period) somapacitan 0.16 mg/kg/week or somatropin 0.034 mg/kg/day (2:1) Week 52 to 208 (extension period) somapacitan 0.16 mg/kg/week (all children)

Abbreviations: FAS: full analysis set, GHD: growth hormone deficiency; PD: pharmacodynamic; PK: pharmacokinetic.
[a] Study 4172 was open-labelled with respect to somapacitan vs. somatropin medicinal product Norditropin® and double-blinded with respect to somapacitan dose level (week 0 to 52).
[b] Only data for the original study population (cohort I) in study 4172 are included in modelling analyses.
[c] Study 4172, Global incl.: Austria, Brazil, Germany, India; Israel, Japan, Slovenia, Sweden, Turkey, Ukraine, and US.
[d] Numbers represent the FAS (57 subjects).

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

In paediatric patients with GHD, the recommended dose is 0.16 mg/kg once weekly in treatment-naïve patients and patients switching from other growth hormone products.

Three new clinical studies were conducted in paediatric patients with GHD to support the line-extension. One was a single dose escalation study in non-naïve paediatric patients with GHD aged 6 to 11 years versus active comparator Norditropin with full PK sampling. The second one was a multiple-dose finding, efficacy and safety study in naïve paediatric patients with GHD (aged ≥2.5 years to ≤9 years for girls and ≤10 years for boys) versus active comparator Norditropin with sparse PK sampling. A third one was a multiple-dose efficacy and study (≥2.5 years of age to <10 years for girls, <11 years for boys) study in naïve paediatric patients with GHD versus active comparator Norditropin with sparse PK sampling. PopPK modelling was used to determine the PK in paediatric patients following repeated dosing. No PK studies were conducted in paediatric patients aged <2.5 years old and between 12 and <18 years.

The initial PopPK model from MAA was extended with the paediatric PK and PD data. Pen strength was not a pre-specified covariate but was investigated as a covariate (15 mg/1.5 mL versus 5-10 mg/1.5 mL) in a *post-hoc* analysis based on the full model.

Absorption

During the initial marketing authorisation assessment, the Applicant showed that injection into thigh and abdomen had no effect om the PK of somapacitan. It is agreed that this is also most likely the case in paediatric patients. However, the Applicant also included the injection sites upper arm and buttocks. In the paediatric patient studies the injection site for each individual dosing occasion was not registered and therefore it cannot be investigated if injection into upper arm and buttocks leads to similar PK as injection into thigh and abdomen. However, it is not considered that this needs to be investigated further.

Distribution

The PopPK model (incorporating rate-limiting absorption) estimated a volume of distribution of 14.6 L in adults, which would be in line with the volume of distribution of albumin (13.6 L). The paediatric model predicted a V/F at steady state of 1.73 L.

Elimination

No differences in metabolism and excretion are expected between paediatric and adult patients.

In adults, there was no indication of increased risk of anti-somapacitan/anti-GH antibody development for somapacitan compared to somatropin. No comparison was provided for paediatrics. Fifteen to 22% of the paediatric patients tested positive for anti-drug antibodies, but none had neutralising anti-drug antibodies. The formation of anti-somapacitan antibodies in paediatric patients did not appear to affect PD, efficacy or adverse events reported.

Dose proportionality and time dependencies

In paediatric patients with GHD, a non-linear dose-exposure relationship with a greater than dose-proportional increase in exposure was observed. This was in accordance with the non-linearity observed in adult patients with GHD and healthy adults. Steady-state occurred after 1−2 doses following treatment initiation and low accumulation was seen (R_{acc} of 1.06). This was similar to that observed in adult patients with GHD.

Special populations

Overall, body weight, gender and race did not clinically affect somapacitan PK in children with GHD following weight-based dosing.

Pharmacokinetic interaction studies

No specific DDI studies were conducted at the time of the initial marketing authorisation. This is acceptable considering the similarity of somapacitan with growth hormone. The drug-drug interaction

potential is expected to be similar to other marketed growth hormone products and no additional DDI studies are warranted since no additional DDIs are expected in children.

2.6.2.2. Pharmacodynamics

Mechanism of action

The mechanism of action of somapacitan is either directly via the GH-receptor and/or indirectly via IGF-I produced in tissues throughout the body, but predominantly by the liver.

Primary and Secondary pharmacology

Pharmacodynamic endpoints

In the somapacitan development programme, circulating IGF-I was used as biomarker to assess the pharmacodynamic properties of somapacitan. Standard deviation score (SDS) data were derived for IGF-I. The SDS reflects the number of standard deviations below or above a reference population mean and allows for comparison of IGF-I data across the study population.

More than 90% of IGF-I is bound to insulin-like growth factor binding proteins (IGFBPs), primarily IGFBP-3.[4] Because of this, IGFBP-3 was used as a supportive biomarker to evaluate somapacitan pharmacodynamics.

IGF-I and IGFBP-3 were determined in central laboratories.

To be more specific, the pharmacodynamic properties of somapacitan were evaluated using pharmacodynamic parameters based on concentration–time profiles for IGF-I and IGFBP-3.

In addition, the IGF-I data collected in phase 2 and 3 studies in children with GHD (study 4172 and 4263) were used to estimate pharmacodynamic parameters based on modelling analyses (see population PK/PD modelling above). Finally, exposure-response analyses were conducted.

Pharmacodynamic evaluations

In the clinical pharmacology trial 4042, the pharmacodynamics (as measured by IGF-I and IGFBP-3) of somapacitan following single dose exposure was investigated in children with GHD. The single doses ranged from 0.02 to 0.16 mg/kg. The pharmacodynamic results for IGF-I are summarised in Table 3.

Table 3 Pharmacodynamics of somapacitan in children with GHD in study 4042

Study	N	Regimen	Dose (mg/kg)	IGF-I AUC0-168h (ng·h/mL) Geometric mean (CV)	Change from baseline (96 hours) IGF-I SDS Mean (SD)	IGF-I Cmax SDS Mean (SD)	IGF-I tmax (hours) Median (min; max)
4042	6	SD	0.16	34350 (13.5)	3.22 (1.24)	1.44 (0.74)	71.5 (47.2;95.8)
	6	SD	0.08	42218 (28.1)	1.02 (0.59)	2.31 (1.15)	41.8 (35.6;47.9)
	6	SD	0.04	24199 (86.6)	1.63 (1.11)	0.76 (1.32)	36.0 (23.9;71.5)
	6	SD	0.02	16153 (57.0)	0.44 (0.48)	-0.79 (1.64)	30.0 (12.0;48.0)

[4] Ranke MB. Insulin-like growth factor binding-protein-3 (IGFBP-3). Best Pract Res Clin Endocrinol Metab. 2015;29(5):701-11.

Abbreviations: AUC_{0-168}: area under the concentration-time curve from 0 to 168 hours after dosing; C_{max}: maximum concentration; CV: coefficient of variation; IGF-I: insulin-like growth factor I; max: maximum; min: minimum; SD: single dose; SDS: standard deviation score; t_{max}: time to maximum concentration.

Multiple doses of once-weekly somapacitan (0.04, 0.08, and 0.16 mg/kg/week), and once daily somatropin medicinal product (0.034 mg/kg/day (total 0.24 mg/kg per week)) were administered to paediatric GHD patients in study 4172. During a follow-up period of one year, IGF-I SDS and mean IGF-I SDS levels increased in a dose-dependent manner with increasing somapacitan dose. Somapacitan at a dosage of 0.16 mg/kg/week was considered the most appropriate starting dosage, taking into account IGF-I SDS levels, but also growth parameters, safety, and tolerability. This somapacitan dosage was subsequently evaluated in Phase 3 study 4263.

Steady state pharmacodynamics

The steady-state pharmacodynamic (PD) properties of somapacitan were evaluated by population PK/PD modelling analyses based on sparse PK/PD sampling from study 4172 (Phase 2) and study 4263 (Phase 3). The evaluation of the steady state pharmacodynamic properties of somapacitan for the 0.16 mg/kg/week dose level focused on parameters estimated from the combined data obtained in studies 4172 and 4263.

The steady-state model-estimated IGF-I SDS profile for somapacitan 0.16 mg/kg/week in studies 4172 and 4263 indicated that somapacitan is suitable for once-weekly dosing. Steady-state occurred after 1−2 doses following treatment initiation in children with GHD.

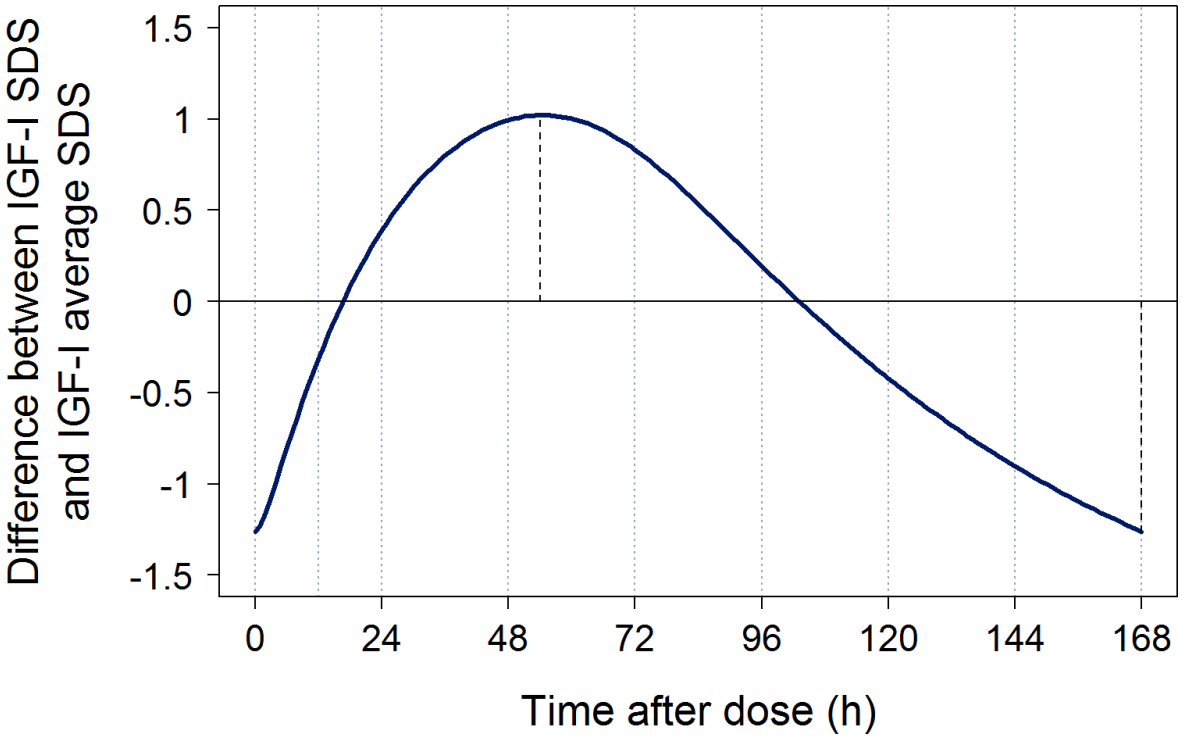
Mean IGF-Iavg SDS for somapacitan 0.16 mg/kg/week was 0.53 [90% CI -0.83; 1.64] range for studies 4172 and 4263 combined. The mean time to maximum IGF-I levels at steady state (IGF-I Tmax) was 57.6 hours.

Steady-state occurred after 1−2 doses following treatment initiation. After treatment discontinuation, IGF-I levels reached baseline levels 1-2 weeks after the last dose.

IGF-I monitoring

The difference between estimated average IGF-I SDS and steady-state IGF-I SDS levels at different times after dose are illustrated in Figure 4.

Figure 4 Differences between IGF-Iavg SDS and IGF-I SDS



Notes: The dark blue line indicates the difference between IGF-I SDS and IGF-Iavg SDS as predicted by the formulas for IGF-Iavg by time after dose. Dotted lines indicate the time of maximum and minimum IGF-I SDS levels.
Abbreviations: IGF-Iavg: average IGF-I in a dosing interval.

Formulas for calculation of average IGF-I SDS based on samples taken in specified time intervals over the somapacitan dosing interval are provided in Table 6. Sampling 2 days after the injection provides a value that closely approximates the expected maximum IGF-I SDS value, whereas the average IGF-I SDS over the weekly dosing interval is most closely approximated with a sample taken 4 days after injection. The weekly average IGF-I SDS can be calculated based on blood samples taken on any day of the week following somapacitan injection. Sampling for IGF-I measurements within the first 24 hours after dosing is not advised.

Table 4 Formulas for prediction of IGF-Iavg SDS by time after dose

Time after dose to approximate average IGF-I SDS	Adjustment of measured IGF-I SDS
1 day after dose (25-48 hours)	IGF-I SDS -0.8
2 days after dose (49-72 hours)	IGF-I SDS -1.0
3 days after dose (73-96 hours)	IGF-I SDS -0.5
4 days after dose (97-120 hours)	IGF-I SDS +0.1
5 days after dose (121-144 hours)	IGF-I SDS +0.7
4 days after dose (145-168 hours)	IGF-I SDS +1.1

IGFBP-3

IGFBP-3 was used as a supportive biomarker to assess somapacitan pharmacodynamics in study 4042. A dose-dependent increase was observed in IGFBP-3 following somapacitan dose administration. Results for IGFBP-3 overall supported the findings for IGF-I.

Pharmacodynamics over time

To evaluate IGF-I levels over time, IGF-Iavg SDS was estimated by treatment year over the duration of study 4172 (4 years) and study 4263 (1 year) for the somapacitan 0.16 mg/kg/week dose level. IGF-Iavg SDS levels were overall similar over the 4-year treatment period.

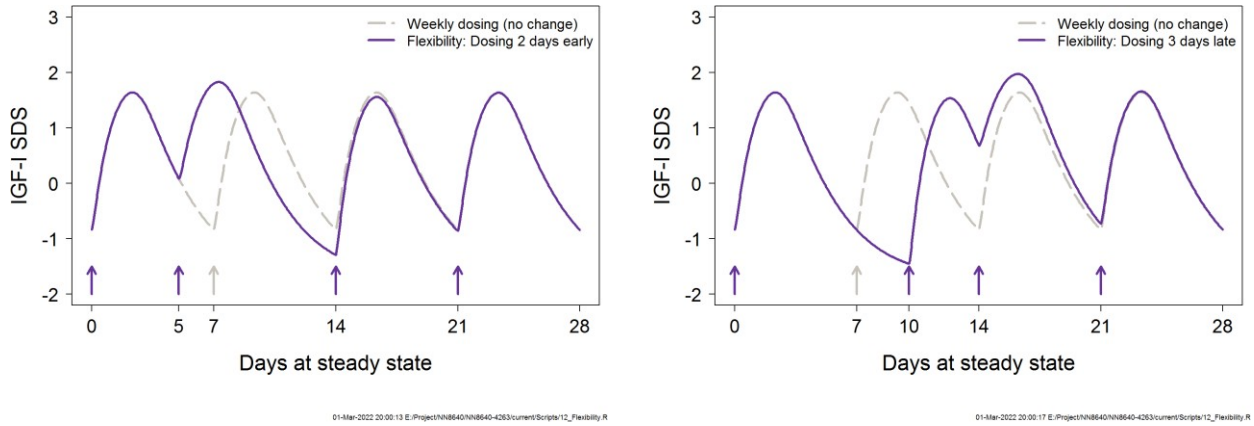
Flexibility in dosing and change of dosing day

Simulations of PK and IGF-I SDS profiles were used to assess the impact of allowing flexibility in the weekly dosing regimen of somapacitan or change of the weekly dosing day, while maintaining a minimum of 4 days (96 hours) in between doses.

On occasions when administration at the scheduled dosing day is not possible, somapacitan can be taken up to 2 days before or 3 days after the scheduled weekly dosing day as long as the time between two doses is at least 4 days. The impact on the IGF-I SDS profile of allowing dosing two days prior to or three days after the regular dosing day and then proceeding with weekly dosing on the regular dosing day is shown in Figure 5.

Figure 5 IGF-I SDS profiles for dosing flexibility

A B



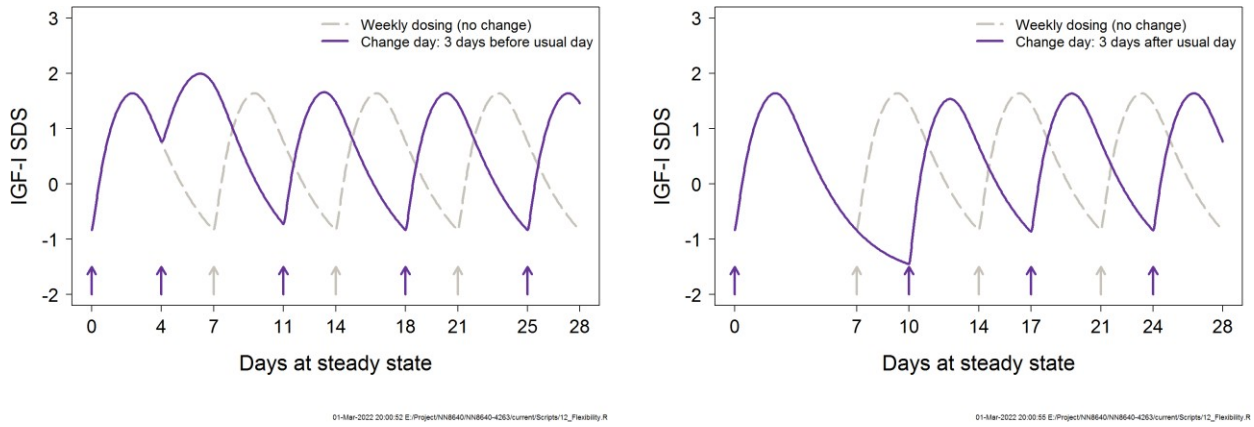
Notes: Lines are means of individual predictions. Dotted lines represent profiles at steady state with a weekly dosing interval.

The day of the weekly injection can be changed as long as the time between two doses is at least 4 days. The impact of changing the regular dosing day by dosing three days earlier or by postponing a dose for three days is shown in Figure 6.

In all cases, the impact on PK and IGF-I SDS was limited, and steady-state occurred 1-2 doses after regular weekly treatment was resumed.

Figure 6 IGF-I SDS profiles for change of dosing day

A B

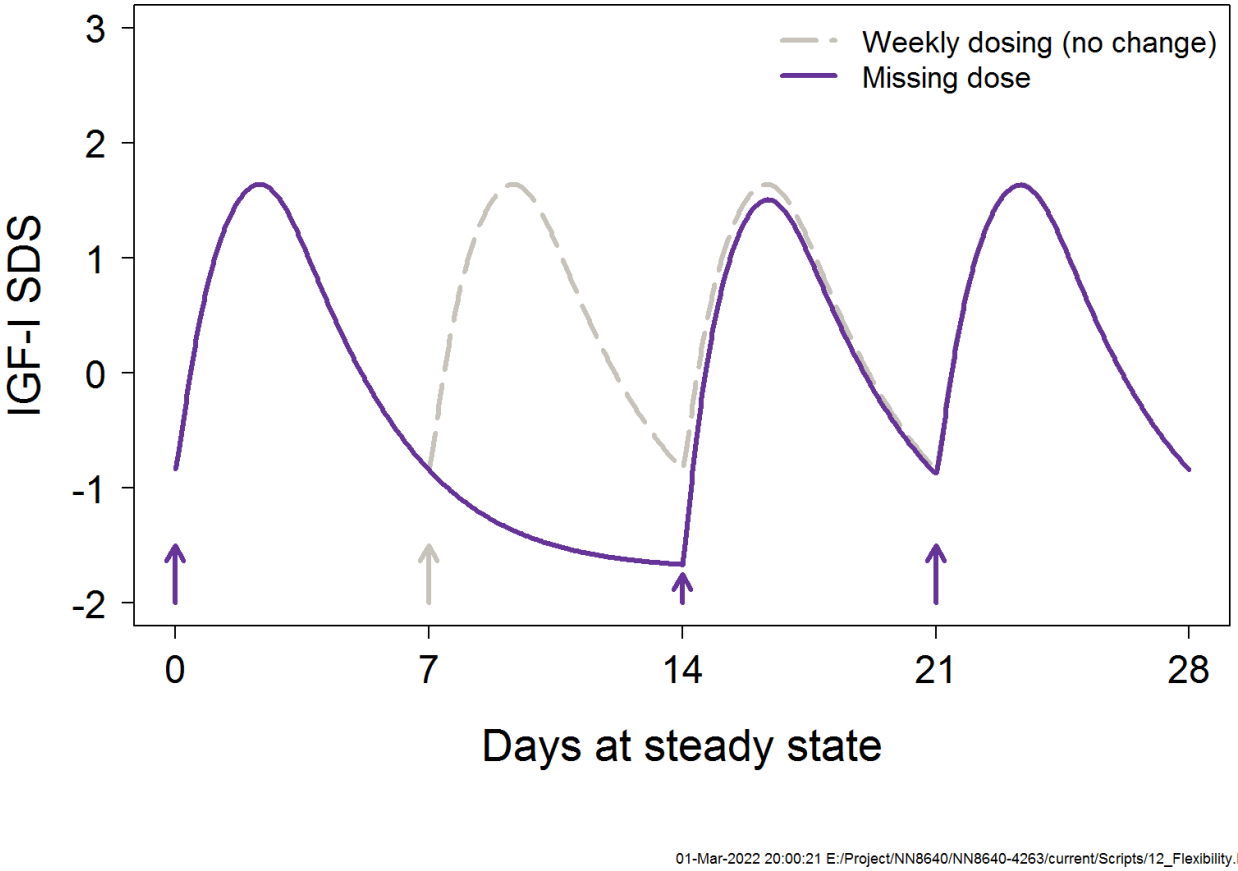


Notes: Lines are means of individual predictions. Dotted lines represent the regular dosing interval with no change of dosing day.

Missed dosing

A missed dose of somapacitan can be administered up to 3 days after the regular dosing day with limited impact on the somapacitan IGF-I SDS profile (Figure 5 and Figure 6). If more than three days have passed, the dose should be skipped and dosing should be resumed on the regular dosing day in the following week, as illustrated in Figure 7. A steady-state occurred 1-2 doses after the regular weekly treatment regimen was resumed.

Figure 7 IGF-I SDS profile following one missed dose



Notes: Lines are means of individual predictions. Dotted lines represent the regular dosing interval if no dose was missed.

Comparison to somatropin medicinal product Norditropin

The clinical pharmacology study 4042 and the phase 2 and 3 studies (studies 4172 and 4263) included somatropin medicinal product Norditropin as an active comparator. The somatropin dose was 0.034 mg/kg/day in studies 4172 and 4263, corresponding to the highest approved somatropin dose for children with GHD. In study 4042, a somatropin dose of 0.03 mg/kg was selected as representing a dose within the recommended dose range for human growth hormone (hGH) treatment of children with GHD.

IGF-I SDS levels following treatment with somapacitan 0.16 mg/kg/week and somatropin were compared based on observed and model-estimated data from studies 4042, 4172 and 4263.

In study 4042, IGF-I levels for somapacitan and somatropin were compared in an exploratory statistical analysis for IGF-I AUC0-168h and Cmax. The results of this analysis are provided in Table 7 for the somapacitan 0.16 mg/kg dose level. There was no statistically significant difference in AUC0-168h for somapacitan 0.16 mg/kg and somatropin 0.03 mg/kg, but Cmax was significantly higher for somapacitan 0.16 mg/kg compared to somatropin, indicating a higher variation over the weekly dosing interval for once-weekly somapacitan compared to daily somatropin.

Table 5 Exploratory statistical analysis of IGF-I comparing somapacitan and somatropin in study 4042

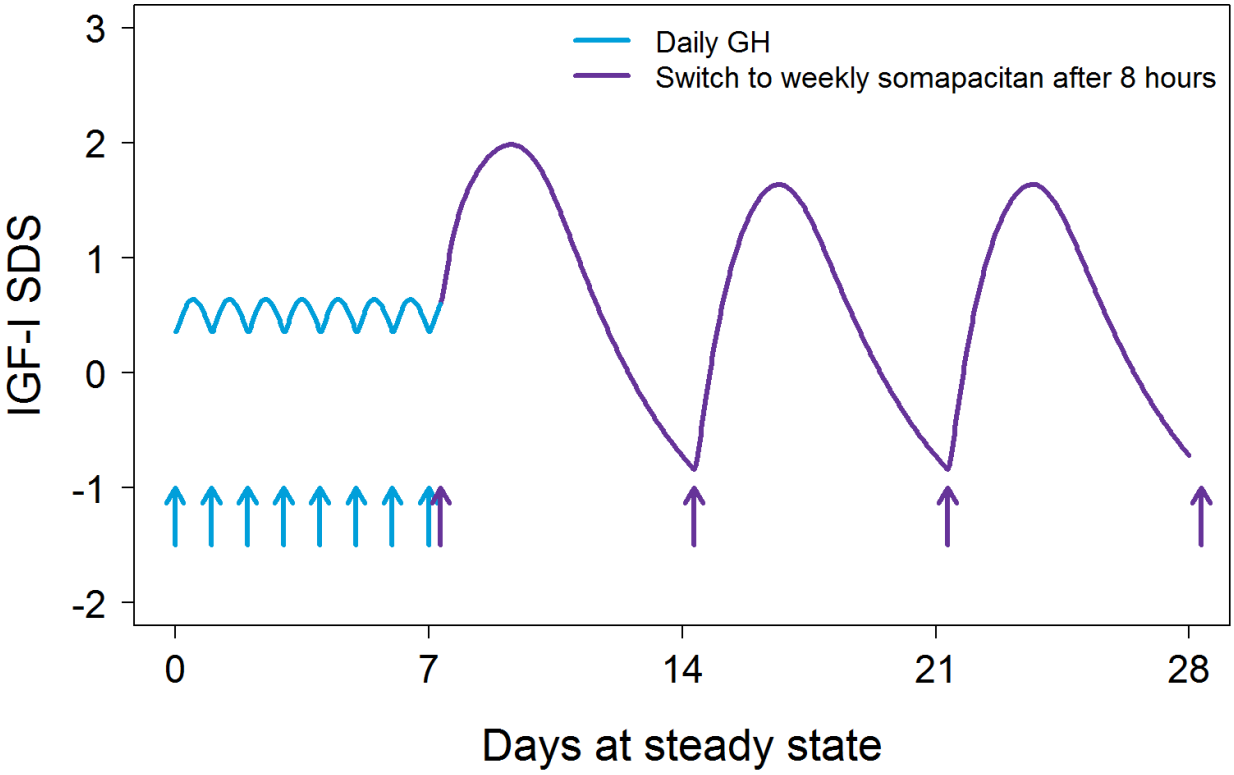
PD parameter	Somapacitan 0.16 mg/kg compared to somatropin 0.03 mg/kg/day Estimate (95% CI)	p-value for test of ratio= 1
AUC0-168h (ng*h/ml)	1.25 (0.98-1.59)	0.07
Cmax (ng/ml)	1.61 (1.26-2.05)	<0.01

Analysis using an ANCOVA model on log transformed data with ln(baseline value) as covariate and treatment as a factor.

