EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

19 September 2024
EMA/436219/2024
Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Sogroya

Somapacitan

Procedure no: EMEA/H/C/005030/P46/008

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

Status of this report and steps taken for the assessment				
Current step	**Description**	**Planned date**	**Actual Date**	**Need for discussion**
☐	Start of procedure	22/07/2024	22/07/2024	☐
☐	CHMP Rapporteur Assessment Report	26/08/2024	09/08/2024	☐
☐	CHMP members comments	09/09/2024	09/09/2024	☐
☐	Updated CHMP Rapporteur Assessment Report	12/09/2024	12/09/2024	☐
☒	CHMP adoption of conclusions:	19/09/2024	19/09/2024	☐

Table of contents

Abbreviations

AE	adverse event
ANCOVA	analysis of covariance
CI	confidence interval
COVID-19	coronavirus disease 2019
CT	computerised tomography
CTR	clinical trial report
ECG	electrocardiogram
FAS	full analysis set
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
GHD-CIM	growth hormone deficiency – child impact measure
GHD-CTB	growth hormone deficiency – child treatment burden
GHD-PTB	growth hormone deficiency – parent treatment burden
HbA1c	glycated haemoglobin
hGH	human growth hormone
HV	height velocity
HVSDS	height velocity standard deviation score
HSDS	height standard deviation score
IGF-I	insulin-like growth factor I
IGFBP-3	insulin-like growth factor binding protein 3
IMP	investigational medicinal product
IND	investigational new drug
INN	international non-proprietary name
LAR	legally acceptable representative
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed model for repeated measurements
MRI	magnetic resonance imaging
PD	protocol deviation
PK	pharmacokinetics
PP	per-protocol analysis set
PRO	patient reported outcome
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SD	standard deviation
SDS	standard deviation score
s.c.	subcutaneous
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment emergent adverse event
WHO	World Health Organisation

1. Introduction

On 25 June 2024, the MAH submitted a completed paediatric study for Sogroya, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that trial NN840-4468 is a standalone study.

Trial NN8640-4468 (REAL 6) in children with GHD will serve as the basis for market authorisation application within this indication in China. The trial is not part of a Paediatric Investigational Plan (PIP), as Sogroya (somapacitan) has been granted a PIP waiver (EMEA-001469-PIP01-13).

The trial design of NN8640-4468 was overall similar to the design of the global, pivotal trial in children with GHD (trial NN8640-4263).

2.2. Information on the pharmaceutical formulation used in the study

Somapacitan is provided as a ready-to-use liquid formulation of 5, 10 or 15 mg in a 1.5 mL cartridge, provided in a disposable prefilled PDS290 pen-injector for multiple dosing. The formulation of somapacitan drug product investigated in trial NN8640-4468 is identical to the formulation investigated in the pivotal paediatric trial NN8640-4263 and to the formulation in the approved product Sogroya.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

Trial NN840-4468; a trial comparing the efficacy and safety of once weekly dosing of somapacitan with daily somatropin (Norditropin) in Chinese children with growth hormone deficiency.