Switching from daily GH treatment to once-weekly somapacitan

Patients switching from daily hGH to once-weekly somapacitan should take the final dose of daily treatment the day before (or at least 8 hours before) taking the first dose of once-weekly somapacitan. The IGF-I SDS profile when switching from daily GH (somapacitan medicinal product Norditropin 0.034 mg/kg/day which is equivalent to a total weekly dose of 0.24 mg/kg/week) to once-weekly somapacitan (0.16 mg/kg/week) 8 hours after the latest dose of daily GH is shown in Figure 8. Steady-state is expected to occur after the second somapacitan dose.

Figure 8 IGF-I SDS profile during switch from daily growth hormone treatment



Notes: Lines are means of individual predictions for somatropin medicinal product Norditropin® 0.034 mg/kg/day and somapacitan 0.16 mg/kg/week based on an exploratory model for combined effect of daily somatropin followed by weekly somapacitan. The profile for daily GH represents the steady state profile for the last week of treatment prior to the switch.

Secondary pharmacology

No data on secondary pharmacology in paediatric GHD patients were submitted.

Genetic differences in PD response

Effects of intrinsic factors on somapacitan PK and PD properties

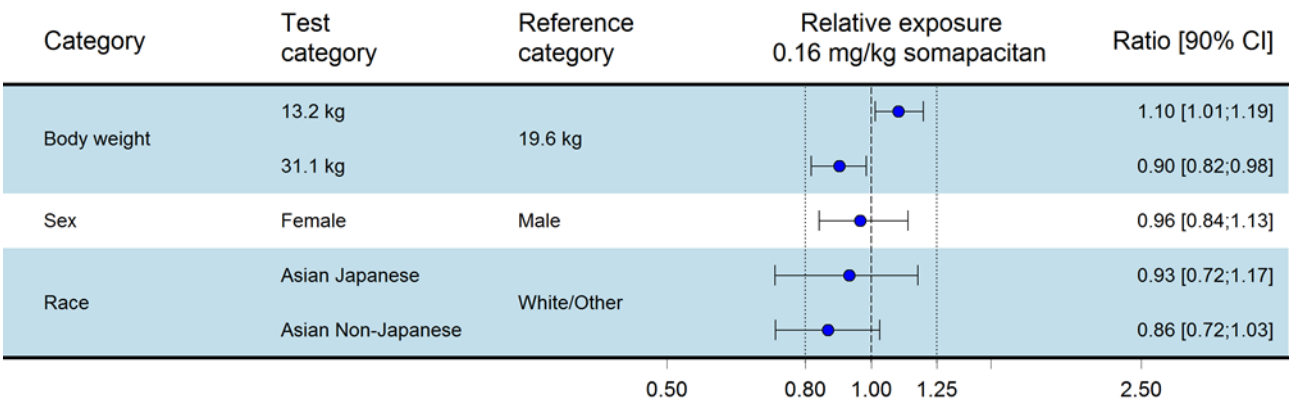
The potential impact of intrinsic factors on the pharmacokinetic and pharmacodynamic properties of somapacitan was addressed using modelling analyses based on data from clinical pharmacology study 4042, study 4172 (Phase 2) and study 4263 (Phase 3) in children with GHD. The factors evaluated were: body weight, sex, and race. Age was not investigated as a separate intrinsic factor, as age and body weight are strongly correlated in children.

Body weight was the only significant covariate on PK in children with GHD (Figure 9). The results of the modelling analysis for somapacitan PK are visualised as exposure for each covariate category relative to the exposure of a reference subject's profile in Figure 9. The effects of body weight, sex and race on the IGF-I response, as evaluated by the change from baseline IGF-I_{avg} SDS, were relatively small (≤0.5 SDS) or not significant.

Based on population PK/PD modelling, body weight, sex and race did not have a clinically meaningful effect on somapacitan PK and IGF-I response in children with GHD following weight-based dosing.

Somapacitan PK and PD were also compared between healthy adult Japanese subjects and healthy adult non-Asian subjects in study 3915, which was included in the initial application in AGHD. Somapacitan exposure ($AUC_{0\text{-}168h}$ and C_{max}) and IGF-I response ($AUC_{0\text{-}168h}$ and C_{max}) were similar between Japanese and non-Asian subjects at the same dose per kg in study 3915.

Figure 9 Population pharmacokinetic covariate analysis of somapacitan exposure in children with GHD



Notes: The plot shows relative exposure in terms of average somapacitan concentrations during a dosing interval at steady state for somapacitan 0.16 mg/kg/week. The points and bars show estimated means and 90% confidence intervals relative to the reference subject (white male with a body weight of 19.6 kg). Body weight categories (13.2 and 31.1 kg) represent the approximate 5% and 95% percentiles at week 52. Vertical dotted lines indicate the [0.80–1.25] interval.

The association between estimated IGF-Iavg SDS by Tanner stage and gender at a somapacitan starting dosage of 0.16 mg/kg/week in studies 4172 and 4263 is presented in Table 6 and Figure 10.

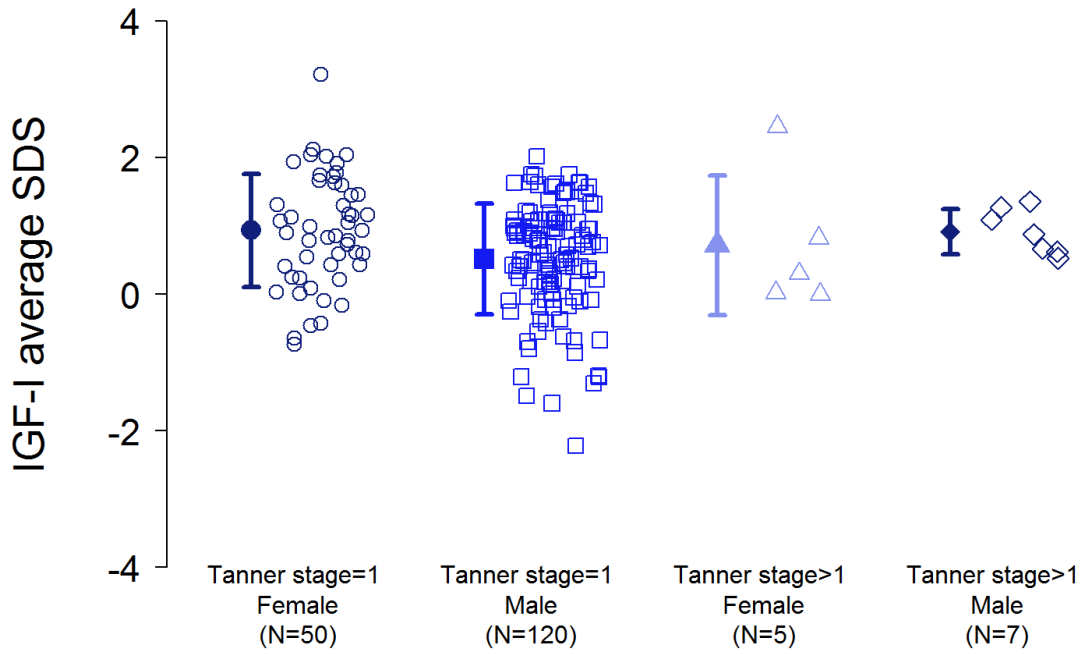
Table 6 Modelled estimates for C_{avg} and IGF-I_{avg} SDS by Tanner stage and gender at a somapacitan starting dosage of 0.16 mg/kg/week (studies 4172 and 4263)

Study	Somapacitan dose (mg/kg/week)	Tanner stage	Gender	n	C_{avg} (ng/mL) Geometric mean (CV)	IGF-I_{avg} SDS Mean (SD)
4172, cohort I and 4263	0.16	Tanner stage = 1	Female	50	79.8 (45.7%)	0.93 (0.82)
	0.16	Tanner stage = 1	Male	120	83.4 (48.3%)	0.51 (0.81)
	0.16	Tanner stage > 1	Female	5	59.4 (68.0%)	0.72 (1.02)
	0.16	Tanner stage > 1	Male	7	78.9 (45.7%)	0.92 (0.33)

Notes: Data for study patients treated with somapacitan 0.16 mg/kg/week in study 4172, cohort I (year 4 or latest available estimate) and study 4263 (year 1). Two (2) study patients had no information on Tanner stage.

Abbreviations: C_{avg}: average concentration during a dosing interval; CV: coefficient of variation; IGF-I: insulin-like growth factor I; n: number of subjects; SD: standard deviation; SDS: standard deviation score.

Figure 10 Individual estimated IGF Iavg SDS by Tanner stage and gender, somapacitan 0.16 mg/kg/week (studies 4172 and 4263)



Notes: Open symbols are individual estimated average IGF-I SDS. Closed symbols and bars indicate means and standard deviations. The plot is based on data for study patients treated with somapacitan 0.16 mg/kg/week in study 4172, cohort I (year 4 or latest available estimate) and study 4263 (year 1). Two (2) study patients had no information on Tanner stage.

Effects of extrinsic factors on somapacitan PK and PD properties

No investigation of extrinsic factors was performed in children with GHD. Potential drug-drug interactions for somapacitan were evaluated in the initial application for patients with AGHD.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Three new clinical studies were conducted in paediatric patients with GHD aged ≥2.5 years up to 11 years to support the line-extension. No PK studies were conducted in paediatric patients aged <2.5 years and 12 to <18 years.

Somapacitan pen injectors with 5 mg, 10 mg and 15 mg in 1.5 ml were used in the confirmatory Phase 3 study 4263 and in the Phase 2 study 4172. Based on the exposure and IGF-I response (PopPK modelling) and considering that the excipients are similar, no difference in exposure is expected when using the different pen strengths. Hence, a somapacitan dose strength of 15 mg somapacitan per 1.5 ml solution is acceptable.

One single dose escalation (0.02, 0.04, 0.08 and 0.16 mg/kg) study was conducted with full PK sampling. In addition, two multiple dose (0.04, 0.08 and 0.16 mg/kg/week) studies were conducted with sparse PK sampling. PopPK modelling was used to determine the PK in paediatric patients following repeated dosing. The exposure in paediatric patients with growth hormone deficiency is higher at a similar dose compared to adult patients with growth hormone deficiency. At a dose of 0.08 mg/kg/week, the C_{max} is 125 ng/mL (CV%=67) in paediatric patients and 45.4 ng/mL (CV%=128) in

adult patients with growth hormone deficiency. The AUC is 4367 ng × h/mL (CV%=50) in paediatric patients and 2085 ng × h/mL (CV%=102) in adult patients at a dose of 0.08 mg/kg/week. At a dose of 0.04 mg/kg/week, the C_{max} is 34.7 ng/mL (CV%=48) in paediatric patients and 20.6 ng/mL (CV%=201) in adult patients with growth hormone deficiency. The AUC is 1313 ng × h/mL (CV%=24) in paediatric patients and 986 ng × h/mL (CV%=93) in adult patients at a dose of 0.08 mg/kg/week. Higher levels of growth hormone are needed in children to normalise IGF-I levels and induce normal longitudinal growth. The difference in exposure between children and adults treated with growth hormone is also seen in populations treated with daily growth hormone. Therefore, the higher exposure in paediatric patients compared to adult patients with growth hormone deficiency is acceptable at a similar dose.

Pharmacodynamics

Somapacitan acts similar to the endogenous growth hormone, and the well-known effects are either direct (for example, on the fat tissue or growth in children) of indirect (for example, increase in muscle mass). The primary pharmacodynamic effect is an increase in IGF-1, IGFBP3 and acid-labile subunit levels. The most important secondary pharmacologic effects (i.e. IGF-I mediated) are elevations of fasting glucose and insulin concentrations.

The steady-state model-estimated IGF-I SDS profile for somapacitan 0.16 mg/kg/week indicated that IGF-I SDS levels increased up 2-3 days after somapacitan administration in paediatric GHD patients. Thereafter, IGF-I SDS levels decreased during days 4-7. A steady state occurred after 1-2 once-weekly somapacitan administration.

In the first year of treatment, the observed IGF-I responses tended to be higher with increasing somapacitan dosages in paediatric GHD patients. Moreover, the height velocity and the results for supportive efficacy endpoints tended to be larger for increasing changes from baseline IGF-Iavg SDS. Hence, there is a positive dose-response relationship for somapacitan treatment. Model-derived change from baseline average IGF-I SDS for somapacitan was similar to the observed change from baseline IGF-I SDS for somatropin at week 52 in the pivotal Phase 3 study 4263. The applicant showed later that similar results were obtained upon comparison of observed IGF-I SDS levels for somapacitan and somatropin.

It was shown that the average IGF-I SDS levels remained similar during 4 consecutive periods of one year upon somapacitan dosing of 0.16 mg/kg/week in conducted clinical studies.

The effects of body weight, gender and race on the IGF-I response, as evaluated by the change from baseline IGF-I_{avg} SDS, were relatively small (≤0.5 SDS) or not significant.

The day of weekly injection can be changed as long as the time between two doses is at least 4 days. If somapacitan administration at the scheduled dosing day is not possible, somapacitan can be taken up to 2 days before or 3 days after the scheduled weekly dosing day as long as the time between two doses is at least 4 days. Steady-state will recur 1-2 doses after regular weekly somapacitan treatment.

According to the proposed SmPC, patients switching from daily somatropin to once-weekly somapacitan should take the final dose of somatropin the day before (or at least 8 hours before) taking the first dose of once-weekly somapacitan.

A considerable proportion of study patients had IGF-I levels above +2 SDS during some time in clinical studies 4172 and 4263, especially within the first 3 days after somapacitan administration. In adult GHD patients, short intervals of IGF-I levels above +2 SDS were not associated with increased safety risks of somapacitan. The applicant later indicated that this also applies to paediatric GHD patients.

At a somapacitan starting dosage of 0.16 mg/kg/week, IGF-I SDS levels within the range of -2 and +2 were obtained in paediatric GHD patients of different gender and pubertal status. Hence, a somapacitan starting dosage of 0.16 mg/kg/week is appropriate for the subgroups of paediatric GHD patients (i.e. pre-pubertal, and post-pubertal), male pubertal GHD patients, and female pubertal GHD patients with or without concomitant oestrogen use.

2.6.4. Conclusions on clinical pharmacology

The PK was investigated in paediatric patients with GHD aged ≥2.5 to 11 years. No PK studies were performed in paediatric patients aged <2.5 years and 12 to <18 years. The pharmacokinetic profile of somapacitan 15 mg in 1.5 ml solution is in line with that of the authorized dose strengths of 5 and 10 mg somapacitan in 1.5 ml solution.

Submitted data support the pharmacodynamic effects of somapacitan in paediatric GHD patients. A positive dose-response relationship for somapacitan treatment in these patients was observed.

2.6.5. Clinical efficacy

2.6.5.1. Dose response study

Study NN8640-4172, further abbreviated into study 4172, and also indicated as REAL 3, is a randomised, multinational, active-controlled, dose-finding, parallel-group study investigating efficacy and safety of once-weekly somapacitan treatment compared to daily GH treatment (somatropin medicinal product Norditropin) in GH treatment-naïve, pre-pubertal children with GHD (Figure 11).

Main study plus extension

Fifty- nine (59) study patients were randomised (1:1:1:1) to either somapacitan (0.04, 0.08 or 0.16 mg/kg/week) or somatropin (0.034 mg/kg/day i.e. a total weekly dose of 0.24 mg/kg) during a 26-week main period and a 26-week extension period (completed). In the main period, treatment was double-blinded between the three somapacitan cohorts and open-label between the somapacitan cohorts and the somatropin cohort.

Safety extension

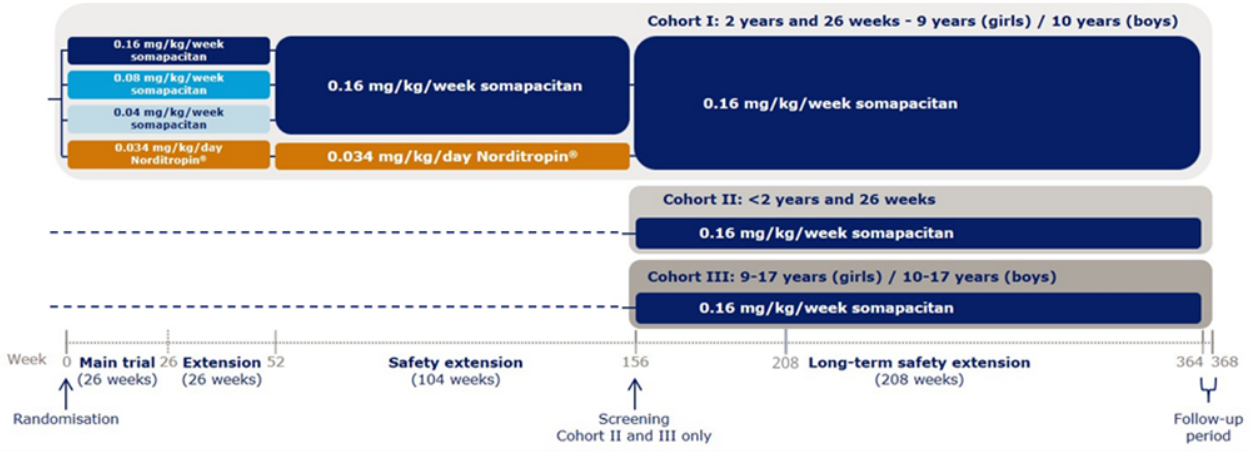
The initial 52 weeks were followed by 104-weeks open-label safety extension period (completed). In this period, all patients who were initially treated with different dosages of somapacitan were treated with somapacitan at a dosage of 0.16 mg/kg/week. Study patients who were initially randomized to 0.034 mg/kg/week somatropin continued this treatment in the 104-week safety extension period.

Long-term safety extension

The safety extension period was followed by a 208-week ongoing long-term safety extension in which all study patients were treated with somapacitan at a dosage of 0.16 mg/kg/week.

Two new cohorts were added in the long-term safety extension period of the study to collect data on children in age groups not included in cohort I of study 4172 or in the Phase 3 study 4263, namely cohort II: children under 2.5 years, and cohort III: children above 9 years (girls) / 10 years (boys) at enrolment. All study patients in these new cohorts were treated with somapacitan at a dosage of 0.16 mg/kg/week.

Figure 11 Study design of Phase 2 study 4172



Study participants

Growth hormone treatment-naïve paediatric patients aged 2.5 years and older at Tanner stage I with a confirmed diagnosis of GHD diagnosis of GHD within 12 months prior to screening defined as a peak growth hormone level of ⩽7.0 ng/ml, and exclusion of other diagnoses were included in study 4172.

Treatments

Somapacitan 0.04, 0.08 or 0.16 mg/kg/week

Somatropin medicinal product Norditropin 0.034 mg/kg/day

Study patients in study 4172 were randomised to either somatropin (0.034 mg/kg/day i.e. a total weekly dose of 0.24 mg/kg) or one of three somapacitan doses (0.04/0.08/0.16 mg/kg/week) from baseline to week 52. From week 52 and for the remaining duration of the study, all study patients allocated to somapacitan were administered 0.16 mg/kg/week. The study patients allocated to somatropin were switched to somapacitan (0.16 mg/kg/week) at week 156 for the remaining duration of the study.

Dose reduction in consecutive steps of 25% of the current dose could be considered at the investigator's discretion, for adverse events judged as probably related to the study medicinal product by the investigator. If the adverse event persisted, the study patient could be discontinued and if the adverse event resolved, the dose could then be resumed to the original planned dose at the investigator's discretion.

Objective

The objectives of cohort I were to evaluate the efficacy, safety, and the impact of study treatment on well-being, psychosocial functioning, treatment satisfaction and preference in growth hormone treatment in growth hormone treatment naïve pre-pubertal children with GHD primarily after 26 weeks of treatment, up to 364 weeks of treatment.

The objective of cohorts II and III was to evaluate the safety of once-weekly somapacitan during at least 13 weeks and up to 208 weeks of treatment in children with GHD.

Randomisation and blinding

Study patients were randomized in a 1:1:1:1 (0.04 mg/kg/week somapacitan; 0.08 mg/kg/week somapacitan; 0.16 mg/kg/week somapacitan; 0.034 mg/kg/day (i.e. a total weekly dose of 0.24 mg/kg) somatropin) manner with a block size of four to receive either somapacitan or somatropin medicinal product Norditropin. The randomisation was stratified by region (Japan versus the rest of the

world). The randomisation within the rest of the world region was additionally stratified by gender (boys versus girls) and age (<6 versus > 6 years) to minimize the bias of these two parameters on the primary endpoint. A study-specific interactive web response system was used, which could be accessed at any time via the internet or telephone.

The main study period (26 weeks) was double-blinded with regard to different dose levels of once-weekly somapacitan but open-labelled with regard to daily somatropin as the active control arm. After the double-blinding of the main study period, the sponsor was unblinded, while the study patients and site staff remained blinded with regards to somapacitan dose level allocation until the end of the extension study period (week 52). The rest of the study was open-label as only one dose of somapacitan (0.16 mg/kg/week) was used. The study was observer-blinded with regards to the primary endpoint, i.e., the person performing the height measurements was blinded to treatment allocation.

Two additional cohorts were added to the study (after 156 weeks of treatment for cohort I) accordingly; study patients are currently being enrolled to receive unblinded somapacitan 0.16 mg/kg/week for 13 weeks minimum in Cohort II: children with GHD of age <2.5 years and Cohort III: children with GHD of age 9-17 (girls) and 10-17 (boys).

Endpoints

An overview of efficacy endpoints in study 4172 is provided in Table 7

Table 7 Efficacy endpoints in study 4172

Endpoints	Study 4172 (dose-finding)
Growth related parameters	Height velocity (primary endpoint, week 52) Change in height standard deviation score (HSDS) Change in height velocity standard deviation score (HVSDS) Change in bone age
Pharmacodynamic parameter	Change in IGF-I SDS[b] Change in IGFBP-3 SDS
Additional outcomes	
Patient- reported outcomes (PRO)a	Treatment Burden Measure- Child GHD- Observer (TB- CGHD-O) Treatment Burden Measure- Child GHD- Parent (TB- CGHD-P) Change in Treatment Related Impact measure-Child-Growth Hormone Deficiency-Observer (TRIM-CGHD-O) Patient-Preference-Questionnaires (PPQ)

[a] The PROs were not used in cohorts II and III.

[b] Samples were taken at different points in time compared to dosing day at the different visits (to cover the weekly interval for somapacitan exposure and IGF-I SDS): week 4, week 13 and week 39 assessments were taken at IGF-I SDS trough (dosing day before dosing) and week 26 and week 52 assessments were taken at IGF-I SDS peak (day 1-4 after dosing). The observed IGF-I SDS levels and the modelled IGF-Iavg SDS levels, which account for the weekly IGF-I SDS profile were analyzed.

Notes: Secondary endpoints were not tested.

Statistical methods

Sample size

Fifteen subjects randomised per treatment arm should assure 87% power for getting a 95% confidence interval for the estimated treatment difference that lies completely above -3.8 (the chosen delta value) when comparing a somapacitan treatment arm (0.04 mg/kg, 0.0 8mg/kg, 0.16 mg/kg) to the

somatropin treatment arm, given that the two treatments are equal, and expecting at most 7% dropout during the trial. The sample size calculation was based on an assumption of a standard deviation of 3.1 cm/year for height velocity after 26 weeks of treatment and the use of a delta value of -3.8 cm/year and a one-sided significance level of 2.5%.

Definition of analysis sets

The following analysis sets were defined in the protocol:

Full analysis set (FAS): all randomised study patients who received at least one dose of randomised treatment. Subjects were analysed “as treated”.

Per protocol (PP) analysis set: study patients from the FAS, who had not violated any inclusion/exclusion criteria and who had used the randomised treatment for at least 22 weeks (for study patients receiving somapacitan) or 154 days (for study patients receiving somatropin) during the main study period.

Safety analysis set (SAS): all randomised study patients were exposed to at least one dose of randomised treatment. Study patients were analysed “as treated”.

Analyses of cohorts II and III for study 4172 included all study patients who received at least one dose of somapacitan 0.16 mg/kg/week.

Analysis of primary endpoint height velocity

The primary endpoint for cohort I was height velocity (HV)(cm/year) during the first 26 weeks of treatment. Annualized height velocity after 26 weeks was analysed using a MMRM with treatment, age group, gender, region and sex by age group interaction term as factors and height at baseline as a covariate, all nested within week as a factor. From the MMRM, the treatment differences at week 26 between somapacitan treatment arms and somatropin was estimated with the corresponding 95% CI.

The primary analysis of the primary endpoint was based on the FAS. The analysis was repeated on the PP analysis set as a sensitivity analysis.

The height velocity analysis was repeated at week 52 as a secondary, supportive endpoint, while height velocity at 104 weeks and 156 weeks was analysed using post-hoc statistical analysis. From 208 weeks, height velocity was described using descriptive statistics.

Analysis of secondary endpoints

The secondary efficacy endpoints: were the change in HSDS, HVSDS, IGF-I SDS, IGFBP-3 SDS and TRIM-CGHD-O from baseline and the two TB-CGHD PROs at week 52 analysed using an MMRM similar to the MMRM used for the primary endpoint, but with the specific baseline assessment as covariate. The analyses were based on assessments from week 13, 26, 39 and 52 (26 and 52 for the PRO based endpoints). Somapacitan and hGH serum concentrations during the trial, PPQ assessment at week 160, as well as bone age progression versus chronological age up to week 208 were analysed using descriptive statistics.

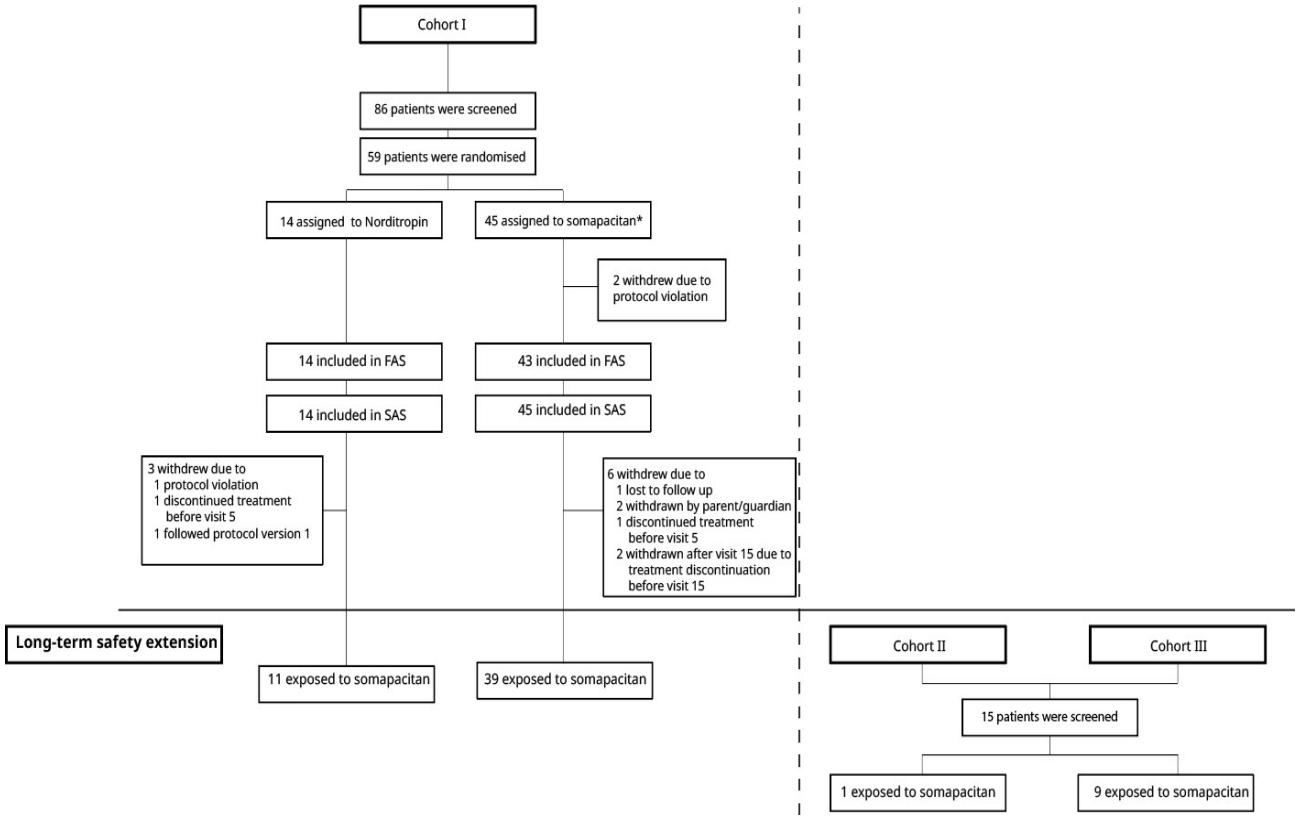
For assessments up to and including week 52, analyses were done between all three somapacitan dose groups (0.04, 0.08 and 0.16 mg/kg/week) and somatropin (0.034 mg/kg/day). Subsequent analyses of all secondary efficacy endpoints (after week 52) were performed using descriptive statistics. Secondary endpoints were not included in any kind of test hierarchy and no adjustment for multiplicity was performed.

For cohorts II and III, height velocity and change from baseline in HVSDS, HSDS, IGF-I SDS and IGFBP-3 SDS, were all analysed using descriptive statistics.

Subject disposition

An overview of the trial population and subject disposition for all three cohorts in study 4172 is presented in Figure 12.

Figure 12 Study patient disposition overview study 4172



Abbreviations: FAS: full analysis set; SAS: safety analysis set

For cohort I, 86 Children were screened. Fifty-nine (59; 100%) study patients were randomised and exposed to treatment in the originally planned cohort I. Two (2) study patients (somapacitan 0.04 mg/kg/week) were excluded from the FAS as they were randomised in error (violation of inclusion/exclusion criteria) and discontinued treatment prior to visit 3 (week 4). Fifty (50) study patients were exposed in the long-term safety extension study period following week 156 and completed treatment up to week 208.

Nine (9) children discontinued the study product before week 156, 6 in the somapacitan treatment arms (0.04/0.16 mg/kg/week: 4 children; 0.08/0.16 mg/kg/week: 1 child; 0.16/0.16 mg/kg/week: 1 child) and 3 in the somatropin treatment arm. Of the 9 children discontinuing study treatment, 2 discontinued treatment due to adverse events (nephrotic syndrome and drug hypersensitivity), 2 were withdrawn from treatment by parent/legally authorized representative and 5 discontinued treatment due to protocol violations.

Adherence was above 90% in all treatment groups in cohort I up to week 208 for study patients on treatment.

In cohorts II and III, a total of 10 study patients had been exposed to somapacitan (0.16 mg/kg/week) by the initial cut-off date of 26-Aug-2021 (recruitment still ongoing). None of the study patients in cohorts II or III had discontinued treatment at the cut-off date of 26-Aug-2021.

Baseline data

Study patients enrolled in cohort I of the supportive study 4172 were human growth hormone treatment naïve GHD diagnosed pre-pubertal children (≥2.5 years of age and <9 years for girls, <10 years for boys). The GHD cause was either organic (7%) or unknown/idiopathic (93%).

Of the 57 study patients in cohort I (FAS), 31 (54.4%) were below the age of 6 years. 23 (40.4%) of the study patients were female. The study was conducted globally; most study patients were enrolled from India (24.6%), Japan (21.1.%), United States (14.0%) and Ukraine (12.3%).

Cohort II included 1 child who was 2 years and 5 months (the age was rounded to 2.5 years in the output tables). Cohort III included 2 treatment naïve children (2 boys with age 11.9 years and 15.7 years) and 7 previously treated children (6 boys and 1 girl; mean age: 13.27 years; min: 10.2 years; max: 16.1 years). The cause of GHD was idiopathic for 8 children and organic for 1 child.

In cohort III, the 2 treatment naïve children had entered puberty (Tanner stage > 1) and among the 7 previously treated children, 5 were prepubertal and 2 had entered puberty at screening.

Outcomes and estimation

Primary endpoint height velocity (annualised)

The primary endpoint in study 4172 was height velocity (annualised) from baseline to week 26. A dose-response relationship was observed for somapacitan groups at three different dose levels (0.04, 0.08 and 0.16 mg/kg/week) after both 26 and 52 weeks (Table 10). Height velocity at week 26 numerically favoured somapacitan 0.16 mg/kg/week compared to somatropin 0.034 mg/kg/day (estimated treatment difference (ETD) = 1.67 cm/year [95% CI -0.22; 3.56]).

Table 8 Observed and estimated annualized height velocity in study 4172 after 26, 52, 104 and 156 weeks

	Somapacitan 0.04 mg/kg/week	Somapacitan 0.08 mg/kg/week	Somapacitan 0.16 mg/kg/week	Somatropin 0.034 mg/kg/day
Number of subjects	14	15	14	14
Mean (SD) height velocity (cm/year)				
Baseline	4.0 (1.8)	4.8 (1.4)	3.8 (1.5)	3.5 (1.6)
Week 26 (observed)	8.0 (2.0)	10.9 (1.9)	12.9 (3.5)	11.3 (3.3)
Week 26 (estimated)	7.8	10.9	13.1	11.4
Week 52 (observed)	7.8 (1.8)	9.7 (1.8)	11.5 (2.6)	9.8 (2.3)
Week 52 (estimated)	7.5	9.7	11.7	9.9
Week 104 (observed)	10.6 (1.4)	10.0 (1.6)	9.2 (1.7)	9.0 (2.3)
Week 156 (observed)	8.9 (1.7)	7.8 (1.5)	8.4 (1.7)	7.6 (2.0)

Abbreviations: SD: standard deviation

After week 52, study patients switching to somapacitan 0.16 mg/kg/week from the lower doses showed catch-up in height velocity, and at week 156, the observed height velocity was overall similar between the three individual somapacitan cohorts. No relevant differences in growth parameters were

observed from week 156-208 between the 39 study patients who received somapacitan since week 0 compared to the 11 study patients switching from somatropin to somapacitan at week 156.

In cohort II and Cohort III, Improvements in all height-based outcomes were observed in the treatment naïve study patients of cohort III (age above 9 years (girls) / 10 years (boys) at enrolment). Height based measure effects were maintained in the previously treated study patients in cohort II (age below 2½ years) and cohort III.

Height velocity, HVSDS and HSDS

In cohort I, overall, the values of HV, HSDS and HVSDS increased from baseline to 26 and 52 weeks for all 4 treatment groups (Table 11). A dose-response relationship in the point estimates (and observed values) was generally seen within the somapacitan dose groups after both 26 and 52 weeks for all three height-based endpoints, HV, HVSDS, and HSDS.

The estimates for change from baseline in HVSDS at week 52 did not show nominal statistical significance for either of the two highest doses of somapacitan relative to somatropin (0.16 mg/kg/week: estimated treatment difference= 1.64 [95% CI -0.02; 3.31]; 0.08 mg/kg/week: estimated treatment difference = 0.55 [95% CI -1.18; 2.29]). The difference between somapacitan 0.04 mg/kg/week and somatropin was in favour of somatropin (estimated treatment difference = -2.34 [95% CI -4.01; -0.67]).

At week 52, the HSDS change from baseline was higher for somapacitan 0.16mg/kg/week than somatropin (estimated treatment difference = 0.35 [95% CI 0.05; 0.65]). There was no difference between somapacitan 0.08 mg/kg/week and somatropin (estimated treatment difference = -0.10 [95% CI - 0.39; 0.20]). The difference between somapacitan 0.04 mg/kg/week and somatropin was in favour of somatropin (estimated treatment difference = -0.58 [95% CI -0.88; -0.28]).

Table 9 Height velocity, HVSDS, and HSDS estimates after 26 and 52 weeks in study 4172

Endpoints (estimated values)	Week	Somapacitan 0.04mg/kg/week	Somapacitan 0.08mg/kg/week	Somapacitan 0.16mg/kg/week	Somatropin 0.034mg/kg/day
Number of subjects		14	15	14	15
Height velocity (cm/year)	26	7.8	10.9	13.1	11.4
	52	7.5	9.7	11.7	9.9
HVSDS, change from baseline	26	4.59	8.49	9.85	8.23
	52	4.39	7.29	8.38	6.73
HSDS, change from baseline	26	0.27	0.63	0.87	0.71
	52	0.49	0.98	1.42	1.07

Abbreviations: HSDS: height standard deviation score, HVSDS: height velocity standard deviation score

The obtained efficacy measures for height velocity, HVSDS, and HSDS were largely maintained after 104, 156 and 208 weeks. At 156 weeks, the observed mean (SD) height velocity was 8.4 (1.7) cm/year for 0.16 mg/kg/week somapacitan and 7.6 (2.0) cm/year for somatropin, with similar increases in both groups from the baseline values of 3.8 (1.5) cm/year and 3.5 (1.6) cm/year, respectively. Observed mean (SD) changes from baseline in HSDS at week 156 were also similar with values of 2.67 (1.42) for 0.16 mg/kg/week somapacitan and 2.10 (0.85) for somatropin. Height gains achieved with somatropin were maintained after switching to somapacitan.

The baseline bone age/chronological age ratio was low and similar across all 4 treatment arms and increased moderately throughout all 208 weeks of the study to mean levels staying below 1. None of the study patients in cohort I reached near adult height during 208 weeks of study treatment.

In the previously treated subjects in cohort II and III, treatment effects in terms of the height based parameters (height velocity, HSDS, HVSDS) were maintained and in treatment naïve subjects. Increases in all height-based parameters were observed.

IGF-I SDS and IGFBP-3 SDS

In cohort I, baseline values for IGF-I SDS were similar for all doses of somapacitan and somatropin (ranging from -2.53 to -2.04). The mean IGF-I SDS remained below +2 from baseline up to week 208 in all treatment groups.

Dose-dependent increases in IGF-I SDS were observed for somapacitan up to week 52 with observed changes from baseline to week 52 of +0.98, +2.05 and +3.29 for somapacitan 0.04, 0.08 and 0.16 mg/kg/week, respectively. The observed changes from baseline at week 52 tended to be larger for somapacitan 0.16 mg/kg/week (+3.29) as compared to somatropin 0.034 mg/kg/day (+1.67). Similar trends were observed at week 104 and week 156. In line with these data, IGF-I SDS levels > 2 (peak and trough levels) tended to be observed more frequently among study patients who were treated with somapacitan at a dosage of 0.16 mg/kg/week (0-35.7% at different visits) compared to those who were treated with somapacitan at a dosage of 0.08 mg/kg/week (0% at different visits) during an observation period of one year.

Model-derived average IGF-I SDS levels for somapacitan dosages of 0.08 and 0.16 mg/kg/week at week 52 in study 4172 are presented in Table 10.

Table 10 Average IGF-I SDS at week 52 in study 4172 for somapacitan dosages of 0.08 and 0.16 mg/kg/week

Dosage (mg/kg/week)	N	IGF-I SDS < -2	IGF-I SDS -2 to 2	IGF-I SDS > 2	Mean (SD)	90% range
0.08	15	1 (6.7%)	14 (93.3%)	0 (0%)	-0.91 (0.71)	-2.07; 0.36
0.16	14	0 (0%)	13 (92.9%)	1 (7.1%)	0.55 (0.79)	-0.63; 1.62

The results for IGFBP-3 SDS showed the same tendencies as IGF-I SDS.

No relevant differences in neither IGF-I SDS nor IGFBP-3 SDS were observed from week 156-208 between the 39 study patients who received somapacitan since week 0 compared to the 11 study patients switching from somatropin to somapacitan at week 156.

In the treatment naïve study patients of cohort III, increases were observed in both pharmacodynamic endpoints, IGF-I SDS and IGFBP-3 SDS. IGF-I SDS levels remained in the normal range in these study patients. In the previously treated study patients in cohort II and III, the aforementioned parameters were maintained.

Patient reported outcomes

In cohort I, TRIM-CGHD-O, TB-CGHD-O and TB-CGHD-P all showed point estimates that tended to be larger for the highest dose of somapacitan (0.16 mg/kg/week) compared to somatropin up to week 156.

From 156 to 208 weeks, the TB-CGHD questionnaires showed a tendency of reduced treatment burden in the study patients switching from somatropin to somapacitan at week 156 for both study patients and parents, as compared to the study patients who remained on somapacitan treatment.

Study patients switching from somatropin to somapacitan at week 156 and study patients remaining on somapacitan were observed to have a similar reduction in disease burden from week 156 to 208 as measured by the TRIM-CGHD-O.

Data from the growth hormone preference questionnaire, GH-PPQ, showed that the majority (9 of 11) of the respondents had a strong or very strong preference for the once-weekly (somapacitan) over the daily (somatropin) treatment regimen. The main reasons listed included: less perceived physical pain, and emotional distress for the child.

PROs were not implemented for cohorts II or III.

2.6.5.2. Main study

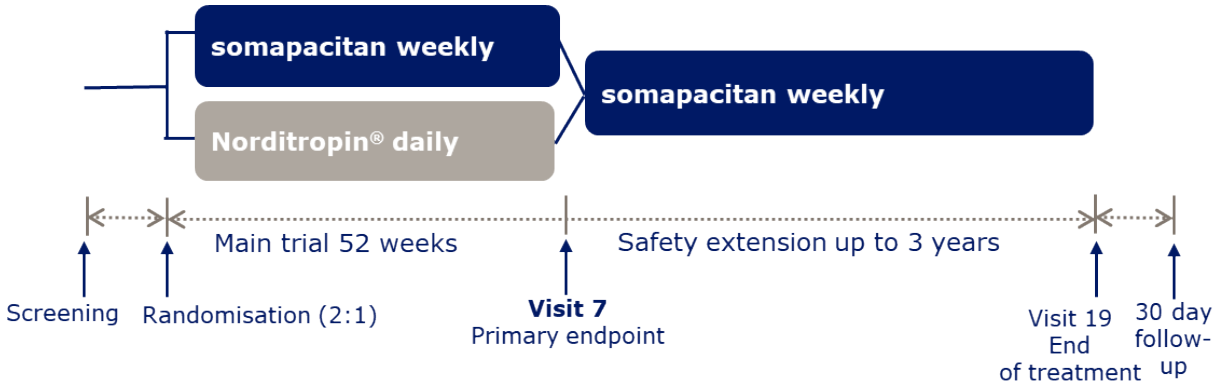
Study NN8640-4263: A study comparing the effect and safety of once-weekly dosing of somapacitan with daily somatropin in children with growth hormone deficiency (REAL 4)

Methods

The Phase 3 study NN8640-4263, further abbreviated into study 4263, is a randomized open-labelled two arm study designed to compare the efficacy and safety of once-weekly dosing of somapacitan with daily dosing of somatropin after 52 weeks in children with GHD, followed by a 3-year single-arm extension period with once weekly dosing of somapacitan to evaluate safety. For efficacy, the specific purpose of the study was to confirm the non-inferiority of somapacitan relative to somatropin medicinal product Norditropin after 52 weeks of treatment.

Two hundred (200) study patients were randomised in a 2:1 manner to receive either somapacitan or somatropin medicinal product Norditropin during the main 52-week period. Fixed doses of somapacitan (0.16 mg/kg/week) and somatropin (0.034 mg/kg/day) were used throughout the first 52 weeks. After the 52-week main period, all study patients in the somatropin group were switched to somapacitan treatment (0.16 mg/kg/week), while all study patients in the somapacitan group continued their once-weekly treatment. The safety extension period is currently ongoing.

Figure 13 Study design of confirmatory phase 3 study 4263



- Study Participants

Eligible were (all required):

- prepubertal children
- confirmed diagnosis of growth hormone deficiency determined by two different growth hormone stimulation tests performed within 12 months prior to randomisation, defined as a peak growth hormone level of ⩽ 10.0 ng/ml using the WHO International Somatropin 98/574 standard,
- FOR JAPAN ONLY: Confirmed diagnosis of growth hormone deficiency within 12 months prior to screening as determined by one growth hormone stimulation test for patients with intracranial organic disease or symptomatic hypoglycaemia and two different growth hormone stimulation tests for other study patients defined as peak growth hormone level of ≤ 6 ng/ml by assay using recombinant growth hormone standard.
- Impaired height, i.e. at least 2.0 SD below the mean height for chronological age and gender at screening,
- impaired height velocity, i.e. annualised height velocity below the 25th percentile for chronological age and gender,
- Insulin-like Growth Factor-I (IGF-I) < -1.0 SDS at screening
- No prior exposure to growth hormone therapy or IGF-I treatment.

Children were excluded with any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements; with current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening; children requiring inhaled glucocorticoid therapy at a dose of greater than 400 µg/day of inhaled budesonide or equivalents for longer than 4 consecutive weeks within the last 12 months prior to screening; diagnosis of attention deficit hyperactivity disorder; concomitant administration of other treatments that may have an effect on growth, e.g. but not limited to methylphenidate for the treatment of attention deficit hyperactivity disorder; a prior history or presence of malignancy including intracranial tumours.

Only pre-pubertal children were enrolled in the confirmatory phase 3 study 4263 to avoid interference of the pubertal growth spurt with the treatment effect.

- Treatments

Somapacitan consisted of a fixed dose of 0.16 mg/kg/week

Somatropin medicinal product Norditropin at a fixed dose of 0.034 mg/kg/day

Patients were treated for a main treatment period of 52 weeks. A 3-year safety extension period, where all study patients are allocated to somapacitan (0.16 mg/kg/week) is ongoing.

Dose reduction in consecutive steps of 25% of the current dose could be considered at the investigator's discretion for adverse events judged as probably related to study product by the investigator. If the adverse event persisted, the study patient could be discontinued and if the adverse event resolved, the dose could then be resumed to the original planned dose at the investigator's discretion. If measures of IGF-I SDS exceeded +2.5 SDS at two consecutive visits, the investigator was informed by the applicant. Dose reduction was then to be done by a 25% reduction of the current dose.

- Objectives

Primary objective

To demonstrate the efficacy of once-weekly dosing of somapacitan compared to daily treatment with somatropin after 52 weeks of treatment on longitudinal growth in children with GHD. The specific purpose of the study was to confirm the non-inferiority of somapacitan relative to somatropin after 52 weeks of treatment.

Secondary objective:

To compare the safety of somapacitan vs somatropin in children with GHD.

- Outcomes/endpoints

An overview of all defined efficacy endpoints in study 4263 (52-week main period) is presented in Table 11.

Table 11 Efficacy endpoints in study 4263

Endpoints	Study 4263 (confirmatory)
Growth related parameters	Height velocity (primary endpoint, week 52) Change in height standard deviation score (HSDS) Change in height velocity standard deviation score (HVSDS) Change in bone age
Pharmacodynamic parameter	Change in IGF-I SDS Change in IGFBP-3 SDS
Additional outcomes	
Patient- reported outcomes (PRO)a	Treatment Burden Measure- Child GHD- Observer (TB- CGHD-O) Treatment Burden Measure- Child GHD- Parent (TB- CGHD-P) Change in Treatment Related Impact measure-Child-Growth Hormone Deficiency-Observer (TRIM-CGHD-O) Growth Hormone Device Assessment Tool (G-DAT)

[a] A PPQ was also filled out by the parents/caregivers at week 56.
Notes: Secondary endpoints were not tested.

Primary endpoint: height velocity

The primary endpoint was annualised height velocity (HV) at week 52, measured in cm/year.

Height velocity was derived from height measurements taken at baseline and the week 52 visit: height velocity = (height at the 52-week visit - height at baseline)/(time from baseline to the 52-week visit in years).

Height SDS (HSDS) was derived using Centre for Disease Control and Prevention (CDC) standards5 and height velocity SDS was derived using Prader standards6 as reference data.

Secondary endpoints: IGF-I SDS and IGFBP-3 SDS and bone age

[5] Kuczmarski RJ. CDC growth Charts: United States. Advanced data from vital and health statistics. 2000.
[6] Prader. Physical growth of Swiss children from birth to 20 years of age: first Zurich longitudinal study of growth and development. Helv Paediatr Acta Suppl. 52:1-1251989 1989.

Blood samples were drawn for the assessment of IGF-I and IGFBP-3. Samples were drawn prior to study drug administration, if planned on a sampling day. The central laboratory and Novo Nordisk were responsible for providing age and sex-appropriate normal reference ranges of IGF-I and IGFBP-3 and for calculation of IGF-I SDS according to the following equation:

For determining bone age, X-ray images of left hand and wrist for bone age assessment according to the Greulich and Pyle atlas were taken. The X-ray images were sent to a central imaging laboratory for evaluation. An X-ray taken within 13 weeks prior to screening could be used as screening data if the image was acquired according to the required standards defined by the central imaging laboratory and available to be sent to the central imaging laboratory.

- Sample size

The sample size of N=200 with a 2:1 randomisation ratio would achieve close to 90% power for the primary estimand using the hypothetical strategy, using conservative assumptions for the SD and taking into account the targeted estimand, with a non-inferiority margin of a -1.8 cm/year difference between somapacitan and somatropin.

The non-inferiority margin was discussed during scientific advice, using of 1.8 cm/year difference advice EMEA/H/SA/2492/3/2018/PED/II, and was in principle supported.

- Randomisation and Blinding (masking)

Study patients were randomised in a 2:1 manner to receive either somapacitan or somatropin treatment, using a central interactive web response system.

To ensure equal distribution of important prognostic factors across treatments, the randomisation was stratified by:

- region (Japan versus rest-of-the-world)
- age group (< 6 versus ⩾ 6 years at randomisation)
- gender (boys versus girls)
- growth hormone peak level (< 7.0 versus ⩾ 7.0 ng/ml).

After the main study period of 52 weeks, all study patients initially randomised to somatropin were switched to treatment with somapacitan.

This study was open-label. The study was observer-blinded with regard to primary endpoint, i.e., the person performing the height measurements was blinded to treatment allocation. Novo Nordisk staff involved in the interpretation of all data was kept blinded during the study conduct until the database lock for the primary endpoint.

- Statistical methods

Statistical methods have been pre-specified in the protocol. No specific SAP has been developed.

Definition of analysis sets

The following analysis sets were defined in the protocol:

Full analysis set (FAS): all randomised study patients. Study patients were analysed “as randomised”.

Per protocol (PP) analysis set: study patients from the FAS who had not violated any inclusion/exclusion criteria and had used 90% of the planned exposure of randomised treatment during the main study period (corresponding to at least 47 weeks for study patients receiving somapacitan or 329 days for study patients receiving somatropin). Study patients were analysed “as treated”.

Safety analysis set (SAS): all randomised study patients were exposed to at least one dose of randomised treatment. Study patients were analysed “as treated”.

The following 2 observation periods were used in the study:

On-treatment: from the first administration and up until the last study contact, visit 7 or 14 days after the last administration, whichever comes first.

In-study: from first administration and up until visit 7 or last study contact, whichever comes first.

The data used in the primary EMA estimand (i.e. up to discontinuation of randomised treatment) was as prespecified in the protocol and described together with the statistical model. The FAS was used for evaluation of all efficacy endpoints. The PP analysis set was used for supplementary, sensitivity efficacy analyses, while the SAS was used for safety data analyses only.

Adjustment for multiplicity

No adjustment was made for multiplicity. Differing primary estimands for EMA and FDA/PMDA were not adjusted for. Secondary endpoints were not included in any kind of test hierarchy and no adjustment for multiplicity was performed. No interim analysis has been performed for the primary endpoint.

The one-sided test used for the primary endpoint is based on an alpha level of 2.5%. All other statistical tests conducted will be two-sided on the 5% significance level.

Definition and analysis of primary estimand

Differing feedback on the primary estimand from the health authorities at end of phase 2 has resulted in establishing distinct estimand strategies for FDA/PMDA and EMA.

Primary estimand for EMA: Hypothetical strategy – ancillary therapy not available: the treatment difference between somapacitan and somatropin in mean annualised HV at week 52 if ancillary therapy had not been available prior to week 52 (i.e. assuming no initiation of ancillary therapy) in children with GHD. When assessing the treatment effect on longitudinal growth, the hypothetical strategy-based estimand is expected to minimise potential confounding from ancillary therapy such as other growth hormone products. The use of ancillary therapy may attenuate the treatment effect of interest or even exaggerate the treatment effect and the estimand, thus aiming to reflect the treatment difference attributable to the initially randomised treatments.

The treatment policy strategy (primary estimand for FDA and PMDA) was considered supportive. This estimand assesses the expected benefit a future paediatric population with GHD can achieve if prescribed somapacitan compared to somatropin. By not placing any restrictions on treatment adherence, this estimand aims to obtain a difference as close as possible to the one expected in clinical practice, provided that the treatment adherence and use of ancillary therapy in trial reflects what would be seen in clinical practice.

The primary analysis of the primary endpoint addressing the hypothetical estimand was based on FAS, but data assessed after discontinuation of randomised treatment was disregarded in the analysis. To estimate this hypothetical strategy a mixed model for repeated measurements (MMRM) with an unstructured covariance matrix was conducted on height velocity data (annualized height velocity at planned visits at week 13, 26, 39 and 52) up to discontinuation of randomised treatment for each treatment group using all randomised study patients and assuming missing at random (MAR) for both

treatment groups. The MMRM included treatment, gender, age group, region, growth hormone peak group and gender by age group by region interaction term as factors and baseline height as a covariate, all nested within week as a factor.

A tipping point analysis was conducted, since one study patient discontinued treatment and thus, this study patient's visit 7 measurement was not made 'on-treatment'.

Supplementary sensitivity analysis of the primary endpoint was conducted on the PP data analysis set.

Choice of non-inferiority margin

A non-inferiority margin of -1.8 cm/year for the primary endpoint was chosen based on placebo-controlled study results for children with small for gestational age from the GHLIQUID-1424 study. In previous phase 3 studies in children with GHD, a non-inferiority margin of -1.8 to -2.0 cm/year has been applied.

Non-inferiority of somapacitan relative to somatropin was considered confirmed if the lower boundary of the two-sided 95% confidence interval of the hypothetical estimand was above -1.8 cm/year. If non-inferiority is confirmed, superiority will be considered confirmed if the lower boundary of the two-sided 95% confidence interval is above 0 cm/year.

Analysis of secondary efficacy endpoints

All supportive, secondary efficacy endpoints were analysed based on the "in-study" observation period within the main study period (52 weeks of treatment), referring to the observation period from first administration and up until visit 7 or last study contact, whichever comes first.

The two pharmacodynamic endpoints, IGF-I SDS and IGFBP-3 SDS, were analysed using the "on-treatment" observation period also (from the first administration and up until the last study contact, visit 7 or 14 days after the last administration, whichever comes first).

Secondary endpoints were not included in any kind of test hierarchy and no adjustment for multiplicity was performed.

Subgroups

In addition to the pre-specified analyses, the treatment effect of somapacitan on the primary endpoint, height velocity after 52 weeks of treatment, was evaluated in different subgroups, to assess whether the overall treatment effect of somapacitan is consistent across subgroups of region (Japan versus rest-of-the-world), age (< 6 years versus ≥ 6 years at randomisation) and gender (boys versus girls).

Results

- Participant flow

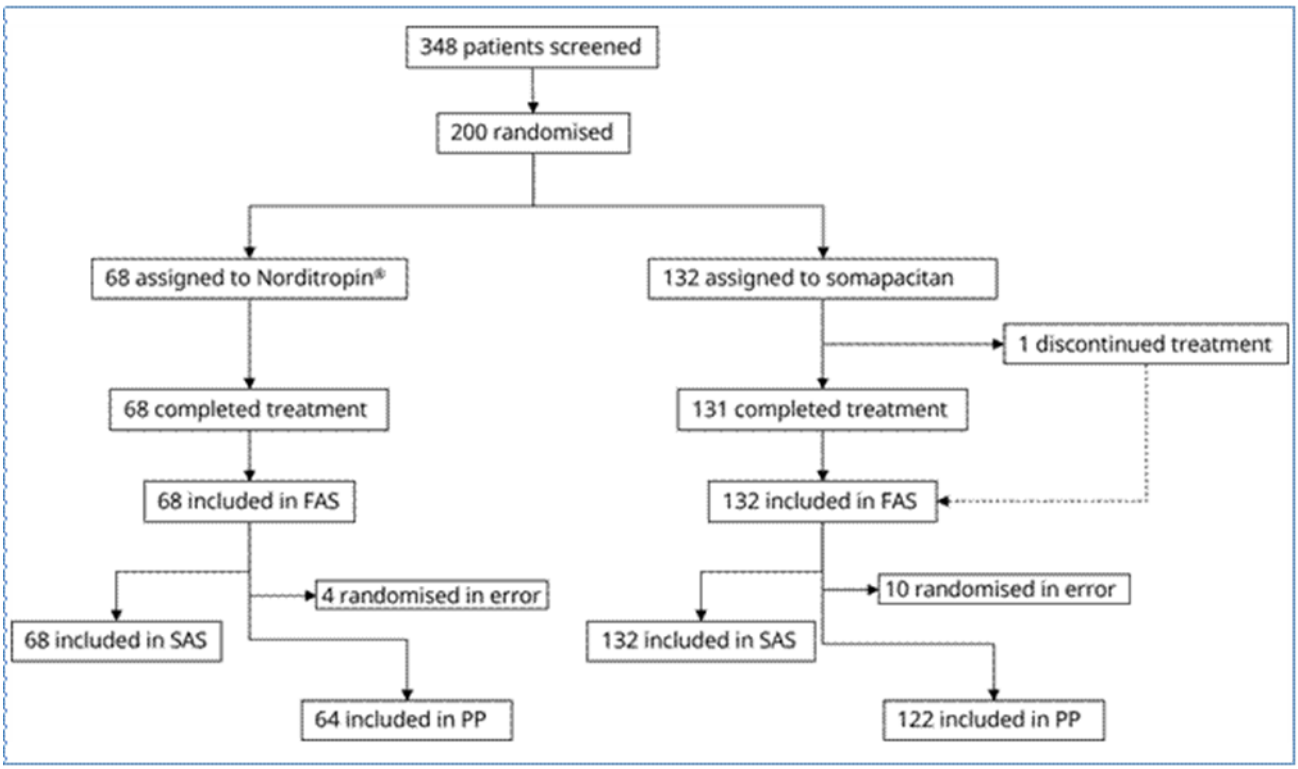
In total, 348 children were screened until the database lock of 03-Dec-2021 (Figure 14). The main reason for screen failure was violating of inclusion criterion 9 (IGF-I < -1.0 SDS at screening). Two hundred (100%) children with GHD were randomised and exposed to treatment. Of these, 132 children were exposed to somapacitan and 68 to somatropin.

Study patients discontinuing treatment were able to continue in the study to attend study visits.

All 200 paediatric GHD patients completed the study period, and 199 (99.5%) children completed the treatment period. One child in the somapacitan group discontinued treatment prematurely due to being included in the study in violation of inclusion and/or exclusion criteria.

In total, 10 children in the somapacitan group and 4 children in the somatropin group were randomised in violation of inclusion or exclusion criteria. Except for the one subject who discontinued treatment, the subjects who were randomised in error remained on treatment, as the applicant assessed that the protocol deviations did not incur any increased safety risk.

Figure 14 Study patient disposition in study 4263



- Recruitment

According to ClinicalTrials.gov the first participant was enrolled May 20, 2019. The main study period was completed on November 10th, 2021, when the primary outcome was measured for the last participant. The study is expected to be completed on December 12th, 2024.

- Conduct of the study

Protocol amendments

The original protocol was version 1.0 29 June 2018, which was amended to version 2.0 16 November 2018 for all countries, to version 3.0 on 01 July 2019 applicable in all countries. Protocol version 4.0, 5.0 and 6.0 entailed changes only applicable for Estonia, Hungary and Spain specifically.

In protocol version 7.0, released 22 February 2021 and applicable in all countries, an additional test for superiority of somapacitan versus somatropin for height velocity (HV) from baseline to week 52 was added, in case non-inferiority of somapacitan versus somatropin for the primary endpoint has been confirmed. Furthermore, some secondary endpoints for effect have been removed, as they are not found relevant in the single-arm extension period of the study.

No GCP inspection was conducted.

- Baseline data

Out of the 200 randomised study patients:

- 48.5% were below the age of 6 years
- 74.5% of the study patients were male
- the study was conducted globally and most study patients were enrolled from the United States (26.0%), Japan (15.0%), Russia (10.5%) and India (10.0%). A total of 57.0 % of the patients were white and 37.0 % were Asian.
- the GHD cause was either organic (12.0%), or idiopathic (88.0%).

Key baseline parameters in children with GHD are presented in Table 12.

Table 12 Mean (SD) baseline characteristics of study patients and endpoints in study 4263

	Somapacitan (N=132)	Somatropin (N=68)
Mean (SD)		
Age (years)	6.38 (2.23)	6.43 (2.42)
Height (cm)	102.3 (12.5)	100.2 (15.0)
Body weight (kg)	16.69 (4.60)	16.01 (4.95)
BMI (kg/m^2)	15.70 (1.59)	15.59 (1.38)
GH peak (ug/l)	4.93 (2.50)	4.10 (2.77)
Mothers height (cm)	159.3 (7.6)	158.1 (7.1)
Fathers height (cm)	171.5 (8.7)	170.3 (8.0)
HV (cm/year)	4.3 (1.4)	4.1 (1.4)
HVSDS	-2.35 (1.51)	-2.52 (1.55)
HSDS	-2.99 (1.02)	-3.47 (1.52)
IGF-I SDS	-2.03 (0.97)	-2.33 (1.03)

Abbreviations: BMI: body mass index, GH: growth hormone, HV: height velocity, HVSDS: height velocity standard deviation score, HSDS: height standard deviation score, IGF-I: Insulin-like growth factor 1

The mid-parental height (standard deviation) in the somapacitan and somatropin treatment groups were similar (168.8 (8.6) versus 167.2 (8.7) cm).

At screening, mean bone age was 4.15 years (min: 0.3 years; max: 9.0 years) in the somapacitan group and 4.24 years (min: 1.3 years; max: 9.0 years) in the somatropin group. The mean chronological age at baseline was 6.38 years (min: 2.5 years; max: 10.8 years) in the somapacitan group and 6.43 years (min: 2.7 years; max: 11.0 years) in the somatropin group.

Measures of laboratory parameters at screening (glucose metabolism, haematology and hormones) and baseline (biochemistry and lipids) were similar between the somapacitan and somatropin group.

Adherence

Adherence to treatment was assessed via study patient e-diaries. The majority of children received the planned treatment with a mean adherence among study patients on treatment (i.e. not counting

exposure duration in 1 study patient after discontinuing treatment) of 95.8% for the somapacitan group and 88.3% for the somatropin group.

- Numbers analysed

All 200 randomised children were included in both the full analysis set (FAS) and the safety analysis set (SAS): 132 children in the somapacitan group and 68 children in the somatropin group.

From the per protocol analysis set 14 (7%) children were excluded, 10 in the somapacitan group and 4 in the somatropin group.

One subject discontinued the study product in the somapacitan group.

- Outcomes and estimation

Primary estimand: height velocity at week 52

The primary endpoint, height velocity at week 52 (annualised) was analysed using two different estimands. For EMA the primary estimand was hypothetical. Only 1 study patient discontinued treatment in the somapacitan group during the 52-week main period of the study. Similar increases in height velocities across all 4 quartiles of the midparental height were observed at week 52.

For FDA and PMDA the treatment policy estimand was the primary estimand. The results are presented below.

Table 13 Height velocity (cm/year) at week 52 in study 4263 (full analysis set)

	Somapacitan estimated mean (n=132)	Somatropin estimated mean (n= 68)	ETD (somapacitan-somatropin)	95% CI
Height velocity-hypothetical strategy – EMA primary (cm/year)	11.2	11.7	-0.5	[-1.1; 0.2]
Height velocity-treatment policy (cm/year)	11.2	11.7	-0.5	[-1.1; 0.2]

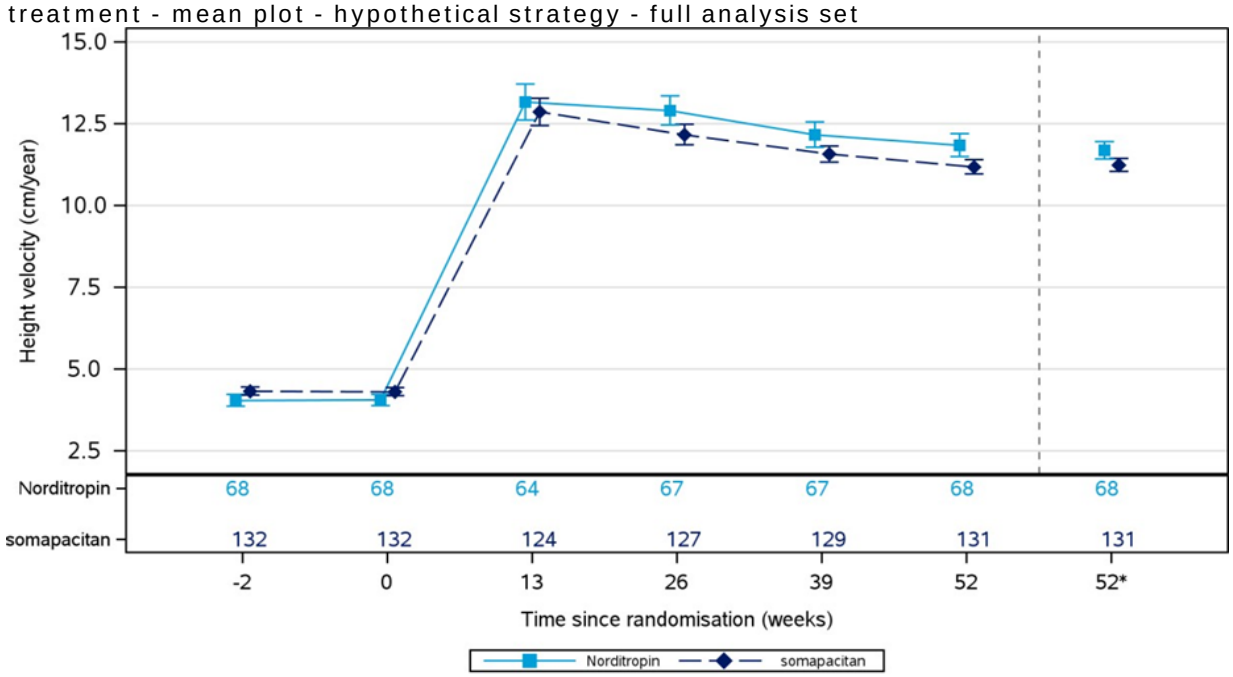
Notes: Height velocity at week 52 was analysed using an analysis of covariance model with treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors, and baseline height, HVSDS, HSDS and bone age, as covariates, respectively. The hypothetical estimand was estimated using MMRM.
Abbreviations: CI: confidence interval; ETD: estimated treatment difference; HSDS: height standard deviation score; HVSDS: height velocity standard deviation scores; N/A: not applicable.

Non-inferiority of somapacitan relative to somatropin medicinal product Norditropin was confirmed for the hypothetical estimand as the lower bound of the 95% confidence interval (-1.1 cm/year) was higher than the predefined non-inferiority margin of -1.8 cm/year. The treatment policy estimand supported this conclusion.

Superiority of somapacitan relative to somatropin was rejected.

Figure 15 presents the height velocity by visit.

Figure 15 Study 4263 (main 52-week period) - Height velocity (cm/year) by visit - on-treatment - mean plot - hypothetical strategy - full analysis set



Error bars: +/- Standard error (mean)
Observed data.
Height velocity at baseline is based on the pre screening height measurement used for inclusion criteria 5.
*Estimated mean from the statistical analysis.

nn8640/nn8640-4263-main/ctr_20220215_er
25FEB2022:07:59:02 - fmeanplot.sas/fvshvmeanontrfas.png

Secondary outcomes (supportive): HVSDS, HSDS and bone age

For the secondary growth-related endpoints, change from baseline to week 52 in HVSDS, HSDS and bone age, the in-study observation data sets were used for all analyses (from first administration and up until visit 7 or last study contact, whichever comes first), resulting in a treatment policy estimand.

Across all growth efficacy measures, increases from baseline were observed for both somapacitan and somatropin after 52 weeks of treatment (Table 14).

Table 14 Estimated change from baseline to week 52 for HVSDS, HSDS and bone age in study 4263

	Somapacitan estimated mean (n=132)	Somatropin estimated mean (n=68)	ETD (somapacitan-somatropin)	[95%CI]
HVSDS	8.05	8.82	-0.78	[-1.63; 0.08]
HSDS	1.25	1.30	-0.05	[-0.18; 0.08]
Bone age/ chronological age	0.06	0.08	-0.02	[-0.06; 0.01]

Notes: Change from baseline in HVSDS, HSDS and change in bone age to chronological age ratio was analysed using an analysis of covariance model with treatment, gender, age group, region, GH peak group and gender by age group by region interaction term as factors, and baseline height, HVSDS, HSDS and bone age, as covariates, respectively.

Abbreviations: CI: confidence interval; ETD: estimated treatment difference; HSDS: height standard deviation score; HVSDS: height velocity standard deviation scores; N/A: not applicable.

From baseline to week 52, the observed mean (SD) HSDS increased from -2.99 (1.02) to -1.78 (0.95) for somapacitan and from -3.47 (1.52) to -2.09 (1.12) for somatropin.

The observed mean (SD) HVSDS increased from -2.35 (1.51) to 5.61 (2.85) for somapacitan and from -2.52 (1.55) to 6.45 (3.51) for somatropin, from baseline to week 52.

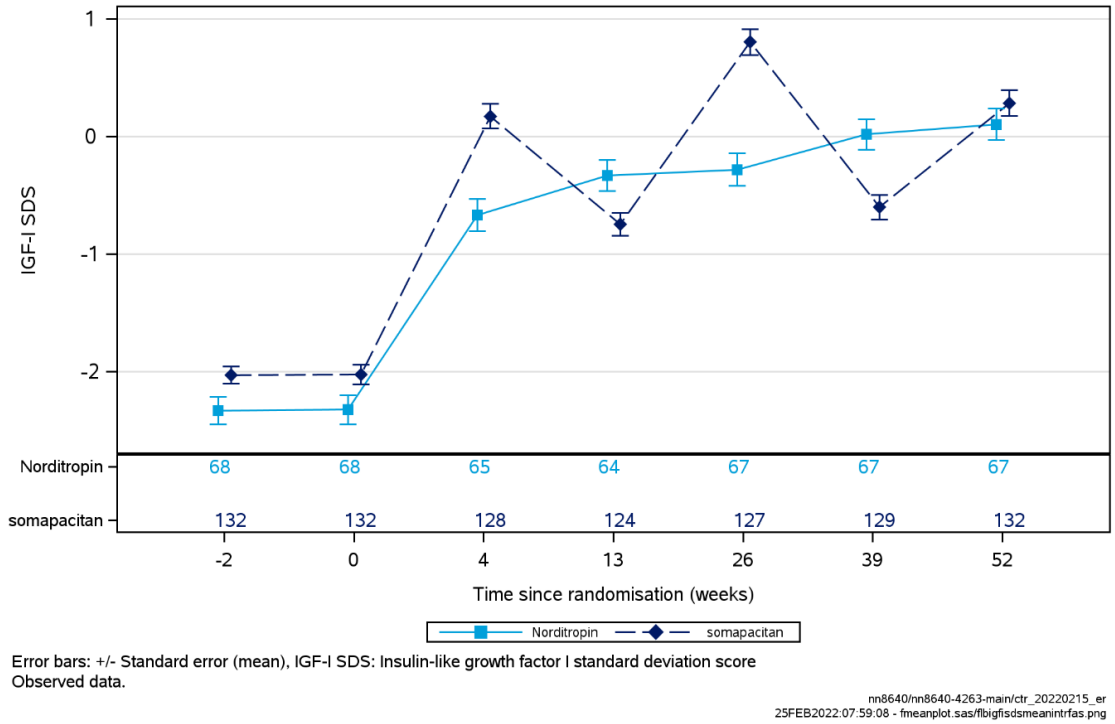
Moderate increases in bone age/chronological age ratio (generally staying below 1) were observed from baseline to week 52 for both treatment groups. The observed mean (SD) bone age (years) increased moderately from 4.15 (1.74) to 5.30 (2.02) for somapacitan and from 4.24 (2.01) to 5.52 (2.22) for somatropin, from baseline to week 52, respectively.

Secondary outcomes (supportive): *IGF-I SDS and IGFBP-3 SDS*

IGF-I SDS increased rapidly from baseline after initiating treatment with both somapacitan and somatropin (Figure 16). The observed mean IGF-I SDS increased from very low baseline levels (below -2) in both treatment groups to week 52 values within the normal range (-2 to +2). The vast majority (97%) of study patients in the somapacitan group had average IGF-I SDS levels within normal range (-2 to +2) after 52 weeks of treatment.

The IGF-I samples depicted here were taken at different time points after dosing: week 4 and week 26: day 1-4 after dosing (around peak IGF-I SDS level); week 13 and week 39: day 7 after dosing (around trough IGF-I SDS level); week 52: day 4-6 after dosing (around average IGF-I SDS level).

Figure 16 Study 4263 (main 52-week period) - IGF-I SDS by visit – in-study – mean plot – full analysis set



Error bars: +/- Standard error (mean), IGF-I SDS: Insulin-like growth factor I standard deviation score
Observed data.

nn8640/nn8640-4263-main/ctr_20220215_er
25FEB2022:07:59:08 - fmeanplot.sas/flbigfisdsmeanintrfas.png

Notes: IGF-I samples in the somapacitan group were taken at different time points after dosing: week 4 and week 26: day 1-4 after dosing (around peak IGF-I SDS level), week 13 and week 39: day 7 after dosing (around trough IGF-I SDS level), week 52: day 4-6 after dosing (around average IGF-I SDS level).

The observed mean IGF-I SDS (SD) at week 52 using the in-study observation period was 0.28 (1.28) for somapacitan and 0.10 (1.09) for somatropin. Change from baseline to week 52 in IGF-I SDS was similar between the two treatment groups; ETD (somapacitan - somatropin) = 0.03 [95% CI -0.30; 0.36]. The estimated increases of IGF-I SDS from baseline at 52 weeks (in-study data) were 2.36 for somapacitan and 2.33 for somatropin.

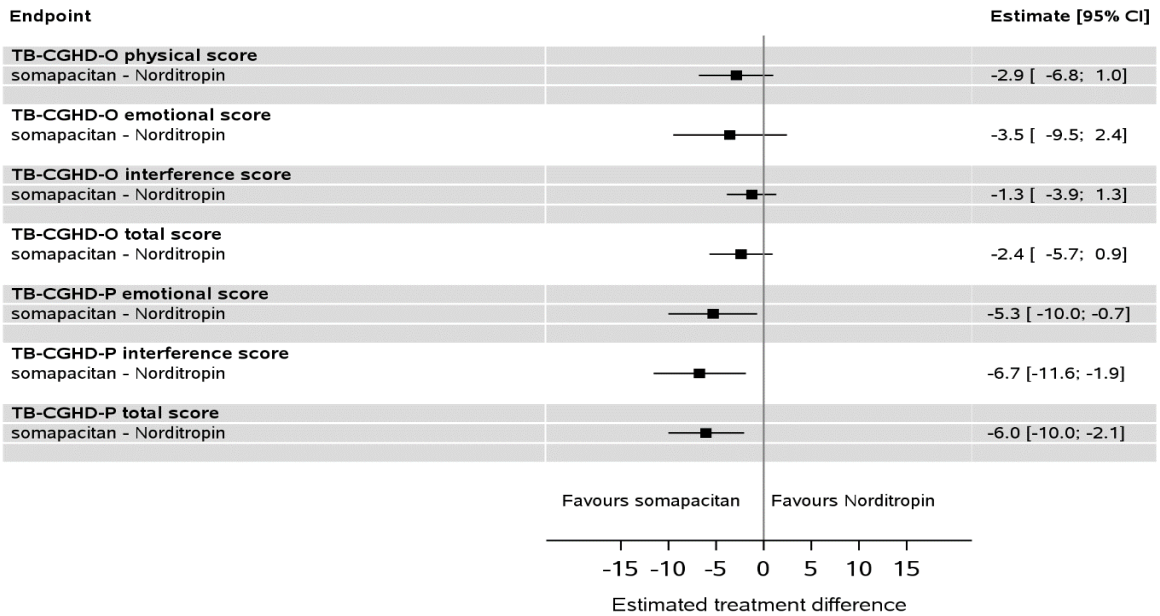
The observed mean (SD) IGFBP-3 SDS levels were -0.33 (0.96) and -0.46 (0.94) for somapacitan and somatropin, respectively (in-study data). The estimated increases from baseline for IGFBP-3 at week 52 were 1.61 in both treatment groups. Changes from baseline in IGFBP-3 SDS levels (in-study data) were similar for somapacitan and somatropin (estimated treatment difference 0.01 (95% CI -0.22; 0.23)).

Patient reported outcomes

The disease specific TRIM-CGHD-O questionnaire was applied to assess the disease burden of growth hormone deficiency on children diagnosed with GHD. Comparable improvements were seen in both treatment groups, assessed as decreased scores relative to baseline in all 3 domain scores (physical functioning, emotional well-being, social well-being) and total score of TRIM-CGHD-O, were observed in both treatment groups after 52 weeks.

Disease specific questionnaires were applied to measure the burden of growth hormone treatment on the study patients (TB-CGHD-O) and on the parents/LARs (TB-CGHD-P). At week 52 results favoured somapacitan over somatropin (Figure 17).

Figure 17 Study 4263 - Treatment burden measure – child growth hormone deficiency – scores after 52 weeks - forest plot



CI: Confidence interval, Estimate: Estimated treatment difference, TB-CGHD-O: Treatment burden measure - child growth hormone deficiency - observer, TB-CGHD-P: Treatment burden measure - child growth hormone deficiency - parent

The same high proportion of respondents (96%) found the somapacitan and somatropin devices to be easy or very easy to use. A high proportion of respondents (>90%) found the devices easy or very easy to learn to use (G-DAT).

- Ancillary analyses

The efficacy of somapacitan on the primary endpoint (height velocity after 52 weeks) was in study 4263 evaluated in different intrinsic subgroups including demographic factors (age, gender and previous growth hormone treatment status).

Meeting selection criteria

15 subject-level protocol deviations were reported for 14 study patients in Phase 3 study 4263 (10 study patients in the somapacitan group [7.6%] and 4 subjects in the somatropin group [5.9%]), who were randomised in violation of inclusion or exclusion criteria. Most of these study patients stayed on treatment since the protocol deviations were assessed not to incur safety issues.

The results for the per protocol analysis i.e. upon exclusion of the 14 subjects who did not meet the selection criteria for inclusion in study 4263 were almost identical to the results from the full on-treatment observation period data set (all included study patients): estimated treatment difference of -0.5 cm/year [95% CI -1.2; 0.2] for the per protocol analysis versus -0.5 cm/year [95% CI -1.1; 0.2] for the primary analysis.

Age group

The estimated treatment differences for height velocity after 52 weeks were similar between the two age groups as seen in Table 17. A slightly greater increase in the estimated height velocity after 52 weeks was observed for the youngest children (<6 years) relative to the older study patients (≥ 6 years) for both treatment groups.

Table 15 Height velocity after 52 weeks by age for somapacitan vs. somatropin in study 4263

Height velocity, 52 weeks	Somapacitan	Norditropin	ETD	[95% CI]
Age < 6 years				
N	64	33		
Height velocity estimate (cm/year)	12.2	12.6	-0.4	[-1.4; 0.7]
Age ≥ 6 years				
N	68	35		
Height velocity estimate (cm/year)	10.3	11.0	-0.7	[-1.5; 0.1]

Notes: Height velocity at week 52 was analysed using an analysis of covariance model with treatment, gender, region, GH peak group and gender by region interaction term as factors, and baseline height as covariate. There were no missing values at week 52, so no multiple imputation was done.
Abbreviations: CI: confidence interval; ETD: estimated treatment difference; N = number of study patients contributing to the analysis

Gender

The estimated treatment differences for height velocity after 52 weeks were similar for both sexes as seen in Table 16.

Table 16 Height velocity after 52 weeks by sex for somapacitan vs somatropin in study 4263

Height velocity, 52 weeks	Somapacitan	Somatropin	ETD	[95% CI]
Female study patients				
N	33	18		
Height velocity estimate (cm/year)	11.8	12.3	-0.5	[-2.2; 1.1]
Male study patients				
N	50	50		
Height velocity estimate (cm/year)	11.1	11.5	-0.4	[-1.1; 0.3]

Notes: Height velocity at week 52 was analysed using an analysis of covariance model with treatment, age group, region, GH peak group and age group by region interaction term as factors, and baseline height as covariate. There were no missing values at week 52, so no multiple imputation was done.
Abbreviations: CI: confidence interval; ETD: estimated treatment difference; N = number of study patients contributing to the analysis

Treatment naïve vs previously treated

All study patients in study 4263 and cohort I of study 4172 were treatment-naïve at randomisation. The previously treated study patients of cohort III from study 4172 showed overall maintained growth and pharmacodynamic endpoint levels after initiating somapacitan treatment.

Growth hormone peak level

In CHMP scientific advice EMEA/H/SA/2492/3/2018/PED/II it was advised to define growth hormone deficiency based on a peak growth hormone level of <7 ng/ml instead of the currently applied level of ≤10 ng/ml in study 4263.

In several *post-hoc* analyses, the pharmacodynamic and efficacy evaluations were analysed for a peak growth hormone level < 7 ng/ml and a peak growth hormone level ≥ 7 ng/ml (Table 17).

Table 17 Results efficacy and pharmacodynamic endpoints in pivotal Phase 3 study 4263 based on peak growth hormone level cut-off at 7 ng/ml.

	Peak growth hormone level <7 ng/ml		Peak growth hormone level **≥7** ng/ml	
	Somapacitan (n= 100)	Somatropin (n=54)	Somapacitan (n= 32)	Somatropin (n=14)
Height velocity (cm/year) at week 52	11.4	12.2	10.6	10.0
Estimated treatment difference (95% CI)	-0.7 (-1.5; 0.1)		0.6 (-0.4; 1.6)	

Change from baseline in IGF-I SDS at week 52	2.39	2.46	2.29	1.81
Estimated treatment difference (95% CI) P-value	-0.07 (-0.45; 0.31) P= 0.70		0.48 (-0.17; 1.12) P= 0.14	
Change from baseline in height SDS at week 52	1.30	1.41	1.08	0.91
Estimated treatment difference (95% CI) P-value	-0.11 (-0.27; 0.05) P= 0.16		0.17 (-0.03; 0.36) P= 0.09	
Height velocity SDS at week 52	8.41	9.49	6.85	6.39
Estimated treatment difference (95% CI) P-value	-1.09 (-2.12; -0.06) P= 0.04		0.47 (-0.84; 1.77) P= 0.47	
Change from baseline in bone age versus chronological age ratio P-value	0.05	0.07	0.07	0.10
Estimated treatment difference (95% CI) P-value	-0.02 (-0.06; 0.02) P= 0.31		-0.03 (-0.09; 0.03) P= 0.32	

Growth parameters for both study treatments tended to increase, for peak growth hormone levels < 7 ng/ml and those ≥ 7 ng/ml.

The observed height velocities at week 52 were similar between the somapacitan and somatropin groups, regardless of growth hormone peak level. Overall similar results for both study patients with growth hormone peak <7 ng/ml (estimated treatment difference (ETD) = -0.7 cm/year [95% CI -1.5;

0.1]) and study patients with GH peak ⩾7 ng/mL (ETD= 0.6 cm/year [95% CI -0.4; 1.6]) compared to the primary analysis of the total population (ETD= -0.5 cm/year [95% CI -1.1; 0.2]).

Analyses of changes from baseline IGF-I SDS showed similar effects of growth hormone treatment on IGF-I level changes for GHD study patients with growth hormone peak <7 ng/ml (ETD= -0.07 [95% CI -0.45; 0.31]), GHD study patients with growth hormone peak ⩾7 ng/mL (ETD= 0.48 [95% CI -0.17; 1.12]), and for the entire study population (ETD= 0.03 [95% CI -0.30; 0.36]).

- Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18 Summary of efficacy for study 4263

NN8640-4263		
Title	A study comparing the effect and safety of once weekly dosing of somapacitan with daily somatropin medicinal product Norditropin® in children with growth hormone deficiency (REAL 4)	
Study identifier	Protocol number: NN8640-4263 EudraCT number: 2018-000231-27 Study 4263 (M 5.3.5.1)	
Data cut-off date	The results presented reflect the data available in the clinical database as of: 1) 03-Dec-2021 (all data except some anti-somapacitan antibody and pharmacokinetic data and 4 bone age assessments). 2) 17-Dec-2021 (adding the remaining anti somapacitan antibody data, pharmacokinetic data and bone age assessments)	
Design	The study was a randomised open-labelled two-group (somapacitan and somatropin) study investigating the effect and safety of once-weekly somapacitan treatment compared to daily somatropin in growth hormone treatment naïve pre-pubertal children with GHD. The study consisted of a 52-week main period (completed), followed by a 3-year single-group extension period (ongoing) with once-weekly dosing of somapacitan to evaluate safety. The total study duration for a study patient will be 4 years and the follow-up period will be a minimum of 30 days. The doses up to week 52 were 0.16 mg/kg/week for somapacitan and 0.034 mg/kg/day for somatropin. After completion of the main phase at week 52, the somatropin study patients were all switched to 0.16 mg/kg/week somapacitan for the rest of the study. This table covers the results of the main 52 week phase.	
	Duration of treatment (main phase) Duration of treatment (extension phase) Duration of observation (extension phase)	52 weeks 156 weeks+30 days follow-up. Ongoing as of 18-Mar-2022. 208 weeks in total
Objectives	Primary objective: • To compare the effect of somapacitan vs somatropin on longitudinal growth in children with growth hormone deficiency, aiming to demonstrate non-inferiority of height velocity during 52 weeks of treatment. Secondary objectives: • To compare the safety of somapacitan vs somatropin in children with growth hormone deficiency.	
Treatment groups	Somapacitan 0.16 mg/kg/week	132 study patients randomised
	Somatropin 0.034 mg/kg/day	68 study patients randomised

NN8640-4263			
Endpoints and definitions	Primary endpoints: • Height velocity (HV) (cm/year) during the first 52 weeks of treatment. Primary estimand (EMA); Hypothetical strategy - ancillary therapy not available: The treatment difference between somapacitan and Somatropin in mean annualised HV at week 52 if ancillary therapy had not been available prior to week 52 (i.e., assuming no initiation of ancillary therapy) in children with GHD. A hypothetical strategy was chosen, as initiation of ancillary therapy may make the treatments look more similar, tending towards non-inferiority. Non-inferiority testing: a non-inferiority margin of -1.8 cm/year for the primary endpoint was chosen. Thus, non-inferiority of somapacitan relative to somatropin would be confirmed if lower bound of the 95% confidence interval was higher than the non-inferiority margin of -1.8 cm/year.		
	Confirmatory secondary endpoint: There were no confirmatory secondary endpoints in study NN8640-4263 (REAL 4)		
	Supportive secondary endpoints: Change from baseline to week 52 in: HVSDS, HSDS, bone age, IGF-I SDS and IGFBP-3 SDS.		
RESULTS AND ANALYSIS			
Analysis description	Primary analysis (hypothetical estimand)		
Analysis set	The full analysis set included all randomised study patients. Study patients will be analysed “as randomised”.		
Results		Somapacitan 0.16 mg/kg/week[a]	Somatropin 0.034 mg/kg/day[a]
	Number of study patients (FAS)	132	68
Growth parameters	HV at week 52 (primary endpoint): Estimated mean values (cm/year): ETD [95% CI] vs Somatropin Non-inferiority relative to somatropin	11.2 -0.5 [−1.1; 0.2] Confirmed as -1.1 > -1.8	11.7 -
	Supportive secondary and exploratory endpoints		
	Change from baseline in HVSDS at week 52 ETD [95% CI] vs somatropin	8.05 -0.78 [−1.63; 0.08]	8.82
	Change from baseline in HSDS at week 52 ETD [95% CI] vs somatropin	1.25 -0.05 [−1.63; 0.08]	1.30
	Change from baseline in bone age/chronological age at week 52 ETD [95% CI] vs somatropin	0.06 -0.02 [-0.06; 0.01]	0.08

NN8640-4263			
Pharmacodynamic parameters	Change from baseline in IGF-I SDS at week 52 ETD [95% CI] vs somatropin	2.37 0.04 [-0.29; 0.37]	2.37
	Change from baseline in IGFBP-3 SDS at week 52 ETD [95% CI] vs somatropin	1.62 0.02 [-0.21; 0.24]	1.61

Abbreviations: CI: confidence interval, ETD: estimated treatment difference.
Values presented for individual treatment groups are estimated means

2.6.5.3. Clinical studies in special populations

No patients aged 65 years and above have been included in conducted clinical studies.

The clinical effects of somapacitan have not been evaluated in paediatric GHD patients with renal or hepatic impairment. However, information on respective impairments is available in the SmPC of somapacitan.

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

2.6.5.5. Analysis performed across trials (pooled analyses and meta-analysis)

Across study comparisons should in general be evaluated with caution, i.e. for study 4263 and 4172 there were differences in study size and exposure duration. Three of the most important growth-related efficacy measures at week 52 for study patients receiving 0.16 mg/kg/week of somapacitan in both studies are shown in Table 19.

Table 19 Efficacy estimates at week 52, comparison of studies 4263 and 4172, in-study

	Somapacitan (0.16 mg/kg/week)		Somatropin (0.034 mg/kg/day)	
Study	4263	4172	4263	4172
Study patients	(n=132)	(n=14)	(n=68)	(n=14)
Endpoint (52 weeks)				
Height velocity (cm/year)	11.2	11.7	11.7	9.9
Change from baseline in HVSDS	8.05	8.38	8.82	6.73
Change from baseline in HSDS	1.25	1.42	1.30	1.07

Abbreviations: HVSDS: height velocity standard deviation score; HSDS: height standard deviation score

Height velocity and change from baseline in HSDS and HVSDS at week 52 were similar for somapacitan (0.16 mg/kg/week) in both studies, whereas the estimates were somewhat lower for somatropin in the smaller study 4172, compared to study 4263. Notably, these lower values were based on 14 study patients only.

Mean IGF-I SDS levels stayed within the normal range in both studies. Observed and average (model-derived) IGF-I SDS at week 52 was similar between the two studies (mean of 0.53 in study 4263 and mean of 0.55 in study 4172).

2.6.5.6. Supportive studies

Study 4263 – after week 52

Efficacy data from the ongoing part of the phase 3 study 4263 are summarised below based on the 'in-study' observation period.

Study patient disposition – ongoing study phase

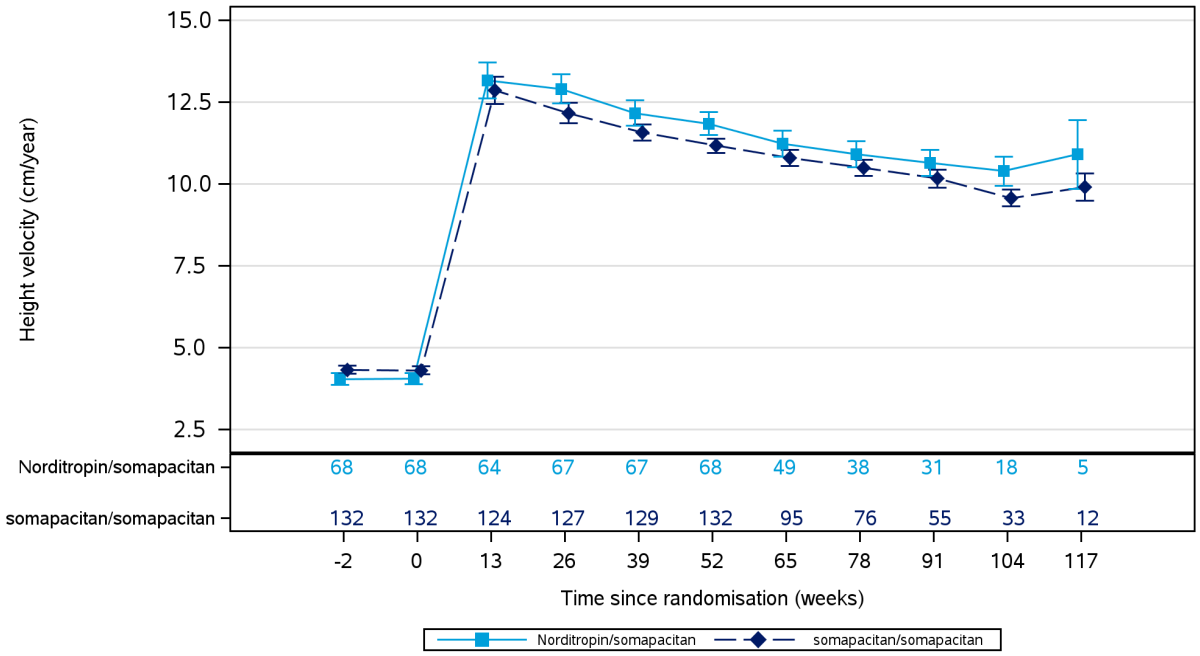
At the data cut point (10-Nov-2021), 68 study patients in the somatropin/somapacitan group and 130 study patients in the somapacitan/somapacitan group had entered into the safety extension phase. At the data cut point (10-Nov-2021), a total of 4 study patients in the somapacitan/somapacitan group had withdrawn from the study due to withdrawal by parent/legally authorized representative, lost to follow-up, or other, non- specified reason.

Growth based parameters – ongoing study phase

Height velocity beyond 52 weeks, in-study

Mean height velocity (cm/year) showed continuously maintained effects beyond week 52 in both the somapacitan/somapacitan group (study patients who were randomised to somapacitan at week 0) and the somatropin/somapacitan group (study patients who were randomised to somatropin at week 0 and switched to somapacitan at week 52) (Figure 18). Overall, increases in height velocity compared to baseline were maintained up to week 117, although height velocity gradually declined over time after the initial increase observed at week 13.

Figure 18 Height velocity up to week 117 by visit, in-study, mean plot, FAS



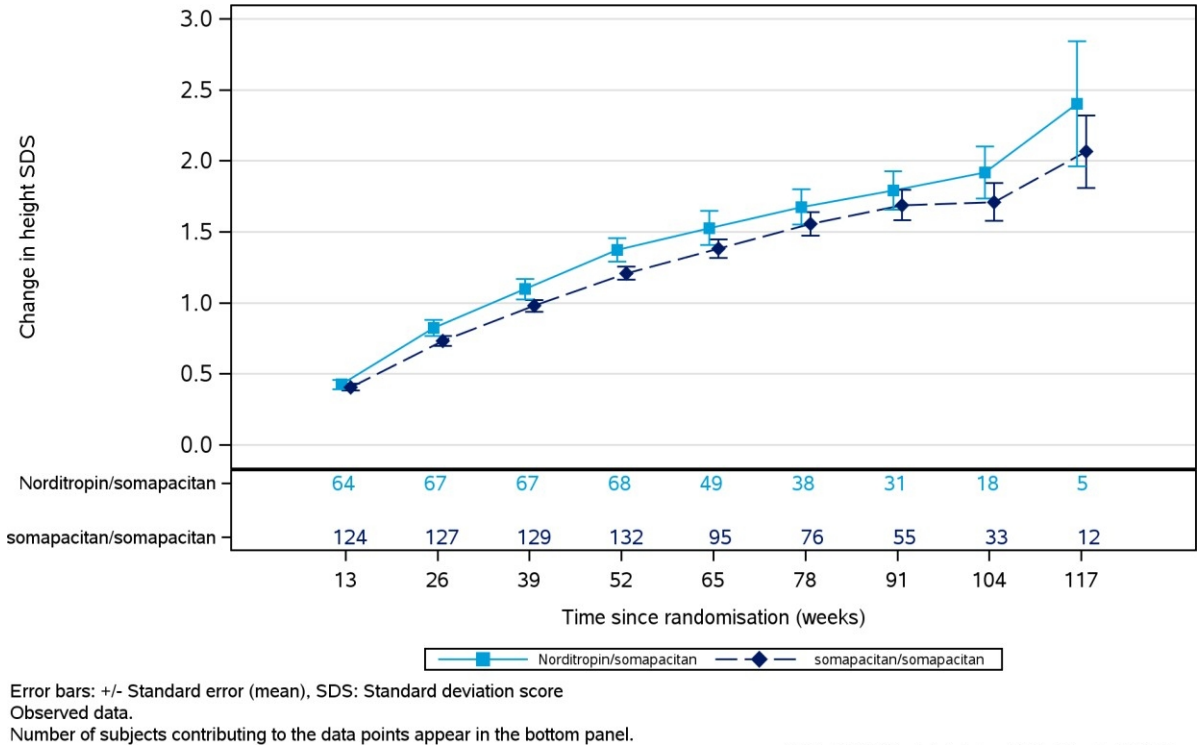
Error bars: +/- Standard error (mean)
Observed data.
Number of subjects contributing to the data points appear in the bottom panel.
Height velocity at baseline is based on the pre screening height measurement used for inclusion criteria 5.

HSDS beyond 52 weeks, in-study

Change from baseline in HSDS followed the trend from the main 52-week phase of the study and increased continuously from week 52 to week 104 for both treatment groups. HSDS appeared to increase to the same extent in the somapacitan/somapacitan group and the somatropin/somapacitan group.

Similar to the results described for height velocity, very few study patients contributed to the later timepoints, causing the apparent decreases at weeks 104 and 117 of observed HSDS. When evaluating HSDS over time solely in the study patients having completed up to week 104 or up to week 117, it was seen that HSDS increased continuously in these study patients in both treatment groups.

Figure 19 Change from baseline HSDS by visit up to week 117– mean plot – in-study - FAS



Error bars: +/- Standard error (mean), SDS: Standard deviation score
Observed data.
Number of subjects contributing to the data points appear in the bottom panel.

HVSDS beyond 52 weeks, in-study

Change from baseline in HVSDS followed the same trend as height velocity from week 52 to week 104, as from week 13 to week 52, i.e. continuing the same expected, slightly, decreasing levels over time.

Similar conclusions regarding decreasing the number of study patients over the last visits as presented above for the observed values of height velocity and HSDS, also apply for HVSDS.

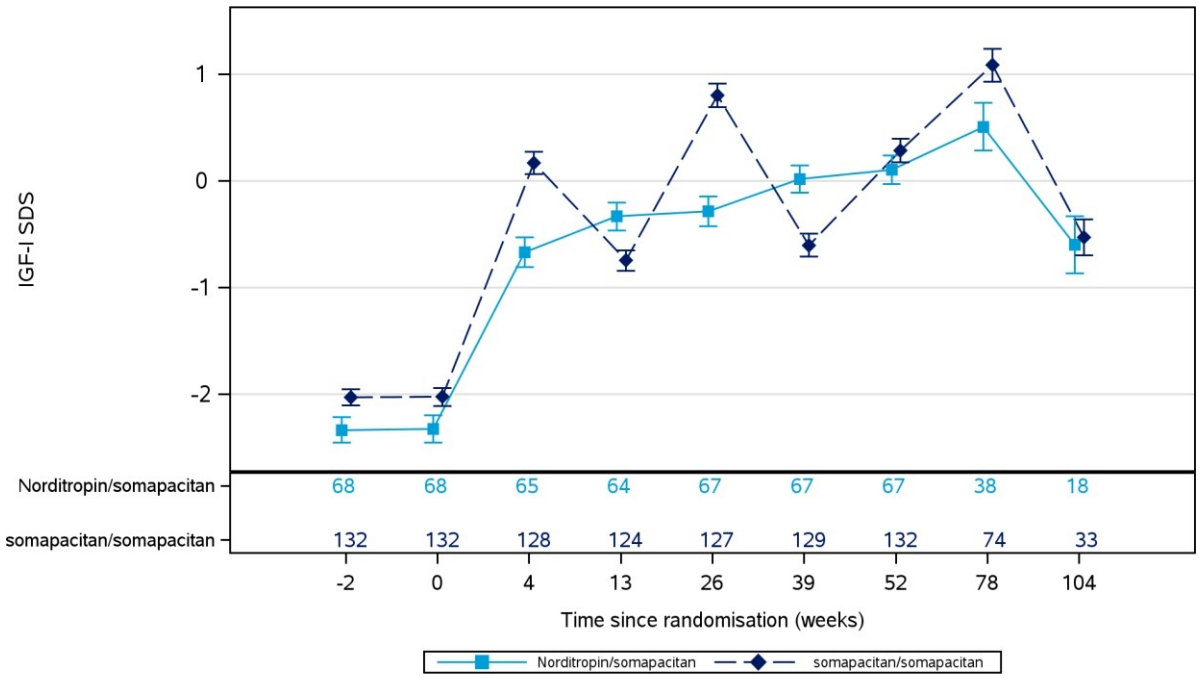
Bone age beyond 52 weeks, in-study

Bone age measures were performed only at baseline and the week 52 and 104 visits. Bone age increased from baseline in both treatment groups until week 104. The bone age to chronological age ratio generally stayed below 1 in both treatment groups, also after 104 weeks of treatment.

IGF-I SDS

Observed IGF-I SDS levels up to week 104 were similar to the levels observed in the 52-week main phase (Figure 20). Mean IGF-I SDS levels up to week 104 (last available assessment) stayed within the normal range [-2; 2] in both the somapacitan/somapacitan group and the somatropin/somapacitan group. The study patients switching from somatropin to somapacitan at week 52 showed a similar development in mean observed IGF-I SDS up to week 104 as the study patients already on somapacitan (-0.53 for somapacitan/somapacitan and -0.60 for somatropin/somapacitan). No IGF-I SDS data for visits later than week 104 were available at the data cut-point.

Figure 20 IGF-SDS by visit up to week 104 -in-study – mean plot – FAS



Error bars: +/- Standard error (mean), IGF-I SDS: Insulin-like growth factor I standard deviation score
Observed data.
Number of subjects contributing to the data points appear in the bottom panel.

PRO data

At the cut-off of 10-Nov-2021, responses to the GH-PPQ at week 56 of study 4263, had been collected for 41 of the 68 study patients switching from somatropin to somapacitan after week 52.

37 of the 41 study patients preferred somapacitan to somatropin, while the remaining 4 study patients had no preference. 31 of the 37 study patients who preferred somapacitan, reported “strong” or “very strong” preference for somapacitan. 28 of the 37 reported they would be more adherent to somapacitan, once-weekly, than to daily growth hormone treatment, while 8/37 reported they did not expect difference in adherence between the two treatments. One study patient (1/37) reported expectation of higher adherence to somatropin.

The top selected reasons listed for preferring somapacitan to somatropin were: “number of times needing to do injections” (20 of 37), “less worried about remembering to give injections” (16 of 37) and “child less worried about getting injections” (12 of 37).

Study 4172 – after week 208

In this section, selected efficacy results for the supportive study 4172 extending beyond week 208 up to week 286 for cohort I and up to week 65 and week 52, for cohorts II and III, respectively, are presented.

Study patient disposition – ongoing study phase

There were no study patient discontinuations in the long-term safety extension period (from week 156 to week 364) in neither cohort I, nor in cohorts II or III.

Growth parameters in cohort I

Growth benefits as assessed by height velocity, HVSDS, and HSDS were at least maintained after week 208 up to week 286. Mean height velocity ranged from 6-8 cm/year at most visits. Mean HVSDS

stayed above 0. Generally, data at the latter visits were available for relatively few study patients, suggesting that results should be interpreted with caution.

No study patients reached near adult height in cohort I.

IGF-I SDS followed the same trajectory as observed until week 156 up to week 286 and overall stayed within normal levels [-2; 2].

The bone age/chronological age ratio followed the same trends as observed until week 156 overall staying below 1 up to week 260.

Growth parameters in cohorts II and III

Data were consistent with initially obtained results: Overall, improvements in all height-based outcomes were observed in the treatment naïve study patients of cohort III (age above 9 years (girls) / 10 years (boys) at enrolment) and were maintained in the previously treated study patients in cohort II (age below 2½ years) and cohort III.

No study patients reached near adult height in cohorts II and III.

2.6.6. Discussion on clinical efficacy

The clinical efficacy of somapacitan treatment in growth hormone treatment-naïve, prepubertal paediatric patients with growth hormone deficiency (GHD) was evaluated in one Phase 2 dose-finding supporting study ((NN8640-)4172) and one Phase 3 pivotal study ((NN8640-)4263).

The on-going phase 2 dose-selection study 4172 consists of the main study plus extension (26+26= 52 weeks), safety extension (104 weeks), and the long-term safety extension (208 weeks). In the main and extension study phase, the clinical effects of three doses (0.04, 0.08, and 0.16 mg/kg/week) of weekly somapacitan (n_{total}= 45), were compared with those of daily somatropin at a dosage of 0.034 mg/kg/day (i.e. a total of 0.24 mg/kg per week) (n= 14) at a 1:1:1:1 ratio. Upon request, the applicant indicated that the block size for worldwide randomisation was four. Both study treatments were administered subcutaneously in this cohort (cohort I). The nature of the study treatment (somapacitan/somatropin) was open-label. Somapacitan-treated patients in the main and extension study phase were blinded for the somapacitan dosage. From week 52 all somapacitan-treated patients received open-label somapacitan at a dosage of 0.16 mg/kg/week. From week 156 this also applied to the patients who were initially treated with somatropin. From week 156 paediatric GHD patients under 2.5 years of age (cohort II) and paediatric GHD patients aged 9-17 years (girls), and 10-17 years (boys)(cohort III) are included. From week 156 onwards, all study patients in all cohorts were treated with somapacitan at a dosage of 0.16 mg/kg/week. The long-term safety extension part of the study is still ongoing.

The selected study treatments and their dosages based on previous studies, including non-clinical studies, and clinical studies in adult GHD patients are acceptable. Applied inclusion and exclusion criteria, and the endpoints of study 4172 are in line with the EMA scientific advice EMEA/H/SA/2492/3/2018/PED/II.

Although double-blind treatment should have been provided in a double-blind manner to all study patients from a scientific perspective, the key endpoints of study 4172 (height parameters, IGF-I SDS levels) were detected in an objective manner by blinded study personnel.

The primary endpoint (the annualized height velocity at week 26), and supportive secondary endpoints including growth-related parameters (e.g. height velocity SDS, height SDS) and IGF-I SDS are acceptable, since these endpoints are important for the evaluation of the clinical effects of growth hormone in paediatric GHD patients.

The annualized height velocity increased from 3.5-4.8 cm per year at baseline to more than 8 cm per year in all treatment arms at week 26. At week 26, a dose-dependent effect in annualized height velocity was observed for increasing weekly doses of somapacitan (0.04 mg/kg: 8.0 cm/year, 0.08 mg/kg: 10.9 cm/year, and 0.16 mg/kg: 12.9 cm/year). A similar trend for this endpoint was observed at week 52 (0.04 mg/kg: 7.8 cm/year, 0.08 mg/kg: 9.7 cm/year, and 0.16 mg/kg: 11.5 cm/year). Similar trends were observed at week 26 and 52 for the changes from baseline in height SDS and IGF-I SDS levels. The available study data at the data cut-off point of 26-Aug-2021 indicate that the clinical effects of somapacitan maintain with time in cohort I, both for study patients who continued to receive somapacitan, and those who switched from somatropin to somapacitan during the study (growth hormone-experienced at the switching time). Limited available data in cohorts II and III indicate comparable clinical effects as in cohort I. The bone age/chronological age ratio remained below 1 throughout study 4172. This observation was later explained that although the bone age will accelerate upon growth hormone treatment, the bone age still lags behind the chronological age.

Patient-reported outcomes in cohort I (not evaluated in cohort II and III) indicated a larger improvement for the highest dose of somapacitan (0.16 mg/kg/week) compared to somatropin up to week 156.

In case IGF-I SDS levels >+2 are observed, the dose needs to be decreased and IGF-I SDS levels re-assessed until IGF-1 SDS levels are below +2 SDS and preferably close to zero. Therefore, guidance on the dose titration for the paediatric population was included in the SmPC., taking into consideration the GHD Modelling Report, but also the possibility that for patients down-titrated to a lower dose level, stepwise dose increases are possible when growth velocity is not satisfactory.

Design and conduct of clinical studies

Study design. Study 4263 is an ongoing pivotal, randomized, open-label, Phase 3 clinical study in paediatric GHD patients in which the clinical effects of once-weekly somapacitan at a dosage of 0.16 mg/kg/week were compared with those of daily treatment with somatropin at a dosage of 0.034 mg/kg/day (i.e. a total dose of 0.24 mg/kg/week) during a 52-week main study phase. Included study patients were centrally allocated to somapacitan or somatropin, at a 2:1 ratio. The primary endpoint, the annualized height velocity, was determined at week 52.
The main study period was followed by an ongoing safety extension period up to 3 years in which all study patients received somapacitan at a dosage of 0.16 mg/kg/week. The clinical database was locked on the 17th of December 2021.

Due to the open-label design of Phase 3 study 4263, the study results of this study may be affected by bias to some extent. However, growth parameters which concern key endpoints in this study, can be measured objectively. For the more subjective patient-reported outcomes a bias can not be excluded. This should be taken into account when interpreting these results.

Study population. In pivotal study 4263, growth hormone treatment-naïve pre-pubertal paediatric GHD patients aged 2.5 years up to 10 years (girls) or 11 years (boys) were included. These study

patients were generally selected in line with general EMA guidance in this respect (EMEA/CHMP/BMWP/94528/2005 Rev. 1) and EMA scientific advice on somapacitan (EMEA/H/SA/2492/3/2018/PED/II). The clinical effects of somapacitan in paediatric GHD patients under 2.5 years of age (cohort II) and those aged 9 years (girls) or 10 years (boys) up to 17 years (cohort III) are currently evaluated as part of dose-finding study 4172 (see above).
In study 4263, a confirmed GHD diagnosis was based on a peak growth hormone level of ≤ 10.0 ng/ml using the WHO International Somatropin 98/574 standard. However, in the CHMP scientific advice (EMEA/H/SA/2492/3/2018/PED/II) a more stringent 7 ng/ml growth hormone level upon stimulation was advised. The applicant showed later that similar results would have been obtained, if the growth hormone peak level for diagnosis of GHD and eligibility into the study would be <7 instead of ≤10 ng/ml.

In the aforementioned scientific advice cycle it was recommended to include a selection criterion accounting for parental height in order to avoid the overrepresentation of children with small parents and thus height targets. Such a selection criterium could not be found. The applicant showed later in post-hoc analyses that the results for the primary endpoint were comparable for each quartile of the midparental height.

Comparator. In study 4263, the clinical effects of weekly somapacitan at a dosage of 0.16 mg/kg/week were compared with those of daily dosed somatropin product Norditropin, both at a total weekly dose of 0.24 mg/kg/week. The selected dosage of somatropin product Norditropin is in line with the recommended posology in the SmPC of this medicinal product. It is acknowledged that a weekly somapacitan dosage of 0.16 mg/kg/week was supported in EMA scientific advice EMEA/H/SA/2492/3/2018/PED/II.

Endpoints. The primary efficacy endpoint in study 4263 was the annualized height velocity at week 52. Secondary efficacy endpoints in this study included changes in height standard deviation score (SDS), height velocity SDS, bone age, and serum IGF-I and IGFBP-3 levels compared to baseline. The aforementioned primary and secondary endpoints are relevant for the evaluation of the clinical effects of growth hormone treatment and were considered acceptable in EMA scientific advice EMEA/H/SA/2492/3/2018/PED/II.

Statistical analysis. The clinical effects of somapacitan and somatropin were compared with respect to the primary endpoint annualized height velocity at week 52 in study 4263. In line with EMA advice, the difference between these treatments with respect to the primary endpoint was analyzed assuming that no ancillary treatment was initiated in paediatric GHD patients (hypothetical strategy). The treatment difference between somapacitan and somatropin in mean annualised height velocity at week 52 for all randomised study patients, regardless of treatment adherence or initiation of ancillary therapy in children with GHD was analysed according to the treatment policy strategy (primary estimand for Food and Drug Administration (FDA) and PMDA). For treatment comparisons between somapacitan and somatropin, a non-inferiority margin of 1.8 cm/year was chosen. Respective non-inferiority margin was supported in EMA scientific advice EMEA/H/SA/2492/3/2018/PED/II.

Since study 4263 was not developed to demonstrate statistical differences with respect to secondary endpoints in the main study phase, no definitive conclusions can be made based on respective endpoints.

The endpoints in the safety extension phase were evaluated in a descriptive manner, since no comparisons between study arms can be made in this study phase.

Efficacy data and additional analyses

Patient disposition. 200 Study patients were randomized in study 4263. 131 Of 132 (99.2%) study patients randomized to somapacitan and all study patients randomized to somatropin completed the study. Hence, premature study dropout was minimal and well-balanced between treatment arms.

In total, 10 children in the somapacitan group and 4 children in the somatropin group were randomised in violation of inclusion or exclusion criteria. The applicant acknowledged later that these patients were randomized by mistake. Although the aforementioned study patients had to be excluded from study participation taking into account the study selection criteria, respective study patients received study treatment and were followed up in the study. The applicant showed at a later stage that the results with respect to the primary endpoint remain similar with and without including the aforementioned 14 study patients in the main analysis.

Baseline characteristics. In study 4263, the demographics and baseline data between the treatment groups were balanced. At baseline, study patients had diminished growth with a mean height velocity of about 4 cm/year (somapacitan: 4.3 cm/year, somatropin: 4.1 cm/year), a mean height SDS of about -3 (somapacitan: -3.0, somatropin: -3.5). The majority of study patients (88.0%) had isolated, idiopathic aetiology of growth hormone deficiency.

The proportions of men of the total study population that was included in study 4263 were respectively 75% and 73.5% in study patients who were treated respectively with somapacitan and somatropin. These proportions exceed the male proportion of growth hormone deficiency patients of 66.7%, i.e. a male: female ratio of 2:1, reported in literature (e.g. Grimberg et al. 2005). The impact of the preponderance of men on the interpretation of the result of study 4263 will be limited.

Compliance. The majority of paediatric GHD patients received the planned treatment with a mean adherence among study patients on treatment of 95.8% for the somapacitan group and 88.3% for the somatropin group. Hence, the compliance rates for study treatment were high.

Annualized height velocity. The estimated mean annualized height velocity at week 52 according to the hypothetical strategy (primary endpoint EMA) was 11.2 cm/year for somapacitan and 11.7 cm/year for somatropin in study 4263. Hence, the estimated treatment difference in height velocity at week 52 between somapacitan and somatropin was -0.5 cm/year (95% CI -1.1; 0.2). Non-inferiority of somapacitan relative to somatropin was confirmed for the hypothetical estimand as the lower bound of the 95% confidence interval (-1.1 cm/year) was higher than the predefined non-inferiority margin of -1.8 cm/year.

Height velocity SDS. In study 4263, the estimated mean changes from baseline in height velocity SDS at week 52 compared to baseline were comparable for somapacitan and somatropin (respectively 8.05 vs. 8.82; estimated treatment difference -0.78 (95% CI -1.63, 0.08)).

Height SDS. In study 4263, the estimated mean changes from baseline in height SDS at week 52 compared to baseline was comparable for somapacitan and somatropin (respectively 1.25 vs. 1.30; estimated treatment difference -0.05 (95% CI -0.18, 0.08)).

Bone age/ chronological age. In study 4263, the estimated mean changes from baseline in bone age relative to chronological age at week 52 compared to baseline was comparable for somapacitan and somatropin (respectively 0.06 vs. 0.08; estimated treatment difference -0.02 (95% CI -0.06, 0.01)).

IGF-I SDS levels and IGFBP-3 SDS levels. In study 4263, mean IGF-I SDS levels increased rapidly from baseline after initiating treatment with both somapacitan and somatropin. The observed mean IGF-I SDS increased from very low baseline levels (below -2) in both treatment groups to week 52 values within the normal range (-2 to +2). Change from baseline to week 52 in IGF-I SDS was similar between somapacitan and somatropin (2.37 for both; estimated treatment difference 0.04 (95% CI -0.29; 0.37)). In line with this, changes from baseline to week 52 in IGFBP-3 SDS levels (in-study data) were similar for somapacitan and somatropin (1.62 vs. 1.61; estimated treatment difference 0.02 (95% CI -0.21; 0.24)).

Treatment evaluation. Guidance for clinicians in clinical practice with respect to the treatment evaluation of somapacitan in paediatric GHD patients was initially missing. Later, the applicant indicated that IGF-I SDS levels should be evaluated in paediatric GHD patients. Since approximately 95% of individuals in a reference population have IGF-I SDS levels within the range from -2 up to +2 SDS[7], this also concerns the IGF-I SDS target range for paediatric GHD patients.[8] In line with general practice the applicant recommends evaluating the efficacy and the safety of somapacitan in paediatric GHD patients at approximately 6 to 12-month intervals by evaluating auxological parameters, biochemistry (IGF-I, hormones, glucose and lipid levels), and pubertal status. More frequent evaluations should be considered during puberty. Moreover, the treatment should be discontinued in patients having achieved final height or near final height, i.e. an annualised height velocity <2 cm/year, and a bone age is > 14 years (girls) or > 16 years (boys) which corresponds to the closure of the epiphyseal growth plates. Once the epiphyses are fused, patients should be clinically re -evaluated for the need for growth hormone treatment. This information has been included in SmPC section 4.2.

Subgroup analyses. With respect to the primary endpoint in study 4263 subgroup analyses were conducted with respect to age (<6 years vs. ≥ 6 years), gender, growth hormone treatment experience, and with respect to the Japanese study population. Regarding the height velocity at week 52 compared to baseline, similar trends in effects between somapacitan and somatropin were observed in GHD patients under 6 years of age (12.2 vs. 12.6 cm/year; estimated treatment difference -0.4 (95% -1.4; 0.7)) and those aged 6 years and above (12.2 vs. 12.6 cm/year; estimated treatment difference -0.4 (95% -1.4; 0.7)) in study 4263. For this endpoint similar trends were also observed in men (11.1 vs. 11.5 cm/year; estimated treatment difference -0.4 (95% -1.1; 0.3)) and women (11.8 vs. 12.3 cm/year; estimated treatment difference -0.5 (95% -2.2; 1.1)).

All study patients in study 4263 and cohort I of study 4172 were treatment-naïve at randomisation. In the study patients in study 4172 who were initially treated with somatropin maintained growth and adequate IGF-I SDS levels after initiating somapacitan treatment.

[7] Bidlingmaier M, Friedrich N, Emeny RT, Spranger J, Wolthers OD, Roswall J, et al. Reference intervals for insulin-like growth factor-1 (igf-i) from birth to senescence: results from a multicenter study using a new automated chemiluminescence IGF-I immunoassay conforming to recent international recommendations. J Clin Endocrinol Metab. 2014;99(5):1712-21.

[8] Johannsson G, Bidlingmaier M, Biller BMK, Boguszewski M, Casanueva FF, Chanson P, et al. Growth Hormone Research Society perspective on biomarkers of GH action in children and adults. Endocr Connect. 2018;7(3):R126-R34.

Somapacitan also increased height velocity (cm/year) in the subgroup of 30 Japanese study patients. The height velocity estimates after 52 weeks were 10.3 cm/year and 9.9 cm/year, for somapacitan and somatropin, respectively, with an estimated treatment difference of 0.3 [95% CI -0.9; 1.5].

Hence, observed trends in effects were similar for study patients of different age (< 6 years and ≥ 6 years), gender, growth hormone treatment experience, and in the geographic region of Japan. This supports the use of somapacitan in naïve and growth hormone treatment-experienced patients of different age and gender, also in Japan.

Treatment burden. In study 4263, the treatment burden tended to be lower upon somapacitan as compared to somatropin treatment at week 52. The estimated treatment differences between somapacitan and somatropin of the total score (-6.0 (95% CI -10.0; -2.1)) of the treatment burden measure–child GHD-parent (TB-CGHD-P) scale tended to be more favourable for somapacitan as compared to somatropin, in line with its emotional sub score (-5.3 (95% CI -10.0; -0.7)), and interference subscores (-6.7 (95% CI -11.6; -1.9)). However, the estimated treatment differences between somapacitan and somatropin of the total score (-2.4 (95% CI -5.7; 0.9)) of the treatment burden measure–child GHD-observer (TB-CGHD-O) scale were similar, in line with its physical (-2.9 (95% CI -6.8; 1.0)), emotional (-3.5 (95% CI -9.5; 2.4)), and interference sub- scores (-1.3 (95% CI -3.9; 1.3)).
At week 52 of study 4263 96% of the respondents in study 4263 found the somapacitan and somatropin devices to be easy or very easy to use. A high proportion of respondents (>90%) found the devices easy or very easy to learn to use (G-DAT).

At the cut-off of 10-Nov-2021, responses to the growth hormone patient preference questionnaire (GH-PPQ) at week 56 of study 4263, had been collected for 41 of the 68 study patients switching from somatropin to somapacitan after week 52. 37 Of the 41 study patients (90.2%) preferred somapacitan to somatropin, while the remaining 4 study patients had no preference. The most selected reasons listed for preferring somapacitan to somatropin were: “number of times needing to do injections” (20 of 37), “less worried about remembering to give injections” (16 of 37) and “child less worried about getting injections” (12 of 37). 28 Study patients (68.3%) reported they would be more adherent to somapacitan, once-weekly, than to daily growth hormone treatment.

Ancillary analyses. The available results of the clinical studies 4172 and 4263 were in line with the literature indicating that growth in paediatric GHD patients continues at a smaller, more constant rate after an initial catch-up growth in treatment-non-naïve paediatric GHD patients.[9]

However, no study patients have thus far reached near adult height. In line with EMA scientific advice EMEA/H/SA/2492/3/2018/PED/II determination of the final height of somapacitan-treated paediatric GHD patients in the conducted clinical studies is important to gain insight into the long-term clinical efficacy of somapacitan in patients who continued to use somapacitan without switching to or addition of alternative growth hormone options. This will be tracked via a post-authorisation measure. Further, the final results of ongoing Phase 2 dose-finding study 4172 and the pivotal Phase 3 study 4263 will be submitted as a post-authorisation measure.

Special populations. As expected, no patients aged 65 years and above are included in these studies. No adjustment of the somapacitan starting dose is needed in patients with renal or hepatic impairment.

[9] Ranke MB, Lindberg A, Mullis PE, Geffner ME, Tanaka T, Cutfield WS, Tauber M, Dunger D. Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. Horm Res Paediatr. 2013;79(2):51-67.

2.6.7. Conclusions on the clinical efficacy

The clinical studies which were submitted support the clinical efficacy of the somapacitan treatment in paediatric GHD patients. The height velocity at week 52 of somapacitan at a once-weekly dosage of 0.16 mg/kg/week was non-inferior to that of somatropin at a once-daily dosage of 0.034 mg/kg/day in paediatric GHD patients.
The CHMP considers the following measures necessary to address issues related to efficacy:
The clinical effects of long-term somapacitan treatment in paediatric GHD patients should be evaluated further (post-authorisation measures including the PASS proposed by the applicant).

2.6.8. Clinical safety

The safety information with somapacitan is based on the data obtained from 3 clinical studies in children with GHD (Phase 1: study 4042; Phase 2: study 4172; Phase 3: study 4263).

The confirmatory global Phase 3 study 4263 provides safety data from the completed main period of the study (52 weeks) which included daily treatment with somatropin medicinal product Norditropin as active comparator. Daily somatropin has been used as the treatment of GHD for more than 30 years, thereby providing a clinically relevant comparator for which extensive safety data has been accumulated.

Safety data is also obtained from the Phase 2 study 4172 (208 weeks completed), which included a somatropin group for the first 156 weeks of the study. For the clinical pharmacology study 4042, limited safety data are available due to the low exposure in the study (single-dose).

The main safety evaluation of somapacitan is based on pooled global data (adverse events) (also referred to as the safety pool). The safety analysis set for the pooled global data comprised all children with GHD enrolled in the clinical studies 4172 and 4263 who received at least one dose of somapacitan 0.16 mg/kg/week (from the visit they start on the 0.16 mg/kg/week level) or somatropin. The somapacitan 0.16 mg/kg/week pool includes 194 children (132 children from study 4263, 52 children from study 4172 cohort I and 10 children from study 4172 cohorts II and III). The somatropin pool includes 82 children (68 children from study 4263 and 14 children from study 4172). Eleven (11) children switched from somatropin to somapacitan in study 4172 at week 156, giving a total of 265 children in the total safety pool.

2.6.8.1. Patient exposure

The cut-off date for study 4172 was 19-Nov-2021 (database lock [DBL] for 208 weeks) and for study 4263 03-Dec-2021 (1st DBL for 52 weeks) and 17-Dec-2021 (2nd DBL including remaining PK data, antibody data and bone age assessments). The cut-off date for inclusion of ongoing safety data was 10-Nov-2021 (data lock point) for both studies 4172 and 4263. An additional cut-off for studies 4172 and 4263 was 31-Dec-2021, providing updated information on serious adverse events after DBL to 31-Dec-2021. No adverse events leading to discontinuation of study product were reported in studies 4263 and 4172 by this cut-off.

A total of 194 children with GHD were exposed to somapacitan 0.16 mg/kg/week in the 2 ongoing clinical studies in GHD (studies 4263 and 4172). In study 4172, some of the children on somapacitan

0.16 mg/kg/week were initially randomised to somapacitan 0.04 and 0.08 mg/kg/week and switched to 0.16 mg/kg/week after 52 weeks. The safety pool contains all children from studies 4263 and 4172 from the day they receive somapacitan 0.16 mg/kg/week. Up to 208 weeks of exposure to somapacitan has been evaluated in GHD (study 4172, ongoing).

A total of 82 children with GHD were exposed to daily somatropin 0.034 mg/kg/day as active comparator in the clinical studies in GHD (up to 156 weeks of exposure). The total exposure was 282.8 patient-years for somapacitan 0.16 mg/kg/week and 104.5 person-years for somatropin.

Table 20 Exposure - children with GHD (safety pool)

	Norditropin	somapacitan (0.16mg/kg/week) safety pooled[a]
Number of exposed subject	82	194
Days of exposure*		
Mean (SD)	464.32 (255.79)	533.38 (360.98)
Median	369.0	371.0
Min ; Max	45 ; 1196	7 ; 1484
Treatment dose** (mg)		
Mean (SD)	2.79 (1.23)	3.90 (1.26)
Median	2.88	3.80
Min ; Max	0.40 ; 5.20	2.00 ; 9.90
Treatment dose** (mg/kg)		
Mean (SD)	0.03 (0.0007)	0.16 (0.0011)
Median	0.03	0.16
Min ; Max	0.03 ; 0.04	0.16 ; 0.16
Total patient years at risk (on treatment)	104.54	282.75

N: Number of study patients, SD: Standard deviation. *Exposure days in the treatment period are calculated as time from first date on randomised treatment to last date on randomised treatment for Somatropin and plus six days for somapacitan or to visit 20 (week 208 for cohort I and week 52 for cohort II and III) for 4172 and for 4263 to visit 7 (week 52), whichever comes first. The somapacitan (0.16mg/kg/week) safety pooled arm contains all study patients from 4263 and 4172 from the day they receive somapacitan 0.16mg/kg/week. **Last prescribed dose.

Through the somapacitan paediatric clinical development programme in GHD, 188 (96.9%) children were exposed to somapacitan for more than 6 months, 183 (94.3%) children were exposed for more than 12 months, and 39 (20.1%) children were exposed for more than 21 months.

2.6.8.2. Adverse events

The safety profile of once-weekly somapacitan (administered s.c. to children with GHD for up to 52 weeks in study 4263) was similar to the well-known safety profile for daily GH (e.g. somatropin). No new safety issues were identified. No local tolerability issues were identified.

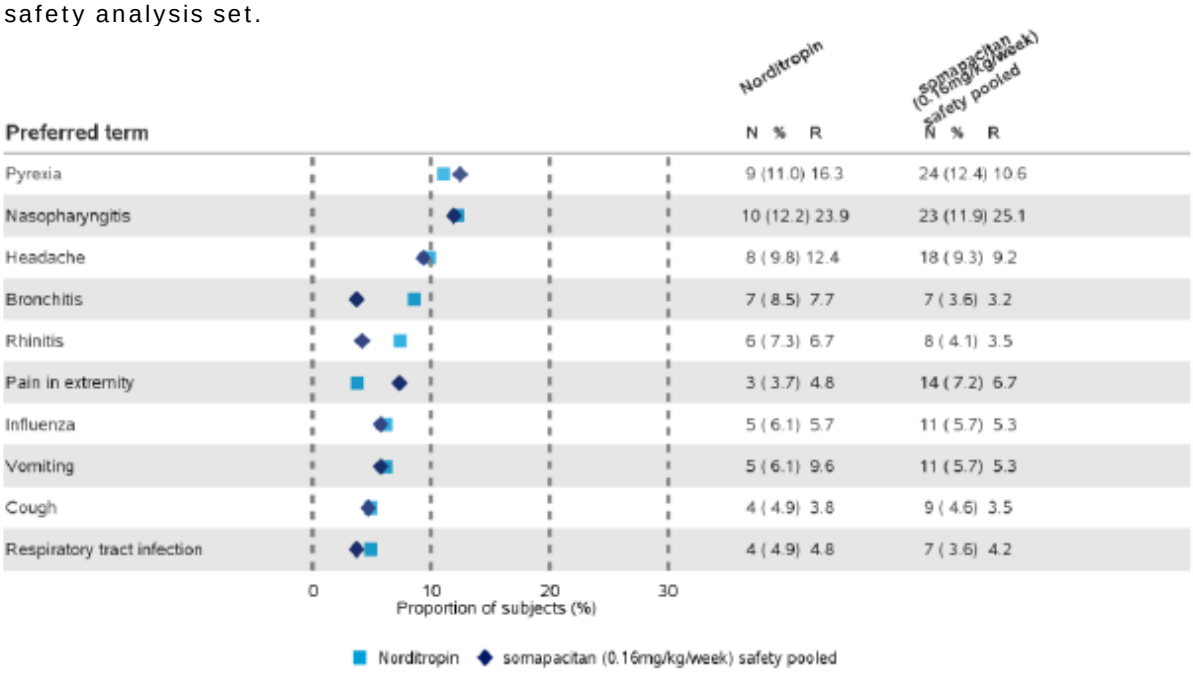
In the safety pool, a similar proportion of children reported adverse events for the somapacitan 0.16 mg/kg/week pool as observed for the somatropin pool (somapacitan 0.16 mg/kg/week: 73.2%; Somatropin: 67.1%).

A similar rate of adverse events was observed for somapacitan 0.16 mg/kg/week (230.9 adverse events/100 patient-years) as for Somatropin (232.4 adverse events/100 patient-years). The majority of the AEs were non-serious for both treatments.

The most frequent adverse events (≥5%) in the somapacitan group were (by proportion) pyrexia (12.4%), nasopharyngitis (11.9%) and headache (9.3%). These adverse events are also events commonly observed in children in general regardless of treatment or underlying disease. Adverse events reported for more than 2% of the children are summarised in Figure 21 and Figure 22.

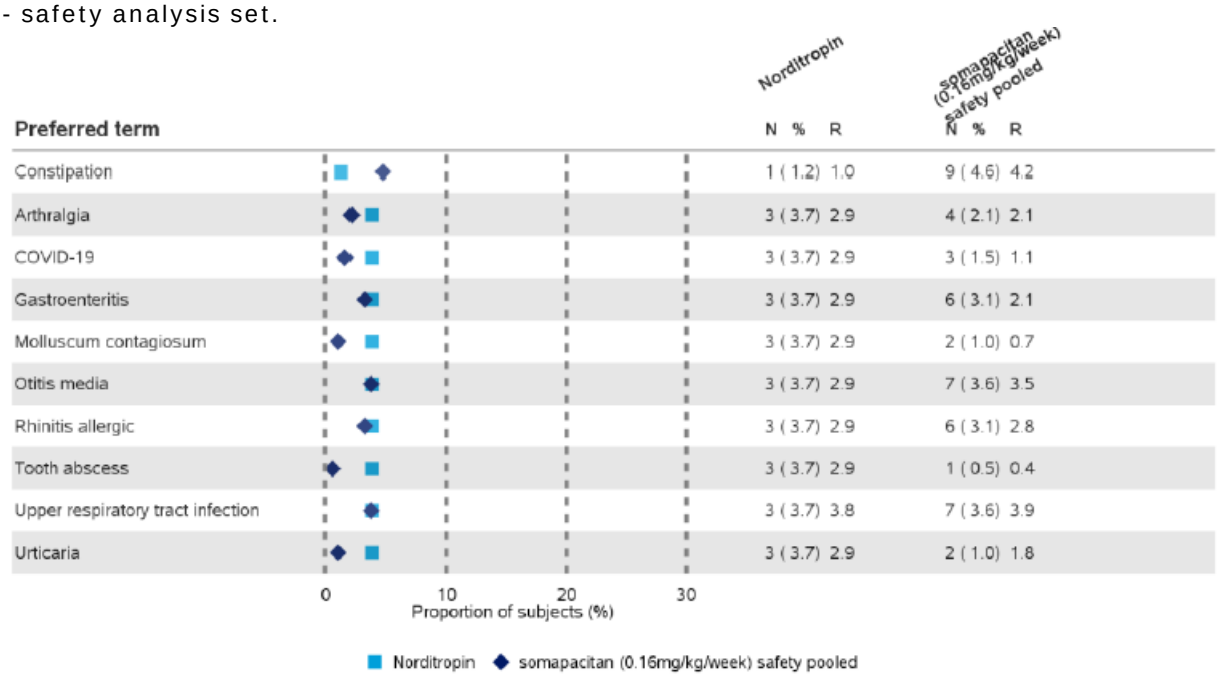
There were no cases of lipohypertrophy or lipoatrophy in study 4263. One (1) case of lipodystrophy acquired was reported in the somapacitan group. The event was considered of mild severity and fully resolved. In study 4172, 2 cases of lipoatrophy (in 2 children treated with somapacitan 0.04 mg/kg/week) were reported during the 4-year study period. None of the 2 cases were reported as serious adverse events. Both cases recovered after change of injection site.

Figure 21 Most frequent adverse events by preferred term (>=2%) - on-treatment - plot 1 - safety analysis set.



%: Percentage, R: Event rate per 100 patient years at risk, MedDRA version 24.1
Only adverse events with an onset after the first administration of trial product and up until 14 days after last trial drug administration for withdrawn subjects, and with an onset after the first administration of trial product and up until visit 7 (week 52) or 14 days after last trial drug administration, which ever comes first, for all other subjects, are included.

Figure 22 Most frequent adverse events by preferred term (>=2%) - on-treatment - plot 2 - safety analysis set.



%: Percentage, R: Event rate per 100 patient years at risk, MedDRA version 24.1
Only adverse events with an onset after the first administration of trial product and up until 14 days after last trial drug administration for withdrawn subjects, and with an onset after the first administration of trial product and up until visit 7 (week 52) or 14 days after last trial drug administration, which ever comes first, for all other subjects, are included.

Severity

In the somapacitan 0.16 mg/kg/week pool, the majority of the adverse events were of mild or moderate severity. Five (5) children experienced 8 adverse events rated as severe, which were all adverse events expected in children. A similar proportion of children experienced severe adverse events in the 2 treatment groups (somapacitan: 2.6%; somatropin: 2.4%). In total, 5 of 8 severe adverse events reported with somapacitan were judged as possibly or probably related to somapacitan by the investigator, whereas 1 of 2 severe adverse events was judged as possibly or probably related to somatropin.

Adverse events possibly or probably related to study products

A similar proportion of children reported adverse events evaluated by the investigator as possibly or probably related to study products in the safety pool (somapacitan: 20.1%; somatropin: 18.3%) compared to study 4263.

In the somapacitan 0.16 mg/kg/week pool, the most frequently reported possibly or probably related adverse events ⩾2% in children with GHD were headaches (somapacitan: 2.6%; somatropin: 8.5%). All other adverse events considered possibly or probably related to somapacitan by the investigator were reported in 1-3 children across different system organ classes and preferred terms.

The majority of the adverse events judged as possibly or probably related to somapacitan were of mild or moderate severity and non-serious. Two (2) adverse events considered possibly or probably related to somapacitan were reported as serious adverse events (vomiting and generalised oedema).

In the somatropin group, the most frequently reported possibly or probably related adverse events ⩾ 2% were headache (see above), pain in extremity (somapacitan: 1.5%; somatropin: 2.4%), vomiting

(somapacitan: 1.5%; somatropin: 3.7%), and hyperglycaemia (somapacitan: 0.5%; somatropin: 2.4%).

Adverse event data from the ongoing parts of the phase 3 study 4263 and phase 2 study 4172 are summarised below.

Adverse events in ongoing parts of study 4263 and study 4172

Study 4263 after week 52

The safety profile in the ongoing part (week 52 to week 117) in study 4263 for serious adverse events and adverse events leading to discontinuation of study product) was similar to the safety profile in the completed main 52-week period of the study.

A similar proportion of children reported adverse events in the 2 treatment groups (somapacitan/somapacitan: 38.5%; somatropin/somapacitan: 39.7%) and similar adverse event rates were also reported (somapacitan/somapacitan: 121.4 adverse events /100 patient-years; somatropin/somapacitan: 123.1 adverse events/100 patient-years).

No deaths or adverse events leading to the discontinuation of the study product were reported.

Two (2) serious adverse events (Covid-19 infection and Gastroenteritis) were reported in 1 study patient. Both events recovered. Somapacitan treatment was temporarily interrupted due to the Covid-19 infection.

Generally, low numbers of adverse events were reported within the safety focus areas.

Four (4) children experienced 4 injection site reactions (reported as adverse events). All cases were of mild severity. None of the injection site reactions was reported as serious adverse events. There were no injection site reactions linked to premature treatment discontinuation.

Lipodystrophy was reported in 2 children, whereof 1 child also reported lipodystrophy in the 52-week main period of the study. The events were mild and moderate, were judged as possibly and probably related to treatment and both events resolved.

Study 4172 – after week 208

The safety profile in the ongoing part (after week 208 up to week 286) in study 4172 (cut-offs: 10-Nov-2021 for all adverse events and additional cut-off of 31-Dec-2021 for serious adverse events and adverse events leading to discontinuation of study product) was similar to the safety profile in the completed 208 weeks of the study.

No deaths or adverse events leading to discontinuation of study product were reported.

One (1) serious adverse event of anaphylactic shock was reported with onset day 1518. The child had a well-known food allergy (wheat and egg) and also experienced an anaphylactic shock with onset day 861. The event resolved and no change in dose was made.

One (1) case of mild scoliosis was reported.

2.6.8.3. Serious adverse event/deaths/other significant events

No deaths were reported in the clinical studies with somapacitan in children with GHD (study 4263, 52 weeks; study 4172, 208 weeks; study 4042, 1 week).

A similar pattern of serious adverse events was observed for the somapacitan 0.16 mg/kg/week safety pool as for the pivotal Phase 3 study. A similar low proportion of children reported serious adverse events in both treatment groups (somapacitan: 10 (5.2%) children reported 14 serious adverse events; somatropin: 4 (4.9%) children reported 6 serious adverse events). Serious adverse events were single events reported in 1 child, except for 2 serious adverse events of vomiting.

Two (2) serious adverse events (generalised oedema, vomiting) occurring in the same study patient were evaluated as probably related to study product (somapacitan 0.16 mg/kg/week) and treatment was temporarily interrupted in both cases.

In study 4172, 2 children experienced an anaphylactic reaction/shock in the somapacitan group. Both had well-known food allergy.

2.6.8.4. Laboratory findings

There were no apparent clinically relevant changes from screening in the clinical laboratory haematology or biochemistry parameters assessed in children with GHD in any of the treatment groups/studies.

Vital signs and ECGs

No clinically relevant changes from baseline in ECGs and vital signs (mean systolic and diastolic blood pressure and pulse) were observed following somapacitan treatment in the clinical studies in children with GHD. Similar mean values were observed for somapacitan and somatropin.

Body weight

As expected in growing children, the mean body weight increased across all treatment groups from baseline to week 52 in study 4263 and from baseline to week 208 in study 4172. There were no adverse events that concerned changes in weight.

Physical examination

A total of 15 children had abnormal physical examinations reported as clinically significant at screening or during the 52-week main period of the pivotal study 4263 (somapacitan: 12 children, 6 at screening; somatropin: 3 children, all at screening). Four (4) cases were reported as adverse events in the somapacitan group (lymphadenopathy, adverse events included fever and rhinitis; exanthema, adverse event rash; dermatitis atopic; skin lesion, adverse event molluscum contagiosum).

In the supportive study 4172, there were 20 abnormal physical examinations reported as clinically significant across treatment groups up to week 208. 3 cases were reported as adverse events in the somapacitan group (haematoma left thigh, lipoatrophy, and skin atrophy).

Bone age

In both clinical studies, bone age approached chronological age. The bone age vs. chronological age ratio for individual study patients was below 1 for most children after 52 weeks (study 4263) and 208 weeks (study 4172) of treatment. There were no clinically relevant differences in change from baseline in bone age between somapacitan and somatropin. There were no adverse events that concerned bone age in the two studies.

Glycaemic control

In the pivotal Phase 3 study 4263, there were no clinically relevant changes in mean fasting blood glucose or HbA_{1c} from baseline to week 52 with somapacitan treatment. At baseline and after 52 weeks of exposure, the mean HbA_{1c} values were similar between the treatment groups

(week 52: somapacitan: 5.31%; somatropin: 5.31%). The mean fasting insulin level was within the reference ranges. The changes observed in fasting insulin were within expectation when administering growth hormone and was similar between somapacitan and somatropin.

In the supportive Phase 2 study 4172, there were no clinically relevant changes from baseline in mean fasting glucose, insulin or HbA_{1c} which were similar for somapacitan and somatropin.

In study 4263, after 104 weeks of exposure, mean fasting blood glucose was similar in the 2 treatment groups (somapacitan/somapacitan: 4.7 mmol/l; somatropin/somapacitan: 4.6 mmol/l). Likewise, mean HbA_{1c} values were similar between the 2 treatment groups (somapacitan/somapacitan: 5.32%; somatropin/somapacitan: 5.35%). The mean fasting insulin level was within the reference ranges.

2.6.8.5. Safety in special populations

In alignment with the ICH M4E guideline, adverse events were also evaluated in the following subgroups in the pivotal study 4263: sex (male/female) and age group (<6 years/ ≥6 years).

Based on the adverse event profiles, there were no specific safety concerns observed in any of the investigated subgroups. Similar trends were observed in the subgroups as for the total patient population.

Adverse events in children with IGF-I SDS above +2 at two or more consecutive visits

No trend was seen in the amount or type of adverse events reported in children with IGF-I SDS above +2 at two or more consecutive visits in the pivotal study 4263 (somapacitan: 5 children, 3.8%; Somatropin: 2 children, 2.9%), compared to the remaining children in the relevant treatment groups. There were no serious adverse events reported for these study patients and no dose reductions due to the adverse events.

One child in each treatment group had dose reductions (of 25%) due to IGF-I SDS exceeding +2.5 SDS at 2 consecutive visits. No safety issues were observed in relation to the IGF-I SDS levels above +2.5 in the 2 children.

In the supportive phase 2 study 4172, no trend was seen in the amount or type of adverse events reported in children with IGF-I above +2 at two or more consecutive visits compared to the remaining study patients in the relevant treatment groups.

2.6.8.6. Immunological events

Overall, the low immunogenicity observed with somapacitan is consistent with that reported for other growth hormone products.

In the main 52-week period of the pivotal study 4263, non-neutralising antibodies were detected in 20 (15.2%) somapacitan-treated children (including 4 children with positive antibodies at baseline which are most likely false positive findings as the children were naïve to growth hormone treatment) and 7 (10.3%) children treated with somatropin. Of these, 2 (1.5%) children in the somapacitan group and 1 (1.5%) child in the somatropin group had at least two consecutive positive antibody samples.

Immunogenicity data in the supportive study 4172 with somapacitan treatment up to 208 weeks were consistent with the Phase 3 data. Non-neutralising antibodies were detected in 10 somapacitan treated

children (22.2%), and 1 child (7.1%) treated with somatropin. Of these, 3 (6.7%) children in the somapacitan groups and 1 (7.1%) child in the somatropin/somapacitan group had at least 2 consecutive positive antibody samples.

Data on immunogenicity from the ongoing part of studies 4263 (after week 52) and 4172 (after week 208) were consistent with data in the completed part of the studies. Hence, based on the totality of data, the formation of anti-somapacitan antibodies did not appear to affect pharmacokinetics, pharmacodynamics, efficacy or adverse events reported (including injection site reactions and allergic reactions) in neither study 4263 nor study 4172.

2.6.8.7. Safety related to drug-drug interactions and other interactions

The potential clinically relevant drug interactions for somapacitan are listed in Table 23. The interaction between glucocorticoids and growth hormone has been further specified in the warnings and precautions for use. These drug interactions are based on the pharmacodynamics and pharmacokinetic properties of somapacitan and well-known interactions for daily growth hormone products.

Table 21 Drug-drug interactions

Topic	**Descriptive text**
Cytochrome P450 metabolised drugs	Data from an interaction trial performed in AGHD patients suggests that GH administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 3A4 (e.g., sex steroids, corticosteroids, anticonvulsants, and cyclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.
Glucocorticoids	GH decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective.
Antihyperglycaemic products	Antihyperglycaemic treatment, including insulin, may require dose adjustment in case of somapacitan co-administration, since somapacitan may decrease insulin sensitivity.
Other	The metabolic effects of GH can also be influenced by concomitant treatment with other hormones, e.g., testosterone and thyroid hormones.
In adults	
Oral estrogen replacement	In women on oral estrogen replacement, a higher dose of GH may be required to achieve the treatment goal.

2.6.8.8. Discontinuation due to adverse events

There were no children who withdrew from the study or discontinued study product due to adverse events in the any of the treatment groups in the 52-week main period of the pivotal Phase 3 study 4263.

In the supportive Phase 2 study 4172 up to week 208, no children who withdrew from the study or discontinued the study product due to adverse events in the somapacitan group. Two children treated

with Somatropin discontinued the study product prematurely due to adverse events (drug hypersensitivity and nephrotic syndrome).

Adverse events leading to temporary discontinuation of study product

In the 52-week main period of study 4263, two (2) children treated with somapacitan and 5 children treated with Somatropin temporarily discontinued study product due to adverse events. In 3 cases, treatment was paused due to headache. Full recovery was reported for all cases and treatment was continued.

In study 4172 up to week 208, eight (8) children treated with somapacitan and/or Somatropin had temporary discontinuation of study product due to adverse events.

Adverse events leading to dose reduction

In the 52-week main period of study 4263, one (1) child treated with somapacitan had the dose reduced due to mild impaired fasting glucose at study day 369 (i.e., occurring at the week 52 visit). Two (2) children treated with somatropin had their dose reduced due to headache.

In study 4172, there were no adverse events leading to dose reductions during the study period up to week 208.

2.6.8.9. Post marketing experience

Post-marketing data on children are not available as somapacitan is not yet marketed in paediatric indications.

2.6.9. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

The pooled safety data including all patients from the phase 2 and phase 3 study who received at least one dose of somapacitan or somatropin is submitted by the MAH as being supportive but will be considered pivotal in the safety assessment since the pooled database will give more insight in the rarer side effects.

Exposure. A total of 194 children with GHD were exposed to somapacitan 0.16 mg/kg/week, the to-be-marketed dose, in the Phase 2 study 4172 and Phase 3 study 4263. The extent of the exposure of children to somapacitan is considered extensive considering the rarity of the disease. 183 (94.3%) children were exposed for more than 12 months, which is also quite extensive. The long-term safety data is somewhat more limited, with only 39 patients exposed for more than 21 months.

Adverse events. Overall, 73.2% of patients in the somapacitan 0.16 mg/kg/week group and 67.1% in the somatropin group experienced an adverse event. The majority of the adverse events were mild to moderate, and for the majority of cases, the adverse event resolved without sequela.

The most frequent adverse events in children treated with somapacitan were pyrexia (12.4%) and nasopharyngitis (11.9%). Together with other frequently reported adverse events such as influenza, couch, respiratory tract infections, gastroenteritis and otitis media, these adverse events are considered common in children and are not likely to reflect drug-related adverse events. This is supported by the comparable numbers in the somatropin group. Headache occurred in 9.3% of

patients and is reported as common in the SmPC of somapacitan and somatropin. Overall, the safety profile of somapacitan resembles that of other growth hormone products.

Constipation occurred more frequently in the somapacitan group compared to the somatropin group (1.2% in the somatropin group and 4.6% in the somapacitan group) in the safety pool. This is supported by data from the phase 3 study 4236. It is reasoned that the constipation might be part of hypothyroidism diagnosed in a reasonable number of patients, although other reasons could be involved as well (e.g. anticholinergics).

Besides constipation, “pain in extremity” is one of the most frequently reported adverse events, with 3.7% of patients in the somatropin group and 7.2% of the somapacitan group. Within the Phase 3 study 4263, this difference is higher; 2.9% in the somatropin group and 9.1% in the somapacitan group. Nevertheless, pain in the extremity is often reported as not being related to treatment. Given the frequency of pain in the extremity in the somapacitan 0.16 mg/kg/week pool (7.2%) and the biological plausibility pain in extremity should be considered an ADR to somapacitan treatment. The approved SmPC is in line with these findings.

In total, 5 events of lipoatrophy/lipodystrophy were reported, 2 events in 2 patients in study 4172 and 3 events in 2 patients in study 4263. For the events in study 4172, the events were judged as severe and probably related to the study drug. More specifically, the events were likely induced by multiple injections at the same site. The event of lipodystrophy in the 52-week part of study 4263 was judged as unrelated but this assessment is questioned. For the other 2 events, occurring in the ongoing part of study 4263, not further information seems to be available. Lipodystrophy is a known but rare side effect of growth hormone injectables. The phrasing in the SmPC currently reflects the diversity of the injection-induced morphological changes in the subcutaneous adipose tissue.

Serious adverse events. In general, the incidence of serious adverse events was low within the safety pool: 10 patients (5.2%) experienced 14 events in the somapacitan group and 4 patients (4.9%) experienced 6 serious adverse events in the somatropin group. The majority of serious adverse events were in the system organ class of infections and infestations, which are not uncommon for children. Two events of anaphylactic reactions were reported, but in patients with known food allergies. Therefore, these cases were not judged as being related to the study treatment. This is supported.

Laboratory parameters. There were no apparent clinically relevant changes from screening in the clinical laboratory haematology or biochemistry parameters.

No adverse events were recorded related to altered glycaemic control.

Safety in subgroups. The safety profile was assessed for the following subgroups in the pivotal study 4263: sex (male/female) and age group (<6 years/ ≥6 years). Based on the adverse event profiles, there were no specific safety concerns observed in any of the investigated subgroups. Similar trends were observed in the subgroups as for the total patient population. Adverse events in children with IGF-I SDS <2 in more than 2 consecutive visits were comparable in both treatment arms.

Immunogenicity. Growth hormone products are known to have, varying degrees of immunogenicity. Anti-somapacitan antibodies were observed in 20 study patients in study 4263 and in 10 study patients in study 4172. Respective anti-somapacitan antibodies were non-neutralizing. In both study 4263 and study 4172, no effect of anti-somapacitan antibodies on the efficacy or safety of somapacitan could be observed.
The frequency of non-neutralising antibodies appears comparable between treatment arms.

Safety in children below the age of 3 years. As no children <2. 5 years old were included in the pivotal study 4263 and only one child <2.5 years old in cohort II of study 4172 the clinical effects of

somapacitan in children <2.5 years old are very limited, and no benefit-risk assessment can be made based on these data. Further, the efficacy and especially the safety of long-acting growth hormone in these hormonally immature very young is unknown from the literature. Further an extrapolation on physiological ground appears difficult as the hormonal homeostasis (i.e. all pituitary axes) of the very young is different from those over the age of 2 – 4 years. Growth velocity in these children is mainly the result of the amount of food and not yet under the control of growth hormone. Further the glucose metabolism is under development with an increased risk of hypoglycaemia in the very young (below the age of 6month, see also EMEA-002692-PIP01-19 for lonapegsomatropin). This risk might be increased by the different IGF-I profile observed in the weekly growth hormone administration.

A flexible daily dosing regimen with more limited amounts of growth hormone per injection is especially relevant in GHD patients under 3 years of age, taking into account the hormonal maturation and glucose homeostasis in these patients. Because of this, weekly somapacitan treatment is limited to paediatric GHD patients aged 3 years and above.

Safety in adolescents GHD patients. The clinical data with somapacitan are at present also limited in adolescent GHD patients from 12 to 17 years old, although it is acknowledged that the clinical effects of somapacitan are still under evaluation in Cohort III of study 4172. It is not common to study the growth in pubertal children as the sexual development (and accompanying changes in sex hormones) dilutes the effect of the growth hormone. The effects in adolescents are commonly extrapolated (as is done for other growth hormone-containing products) from pre-pubertal children. However, given the lack of patients studied with long-acting somapacitan resulting in different IGF-I profiles, the safe and effective use in adolescents will be monitored in the proposed PASS.

Safety in non-naive GHD patients. Information on safety (and efficacy) in non-naïve paediatric patients is lacking. Provided an adequate conversion is advised in section 4.2 the effects from the treatment naïve patients might be extrapolated to this non-naïve populationThe use in non-naïve patients will be part of the PASS.

Long-term safety. The long-term safety data from the ongoing extension studies do not raise additional safety concerns. The applicant is expected to submit the long-term safety data from the ongoing parts of the studies in due time (PAM). A PASS to collect more clinical data with somapacitan in children and adolescents, the near-adult final height and to collect safety data in the long–term especially regarding the potentially long term safety risks of diabetes and cancer has been proposed by the applicant. The study duration will be 10 years, with a minimum follow-up of patients for at least 5 years. This should cover the insufficient duration of the extension parts of the clinical studies (4172 and 4263) of 6.5 years and 3 years, respectively to respond to these uncertainties (NN8640-4787). This study was included in the updated RMP provided by the applicant.

2.6.10. Conclusions on the clinical safety

The safety profile of somapacitan in paediatric GHD patients is in line with that of adult GHD patients and other growth hormone products.

At present, limited data are available on the clinical effects of somapacitan in paediatric GHD patients under 3 years of age, adolescent GHD patients, and paediatric GHD patients who are non-naïve to growth hormone. Because of potential safety risks due to hormonal immaturity in GHD patients below the age of 3 years, the indication of somapacitan is restricted to GHD patients aged 3 years and above. Although efficacy and safety in adolescent GHD patients and non-naïve GHD patients can be assumed,

the clinical efficacy at an acceptable safety level of somapacitan will substantiated further as part of the PASS.

The applicant is expected to submit the long-term safety data from the ongoing parts of the studies in due time, as well as the proposed PASS.

The CHMP considers the following measures necessary to address issues related to safety:

A category 3 paediatric GHD register-based study (PASS) will be conducted. This will be a non-interventional, observational, register-based study to investigate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of safety concerns	
Important identified risks	None
Important potential risks	• Neoplasms • Diabetes mellitus type 2 • Medication errors (incorrect dose administration rate)
Missing information	• Patients with heart failure, NYHA class >2[a] • Patients with severe hepatic impairment[a] • Long-term safety

[a] Applicable for the adult GHD population only.

2.7.2. Pharmacovigilance plan

Study (study short name and title) Status (planned/ongoing)	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit-risk)				
None	N/A	N/A	Protocol submission Final report	N/A N/A

Category 2 – Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances (key to benefit-risk)				
None	N/A	N/A	Protocol submission Final report	N/A N/A
Category 3 - Required additional pharmacovigilance activities				
NN8640-4787 Paediatric GHD register-based study A non-interventional, observational, register-based study to investigate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice. Planned	Primary objective: To investigate long-term safety of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice with special focus on neoplasms and diabetes mellitus type 2. Secondary objective: To investigate safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice. To compare the occurrence of ADRs including neoplasms and diabetes mellitus type 2 in patients treated with somapacitan with historical data from literature of paediatric patients treated with daily somatropin.	Neoplasms Diabetes mellitus type 2 Medication errors (incorrect dose administration rate) Long-term safety	Protocol submission Final report	Pending Q1 2034 *(planned)*
Clinical trial NN8640-4172 (Phase 2) with safety extension part A randomised, multinational, active-controlled (open-labelled), dose finding (double-blinded), parallel group trial investigating efficacy and safety of once-weekly somapacitan treatment compared to daily GH treatment (Norditropin FlexPro) in GH treatment naïve pre-pubertal children with GHD. Design: Interventional clinical trial followed by a safety extension part (observational study) is ongoing. As soon as somapacitan has been approved for paediatric GHD, the observational study part	Primary objective: To evaluate the efficacy of multiple dose regimens of once-weekly somapacitan after 26 weeks of treatment in GH treatment naïve pre-pubertal children with GHD, compared to once-daily hGH administration (Norditropin FlexPro) Secondary objectives: To evaluate the safety of multiple dose regimens of once-weekly somapacitan during 26 weeks of treatment in GH treatment naïve pre-pubertal children with GHD. To evaluate the efficacy and safety of multiple dose regimens of once-weekly somapacitan for up to 364 weeks of treatment in GH treatment naïve pre-pubertal children with	General safety information (AEs/ADRs/ SAEs)	FSFV date LSLV date CTR date	23 Mar 2016 27 Sep 2024 *(planned)* 21 Mar 2025 *(planned)*

will be classified as a category 3 PASS.	GHD, compared to Norditropin FlexPro. To investigate the impact of somapacitan relative to Norditropin FlexPro on wellbeing, psychosocial functioning, treatment satisfaction and preference in GH treatment naïve pre-pubertal children with GHD by using patient reported outcome (PRO) questionnaires. To monitor somapacitan and Norditropin PK properties throughout the trial.			
Clinical trial NN8640-4263 (Phase 3a) with safety extension part A randomised trial comparing the effect and safety of once weekly dosing of somapacitan with daily Norditropin in children with GHD. Design: Interventional clinical trial followed by a safety extension part (observational study) is ongoing. As soon as somapacitan has been approved for paediatric GHD, the observational study part will be classified as a category 3 PASS.	Primary objective: To compare the effect of somapacitan vs Norditropin on longitudinal growth in children with GHD. Secondary objective: To compare the safety of somapacitan vs Norditropin in children with GHD.	General safety information (AEs/ADRs/ SAEs)	FSFV date LSLV date CTR date	20 May 2019 30 Sep 2025 *(planned)* 15 Jan 2026 *(planned)*
NN8640-4515 AGHD PASS A multinational, multicentre, prospective, single arm, observational, non-interventional post-authorisation safety study to investigate long-term safety of somapacitan in adults with GHD (AGHD) under routine clinical practice conditions. Planned	Primary objective: To investigate long-term safety of somapacitan therapy in patients with AGHD in the setting of routine clinical practice with special focus on neoplasms and diabetes mellitus type 2. Secondary objectives: To investigate safety and clinical parameters of somapacitan treatment under routine clinical practice in patients with AGHD. To investigate safety and clinical parameters of somapacitan treatment under routine clinical practice in patients with AGHD for the subgroups childhood-onset GHD and	Neoplasms Diabetes mellitus type 2 Medication errors (incorrect dose administration rate) Patients with heart failure, NYHA class >2 Patients with severe hepatic impairment Long-term safety	Protocol approval date Final report	25 Apr 2022 One year after the end of data collection

	females on oral oestrogen therapy, respectively. To investigate the number of patients achieving the age-adjusted IGF-I SDS levels up to the upper limit of the normal reference range (0 and +2). To evaluate the impact of somapacitan on patient functioning and wellbeing through a patient reported outcome measure (TRIM-AGHD).			

2.7.3. Risk minimisation measures

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
None	N/A	N/A
Important potential risks		
Neoplasms	Routine risk minimisation measures Routine risk communication: • SmPC Section 4.3, where a contraindication concerning any evidence of activity of a tumour is included. Risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4, where a special warning is included on neoplasms. • PL Section 2, where information is included on tumours. Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists. Additional risk minimisation measures • None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • List of relevant questions for spontaneous reporting for neoplasms Additional pharmacovigilance activities • Paediatric GHD register-based study NN8640-4787 • Trial NN8640-4172 with safety extension part • Trial NN8640-4263 with safety extension part • AGHD PASS NN8640-4515 • Novo Nordisk Standard Neoplasm Form for neoplasm relevant adverse event reports obtained from the PASS
Diabetes mellitus type 2	Routine risk minimisation measures Routine risk communication: • SmPC Section 4.2, where information is included concerning individual dose requirements based on the indications of paediatric GHD and AGHD, clinical response and serum IGF-I concentration. Risk minimisation activities recommending specific clinical measures to address the risk: • SmPC Section 4.4, where a special warning is included on glucose metabolism impairment. • PL Section 2, where information is included on high blood sugar. Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists. Additional risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • Paediatric GHD register-based study NN8640-4787 • Trial NN8640-4172 with safety extension part • Trial NN86404263 with safety extension part • AGHD PASS NN8640-4515

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
	• None proposed	
Medication errors (Incorrect dose administration rate)	Routine risk minimisation measures Routine risk communication: • SmPC Section 4.2, where information is included concerning the appropriately qualified and experienced physicians to initiate and monitor somapacitan treatment. In addition, Section 4.2 gives clear instructions regarding once-weekly dose, how to change the dosing day and the steps to follow when a dose is missed. • SmPC Section 5.1, where information regarding maintenance dose is included. Risk minimisation activities recommending specific clinical measures to address the risk: • Labelling Section 5, where the term 'Once weekly' is printed on the carton (on the inner and outer package in multi-package) and preload pen label. • PL Section 3, where information is included concerning how and when to use somapacitan. Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists. Additional risk minimisation measures • None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • Novo Nordisk will provide a detailed evaluation of Medication errors (Incorrect dose administration rate) with each periodic safety update report (PSUR), accompanied by a discussion on whether the risk of Medication errors (Incorrect dose administration rate) remains sufficiently minimised. Additional pharmacovigilance activities • Paediatric GHD register-based study NN8640-4787 • Trial NN8640-4172 with safety extension part • Trial NN8640-4263 with safety extension part • AGHD PASS NN8640-4515 • Novo Nordisk Standard Medication Error Form for reports obtained from the PASS

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Missing information		
Patient with heart failure, NYHA class >2 (for AGHD only)	Routine risk minimisation measures Routine risk communication: • SmPC Section 4.2, where information is included concerning individual dose requirements based on the clinical response and serum IGF-I concentration. Risk minimisation activities recommending specific clinical measures to address the risk: • None proposed Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists. Additional risk minimisation measures • None proposed	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection • None Additional pharmacovigilance activities • AGHD PASS NN8640-4515
Patients with severe hepatic impairment (for AGHD only)	**Routine risk minimisation measures** Routine risk communication: • SmPC Section 4.2, where information is included concerning individual dose requirements based on the clinical response and serum IGF-I concentration. • SmPC Section 4.2, under 'Special population', where information is included on patients with severe hepatic impairment. Risk minimisation activities recommending specific clinical measures to address the risk: • None proposed Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists. **Additional risk minimisation measures** • None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** • None **Additional pharmacovigilance activities** • AGHD PASS NN8640-4515

Safety concerns	Risk minimisation measures	Pharmacovigilance activities
Long-term safety	**Routine risk minimisation measures** Routine risk communication: • None proposed Risk minimisation activities recommending specific clinical measures to address the risk: • None proposed Other risk minimisation measures beyond the Product Information: • Medicine's legal status: • Somapacitan is a restricted prescription-only medicine, prescribed by specialists. **Additional risk minimisation measures** • None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection** • None **Additional pharmacovigilance activities** • Paediatric GHD register-based study NN8640-4787 • Trial NN8640-4172 with safety extension part • Trial NN8640-4263 with safety extension part • AGHD PASS NN8640-4515

2.7.4. Conclusion

The CHMP considered that the risk management plan version 3.2 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to the already approved patient leaflet for the Sogroya 5/10 mg/1.5 mL The bridging report submitted by the MAH has been found acceptable.

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Sogroya (somapacitan) is included in the additional monitoring list as it contains a new active substance and new biological product.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The indication approved at the time of the initial marketing authorisation of the medicinal product was for the replacement of endogenous growth hormone in adults with growth hormone deficiency.

The applicant has proposed to extend the indication to endogenous growth hormone in children and adolescents with growth failure due to GHD.

The proposed indication within the line extension grouped with the variation procedure was:

Sogroya is indicated for the replacement of endogenous growth hormone (GH) in children and adolescents with growth failure due to growth hormone deficiency (GHD) and in adults with growth hormone deficiency (AGHD).

GHD is characterised by too low systemic levels of the growth hormone. The growth hormone is produced by the somatotroph cells of the anterior pituitary gland. The secretion of growth hormone from the pituitary gland is stimulated by growth hormone-releasing hormone (GHRH) and inhibited by somatostatin, both of which are produced by the hypothalamus. GHD is often associated with defects in the pituitary gland or the hypothalamus.

The typical symptom of GHD in children is growth failure. Growth failure is suspected if the growth of paediatric study patients develops at a slower rate than expected based on the growth chart of the local geographic area.

The incidence of growth failure associated with GHD has been estimated to be approximately 1:4000 to 1:10,000.[10] Once GHD is diagnosed, the aim of growth hormone treatment is to normalise the growth rate during childhood and attainment of normal adult height.

In the current procedure, also an additional dose strength (15 mg somapacitan/ 1.5 ml solution) is proposed.

[10] Murray PG, Dattani MT, Clayton PE. Controversies in the diagnosis and management of growth hormone deficiency in childhood and adolescence. Arch Dis Child. 2016 Jan; 101(1):96-100. Epub 2015 Jul 7.

3.1.2. Available therapies and unmet medical need

Available therapies

The aim of the treatment is to normalize the growth rate during childhood and attainment of normal adult height. For over 30 years, GHD has been treated with daily recombinant human growth hormone. The effects of human growth hormone replacement in children can be evaluated by assessing the increase in height velocity and related auxological parameters and bone maturation.

With current treatment algorithms, paediatric recombinant human growth hormone doses are based on the body weight of the growing child, which corrects for the higher physiological need for growth hormone during growth compared to adults. For safety reasons, IGF-I plasma concentrations should be maintained in the normal age and sex-adjusted range. Periodic checks of IGF-I levels are required because they may increase over time, even if the growth hormone dosage does not change.

For paediatric GHD patients, medicinal products for daily (e.g. Omnitrope (EU/1/06/332), Nutropin Aq (EU/1/00/164)) or weekly (e.g. Ngenla (EU/1/21/1617), Skytrofa (EU/1/21/1607)) growth hormone supplementation are available.

Unmet medical need

While daily human growth hormone is safe and effective, its frequency of administration can be burdensome for both children and their caregivers. Although children with GHD treated with daily growth hormone replacement can achieve normal adult height, real-world outcomes have not matched expectations. Due to nonadherence rates ranging from 5 to 82% (Fisher 2013), most GHD patients do not reach their target genetic height (Guyda 1999, Lustig 2004), leaving an opportunity to improve treatment outcomes in paediatric GHD.

3.1.3. Main clinical studies

The pharmacokinetic, pharmacodynamic, and clinical effects of single doses of somapacitan were evaluated in a randomized, open-label Phase 1 study in 32 growth hormone treatment-experienced prepubertal GHD patients (study (NN8640-)4042).

In randomized Phase 2 study (NN8640-)4172, the pharmacodynamic and clinical effects of weekly somapacitan at a dosage of 0.04, 0.08, and 0.16 mg/kg/week were compared with those of daily somatropin at a dosage of 0.034 mg/kg/day (i.e. a total weekly dose of 0.24 mg/kg) in 59 growth hormone treatment-naïve pre-pubertal GHD patients (cohort I) during a 26-week main treatment period, followed by a 26-week extension period (total: 52 weeks). In the safety extension period from week 52 to week 156, all somapacitan-treated study patients received weekly somapacitan at a dosage of 0.16 mg/kg/week, while the same initial daily dosage of somatropin was continued. In the long-term safety extension period from week 156 up to week 364, all included study patients received weekly somapacitan at a dosage of 0.16 mg/kg/week. Paediatric GHD patients under 2.5 years of age (cohort II), female GHD patients aged 9-17 years and male GHD patients aged 10-17 years (cohort III) were also included in this study phase and also received weekly somapacitan at a dosage of 0.16 mg/kg/week. Inclusion and follow-up in the long-term safety extension period are ongoing.

In the randomized, pivotal Phase 3 study (NN8640-)4263, the pharmacodynamic and clinical effects of weekly somapacitan at a dosage of 0.16 mg/kg/week were compared with those of daily somatropin at a dosage of 0.034 mg/kg/day (i.e. a total weekly dose of 0.24 mg/kg) in 200 growth hormone

treatment-naïve pre-pubertal GHD patients during a 52-week main treatment period. In the extension period from week 52 to week 208 all included study patients received weekly somapacitan at a dosage of 0.16 mg/kg/week. The follow-up of study patients in this extension period is ongoing.

3.2. Favourable effects

Annualized height velocity, other growth-related parameters (as described below), and IGF-I SDS levels increased upon initiation of somapacitan treatment in paediatric GHD patients in both clinical studies 4172 and 4263. Overall, respective increases tended to be larger for a somapacitan starting dosage of 0.16 mg/kg/week as compared to 0.08 mg/kg/week in study 4172. It was explained that the somapacitan dosage of 0.16 mg/kg/week was selected as a starting dosage due to its more optimal treatment response.

The observed pharmacological effects with respect to the proposed 15 mg/1.5 ml somapacitan solution are in line with those of the authorized 5 mg/1.5 ml and 10 mg/1.5 ml somapacitan solutions.

Annualized height velocity at week 52. The estimated mean annualized height velocity at week 52 according to the hypothetical strategy (primary endpoint EMA) was 11.2 cm/year for somapacitan and 11.7 cm/year for somatropin in study 4263. Hence, the estimated treatment difference in height velocity at week 52 between somapacitan and somatropin was -0.5 cm/year (95% CI -1.1; 0.2). Non-inferiority of somapacitan relative to somatropin was confirmed for the hypothetical estimand as the lower bound of the 95% confidence interval (-1.1 cm/year) was higher than the predefined non-inferiority margin of -1.8 cm/year.

Height velocity SDS. In study 4263, the estimated mean changes from baseline in height velocity SDS at week 52 compared to baseline was comparable for somapacitan and somatropin (respectively 8.05 vs 8.82; estimated treatment difference -0.78 (95% CI -1.63, 0.08)).

Height SDS. In study 4263, the estimated mean changes from baseline in height SDS at week 52 compared to baseline was comparable for somapacitan and somatropin (respectively 1.25 vs 1.30; estimated treatment difference -0.05 (95% CI -0.18, 0.08)).

Bone age/ chronological age. In study 4263, the estimated mean change from baseline in bone age relative to chronological age at week 52 compared to baseline was comparable for somapacitan and somatropin (respectively 0.06 vs 0.08; estimated treatment difference -0.02 (95% CI -0.06, 0.01)).

IGF-I SDS levels and IGFBP-3 SDS levels. In study 4263, mean IGF-I SDS levels increased rapidly from baseline after initiating treatment with both somapacitan and somatropin. The observed mean IGF-I SDS increased from very low baseline levels (below -2) in both treatment groups to week 52 values within the normal range (-2 to +2). With a somapacitan starting dosage of 0.16 mg/kg/week IGF-I SDS levels within the range -2 up to +2 SDS levels were obtained in about 97% of paediatric GHD patients at week 52 in study 4263.

Change from baseline to week 52 in IGF-I SDS was similar between somapacitan and somatropin (2.37 for both; estimated treatment difference 0.04 (95% CI -0.29; 0.37)). In line with this, changes from baseline to week 52 in IGFBP-3 SDS levels (in-study data) were similar for somapacitan and somatropin (1.62 vs 1.61; estimated treatment difference 0.02 (95% CI -0.21; 0.24)).

Subgroup analyses. With respect to the primary endpoint in study 4263, subgroup analyses were conducted concerning age (<6 years vs. ≥ 6 years), gender, growth hormone treatment experience, and the Japanese study population. Regarding the height velocity at week 52 compared to baseline,

comparable trends in effects between somapacitan and somatropin were observed in GHD patients under 6 years of age (12.2 vs 12.6 cm/year; estimated treatment difference -0.4 (95% -1.4; 0.7)) and those aged 6 years and above (12.2 vs 12.6 cm/year; estimated treatment difference -0.4 (95% -1.4; 0.7)) in study 4263. For this endpoint similar trends were also observed in men (11.1 vs. 11.5 cm/year; estimated treatment difference -0.4 (95% -1.1; 0.3)) and women (11.8 vs 12.3 cm/year; estimated treatment difference -0.5 (95% -2.2; 1.1)). Later, it was shown that the improvements with respect to growth parameters were comparable for GHD patients of both different gender and pubertal status (Tanner stage 1 versus Tanner stage >1).

All study patients in study 4263 and cohort I of study 4172 were treatment-naïve at randomisation. Study patients in study 4172 who were initially treated with somatropin maintained growth and adequate IGF-I SDS levels after initiating somapacitan treatment.

Somapacitan also increased height velocity (cm/year) in the subgroup of 30 Japanese study patients. The height velocity estimates after 52 weeks were 10.3 cm/year and 9.9 cm/year, for somapacitan and somatropin, respectively, with an estimated treatment difference of 0.3 [95% CI -0.9; 1.5].

Hence, observed trends in effects were similar for study patients of different age (< 6 years and ≥ 6 years), gender, growth hormone treatment experience, and in the geographic region of Japan. This supports the use of somapacitan in naïve and growth hormone treatment-experienced patients of different ages and gender, also in Japan.

Treatment burden. In study 4263, the total scores of the treatment burden measure–child GHD-parent (TB-CGHD-P) scale (estimated treatment difference -6.0 (95% CI -10.0; -2.1)) and the treatment burden measure–child GHD-observer (TB-CGHD-O) scale (estimated treatment difference -2.4 (95% CI -5.7; 0.9)) tended to be more favourable for somapacitan as compared to somatropin at week 52.

In line with this, at week 52 of study 4263 96% of the respondents in study 4263 found the somapacitan and somatropin devices to be easy or very easy to use. At the cut-off of 10-Nov-2021, responses to the growth hormone patient preference questionnaire (GH-PPQ) at week 56 of study 4263, had been collected for 41 of the 68 study patients switching from somatropin to somapacitan after week 52. 37 Of the 41 study patients (90.2%) preferred somapacitan to somatropin, while the remaining 4 study patients had no preference. The most selected reasons listed for preferring somapacitan to somatropin were: “number of times needing to do injections” (20 of 37), “less worried about remembering to give injections” (16 of 37) and “child less worried about getting injections” (12 of 37). 28 Study patients (68.3%) reported they would be more adherent to somapacitan once-weekly than to daily growth hormone treatment.

Ancillary analyses. In total, 10 children in the somapacitan group and 4 children in the somatropin group in study 4263 were randomised in violation of inclusion or exclusion criteria. It was clarified later that these study patients stayed on treatment since the protocol deviations were assessed not to incur safety issues. It was shown later that the results with respect to height velocity in an additional per protocol analysis i.e. upon exclusion of the 14 subjects who did not meet the selection criteria for inclusion in study 4263 were almost identical to the results from the full on-treatment observation period data set (all included study patients): estimated treatment difference of -0.5 cm/year [95% CI -1.2; 0.2] for the per protocol analysis versus -0.5 cm/year [95% CI -1.1; 0.2] for the primary analysis.

The association between the treatment response and mid-parental height of the GHD study patients was initially unclear. In additional analyses of study 4263, the mean mid-parenteral height at baseline was comparable for GHD study patients in whom somapacitan or somatropin study treatment was initiated (respectively 168.8 and 167.2 cm). In addition, similar increases in height velocities across all 4 quartiles of the mid-parental height were observed for both somapacitan and somatropin treatment at week 52. Hence, GHD patients responded to somapacitan irrespective of their mid-parental height.

In study 4263, a confirmed GHD diagnosis was based on a peak growth hormone level of ≤ 10.0 ng/ml using the WHO International Somatropin 98/574 standard. However, in the provided CHMP scientific advice (EMEA/H/SA/2492/3/2018/PED/II), a more stringent 7 ng/ml growth hormone level upon stimulation was advised. It was later demonstrated that similar study results would have been obtained if the growth hormone peak level for diagnosis of GHD and eligibility into the study would be <7 instead of ≤10 ng/ml.
Preliminary analyses in studies 4172 and 4263 indicate that the clinical effects of somapacitan concerning growth-related parameters and IGF-I SDS levels are maintained with time.

Antibody development. Anti-somapacitan antibodies were observed in 20 study patients in study 4263 and 10 study patients in study 4172. Respective anti-somapacitan antibodies were non-neutralizing. The efficacy of somapacitan was neither affected by the formation of anti-somapacitan antibodies in study 4263 nor study 4172.

Compliance. The majority of paediatric GHD patients in study 4263 received the planned treatment, with a mean adherence among study patients on treatment of 95.8% for the somapacitan group and 88.3% for the somatropin group. Hence, the compliance rate for study treatment was high.

3.3. Uncertainties and limitations about favourable effects

In both studies 4172 and 4263, there was an open-label comparison between the clinical effects of somapacitan and somatropin treatment. Because of this, the study results of this study may be affected by bias to some extent. Growth parameters which concern key endpoints in this study can be measured objectively. However, subjective evaluations such as the evaluation of treatment burden and patient preferences are at increased risk of information bias. Knowledge about the allocated study treatment may affect the responses of study patients to such endpoints. Because of this, caution is needed with respect to the interpretation of subjective study endpoints.

At week 56 of study 4263, 90.2% of the somapacitan-treated but none of the somatropin-treated study patients preferred the treatment which they had received. Reasons for somapacitan preference included ‘number of times needing to do injections’, ‘less worried about remembering to give injections’, and ‘child less worried about getting injections’. Although a preference for somapacitan treatment is acknowledged, it is remarked that the preference assessment is subjective. In the case of an open-label treatment-comparison as in study 4263, knowledge of the allocated study treatment may affect the responses of study patients to subjective evaluations (information bias). Because of this, caution is needed with respect to the evaluation of treatment preference in study 4263.

The final results of on-going studies 4172 and 4263 paediatric GHD patients will be submitted after the approval of the extension of indication of somapacitan, as part of the post-authorisation measures.

No study patients have thus far reached near adult height. In line with EMA scientific advice, EMEA/H/SA/2492/3/2018/PED/II determination of the final height of somapacitan-treated paediatric GHD patients in the conducted clinical studies is important to gain insight into the long-term clinical efficacy of somapacitan in patients who continued to use somapacitan without switching to or addition of alternative growth hormone options. This will be studied as part of the post-authorisation measures.

3.4. Unfavourable effects

Overall, 73.2% of patients in the somapacitan 0.16 mg/kg/week group and 67.1% in the somatropin group experienced an adverse event. The majority of the adverse events was mild to moderate, and for the majority of cases, the adverse events were resolved without sequela. There were no treatment discontinuations due to adverse events.

The most frequent adverse events in children treated with somapacitan were pyrexia (12.4%) and nasopharyngitis (11.9%), and headache (9.3%). A comparable number of patients experienced these adverse events in the somatropin group.

Constipation occurred more frequently in the somapacitan group (4.6%) compared to the somatropin group (1.2%) in the safety pool.

Pain in the extremity is one of the most frequently reported adverse events, with 3.7% of patients in the somatropin group and 7.2% in the somapacitan group.

In total, 5 events of lipoatrophy/lipodystrophy were reported, 2 events in 2 patients in study 4172 were judged as severe and probably related to the study drug and 3 events in 2 patients in study 4263 were judged as mild-moderate and with causality questioned.

In general, the incidence of serious adverse events was low within the safety pool: 10 patients (5.2%) experienced 14 events in the somapacitan group, and 4 patients (4.9%) experienced 6 serious adverse events in the somatropin group.

Non-neutralizing anti-drug antibodies were found in 15.2% of patients in the somapacitan arm and 10.3% of patients in the somatropin arm in study 4263.

3.5. Uncertainties and limitations about unfavourable effects

The extent of the exposure of children to somapacitan is considered extensive considering the rarity of the disease. 183 (94.3%) children were exposed for more than 12 months, which is also quite extensive. The long-term safety data is somewhat more limited, with only 39 patients exposed for more than 21 months.

Since the majority of patients received the to-be-marketed dose of 0.16 mg/kg/week, no dose-response assessment is possible for adverse events.

Although there are enough clinical data in all subsets of the paediatric GHD population with somatropin, the clinical data are too limited with somapacitan in GHD patients < 2.5 years old as only one child < 2.5 years old was included in cohort II of study 4172. No benefit-risk assessment can be made based on these data. Moreover, the PDCO provided a waiver for all subsets of the paediatric GHD population on the grounds of lack of significant therapeutic benefit and likely lack of safety due to

potential induction of neoplasms and cerebrovascular diseases amongst the greatest theoretical risks of long-acting preparations due to their different PK profiles. Still, the safety of growth hormone preparations has been monitored for decades and no sign of an increased risk of neoplasms has been identified so far. In addition, no neoplasms or cases of onset of diabetes mellitus type 2 have been recorded during the clinical studies conducted in support of the present application. The CHMP also assessed that these important potential risks were addressed by the applicant through adequate routine risk minimization measures (Product Information). In addition, they are also mitigated through the proposed PASS which will address these safety concerns in the post-marketing setting.

Further, the long-term efficacy and safety of long-acting growth hormone in these hormonally immature, very young GHD patients are unknown from the literature, and other long acting medicinal products were only recently authorised for marketing. Therefore, the current indication is restricted to GHD patients aged 3 years and above.

The clinical data with somapacitan are currently limited in adolescent GHD patients from 12 to 17 years old, although it is acknowledged that the clinical effects of somapacitan are still under evaluation in Cohort III of study 4172. It is not common to study the growth in pubertal children as the sexual development (and accompanying changes in sex hormones) dilutes the effect of growth hormone. The effects in adolescents are commonly extrapolated (as is done for other growth hormone-containing products) from pre-pubertal children. However, given the lack of patients studied with long-acting somapacitan resulting in different IGF-I profiles, the applicant will include these patients in the PASS.

Despite the imbalance of incidence of constipation between the somapacitan and somatropin group, these events were often judged as unrelated to treatment. Although alternative causes for constipation can be identified for many patients, it is claimed that hypothyroidism may play a role in the cause of constipation

3.6. Effects Table

Table 22 Effects Table for somapacitan in paediatric GHD patients (data cut-off: 17 December 2021)

Effect	Short Description	Unit	Somapacitan (A)	Somatropin (B)	Uncertainties/ Strength of evidence	References
Favourable Effects						
AHV	Mean annualized height velocity at week 52	cm/ year	11.2	11.7	SoE: Δ A vs. B -0.5 (95% CI -1.1; 0.2). Non-inferiority A relative to B demonstrated (non-inferiority margin: -1.8 cm/year) The effects of A. vs. B with respect to the following secondary endpoints are in line with the primary endpoint: - Mean height SDS at week 52 compared to baseline (1.25 vs. 1.30; difference -0.05 (95% CI -0.18; 0.08)) - Mean height velocity SDS at week 52 compared to baseline (respectively 8.05 vs 8.82; difference -0.78 (95% CI -1.63, 0.08)	Study 4263

					- Mean change from baseline in bone age relative to chronological age at week 52 compared to baseline (0.06 vs. 0.08; difference -0.02 (95% CI -0.06; 0.01)) - Change from baseline to week 52 in mean IGF-I SDS (both 2.37; difference 0.04 (95% CI -0.29; 0.37)) Clinical effects somapacitan comparable for GHD patients of different midparental height, gender and pubertal status (Tanner stage 1 versus Tanner stage >1). Unc: open-label treatment comparison, long-term effects unclear	
Compliance		%	95.8	88.3	Unc: Compliance may decrease with time.	Study 4263
Unfavourable Effects						
Most common adverse events	Pyrexia Nasopharyngitis Headache	% of patients	12.4 11.9 9.3	11.0 12.2 9.8	SoE: As the common adverse event known from growth hormone are comparable this supports the non-inferiority.	Safety pool
ADAs	Occurrence of anti-drug antibodies	% of patients	15.2	10.3	ADA titers were generally low and ADA's were non-neutralising.	Study 4263

Abbreviations: Δ: estimated treatment difference, ADA: anti-drug antibody, CI: confidence interval, IGF-I: insulin-like growth factor I, SDS: standard deviation score, vs.: versus

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Somapacitan is currently authorized for marketing in adult GHD patients (EU/1/20/1501). The study results of conducted clinical studies also support the clinical efficacy of somapacitan in paediatric GHD patients. Results concerning growth-related parameters were in line with each other across different studies. Somapacitan also promotes growth in paediatric GHD patients who have received prior somatropin treatment. Growth was maintained in somapacitan-treated GHD patients. Clinical effects of somapacitan up to a treatment period of 52 weeks were comparable for GHD patients of different mid-parental height, gender and pubertal status (Tanner stage 1 versus Tanner stage >1). Bone age relative to chronological age was similar in study patients treated for one year with either somapacitan or somatropin. The efficacy of somapacitan was also supported by several patient/parent-reported outcomes.

However, clinical data (efficacy and safety) with somapacitan are lacking, in particular, paediatric GHD subgroups, namely children < 2.5 years old, and non-naïve GHD patients. The clinical effects of somapacitan in patients under 2.5 years are currently evaluated in cohort II of study 4172. Especially in GHD patients below the age of 3 years, the benefit-risk cannot be established based on the information provided at the time of marketing authorization application, considering potentially increased safety risks due to hormonal immaturity. As a result of these uncertainties, the indication is restricted to patients 3 years or older.

Altogether, the efficacy data provide robust evidence for the clinical efficacy of weekly somapacitan treatment in paediatric GHD patients studied.

The overall safety profile of somapacitan is in line with that of adults and in line with the known safety profile of growth hormone replacement therapies. Differences in constipation and pain in extremities were observed between the somapacitan and somatropin groups.

Lipodystrophy is a known but rare side effect of injectable growth hormone. The risk of lipodystrophy can be adequately mitigated by injection side rotation as stated in the SmPC.

Anti-drug antibodies were observed in a substantial number of patients. This is not uncommon for growth hormone replacement. In addition, the anti-drug antibodies were found to be non-neutralising and did not affect pharmacokinetics, safety or efficacy.

The observed pharmacological effects concerning the proposed 15 mg/1.5 ml somapacitan solution are in line with those of the authorized 5 mg/1.5 ml and 10 mg/1.5 ml somapacitan solution

3.7.2. Balance of benefits and risks

The study results of conducted clinical studies support the efficacy of once-weekly somapacitan in paediatric GHD patients. This also applies to the proposed additional dose strength of 15 mg somapacitan per 1.5 ml solution. Results concerning different growth-related parameters were in line with each other and consistent over time across different studies. The results of the clinical studies were in line with the literature, indicating that growth in paediatric GHD patients continues at a lower, more constant rate after an initial catch-up growth in treatment-non-naïve paediatric GHD patients.[11]

An improvement concerning different patient/parent-reported outcomes was also demonstrated. The majority of GHD study patients preferred weekly somapacitan above daily somatropin treatment.

From the limited population, a short-term safety profile of somapacitan emerged that appears to be in line with the known growth hormone-containing medicinal products.

Considering, on the one hand, the efficacy of weekly somapacitan as compared to daily somatropin concerning growth-related parameters, the convenience of once-weekly somapacitan administration, and on the other hand, the comparable short-term safety profile of weekly somapacitan as compared to daily somatropin treatments, the benefits of short-term somapacitan treatment outweigh its risks.

The long-term safety risks of somapacitan treatment are yet unknown. A PASS to collect more clinical data with somapacitan in children and adolescents with GHD, the near-adult final height and to collect safety data in the long–term, especially regarding the potentially long term safety risks of diabetes and cancer has been proposed by the applicant. The study duration will be 10 years, with a minimum follow-up of patients for at least 5 years. This should cover the insufficient duration of the extension parts of the clinical studies (4172 and 4263) of 6.5 years and 3 years, respectively to respond to these uncertainties (NN8640-4787). This study will be a category 3 study.

Although the benefit/risk balance of the somapacitan growth hormone replacement treatment for paediatric GHD patients included in the studies is positive, the safety in GHD patients below 3 years of age cannot be established. Because of this, the indication of somapacitan is restricted to GHD patients aged 3 years and above). The CHMP has concluded that the benefit risk ratio for the proposed extension of indication is positive.

[11] Ranke MB, Lindberg A, Mullis PE, Geffner ME, Tanaka T, Cutfield WS, Tauber M, Dunger D. Towards optimal treatment with growth hormone in short children and adolescents: evidence and theses. Horm Res Paediatr. 2013;79(2):51-67.

The CHMP has also agreed on the fact that proposed line extension to add a somapacitan dose strength of 15 mg somapacitan/1.5 ml solution is acceptable.

3.7.3. Additional considerations on the benefit-risk balance

The somapacitan medicinal product Sogroya (EU/1/20/1501) is indicated for the replacement of endogenous growth hormone in adults with GHD. The long-term safety risks of somapacitan are to be evaluated in a PASS.

3.8. Conclusions

The overall benefit/risk balance of Sogroya is positive, subject to the conditions stated in section 'Recommendations'.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Sogroya is not similar to Skytrofa or Ngenla within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See appendix on similarity.

Outcome

Based on the CHMP review of data on quality,safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, Sogroya 15 mg/1.5 mL solution for injection in pre-filled pen is favourable in the following indication(s):

Sogroya is indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD).

The CHMP therefore recommends the extension(s) of the marketing authorisation for Sogroya subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- Risk Management Plan (RMP)

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

In addition, CHMP recommends the variations to the terms of the marketing authorisation, concerning the following changes:

Variations requested		Type	Annexes affected
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIA, IIIB and A
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

Extension application to add a new strength of 15 mg/1.5 mL solution for injection in pre-filled pen grouped with a type II variation C.I.6 to add a new indication 'Sogroya is indicated for the replacement of endogenous growth hormone (GH) in children aged 3 years and above and adolescents with growth failure due to growth hormone deficiency (paediatric GHD), and in adults with growth hormone deficiency (adult GHD).', based on results from the completed main 52-week period of the confirmatory phase 3 trial (4263), supported with long-term data from the phase 2 trial (4172), up to week 208 completed. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC have been updated and the Package Leaflet has been updated accordingly. A revised RMP version 3.2 was provided as part of the application.

5. Appendices

5.1. CHMP AR on similarity dated 25 May 2023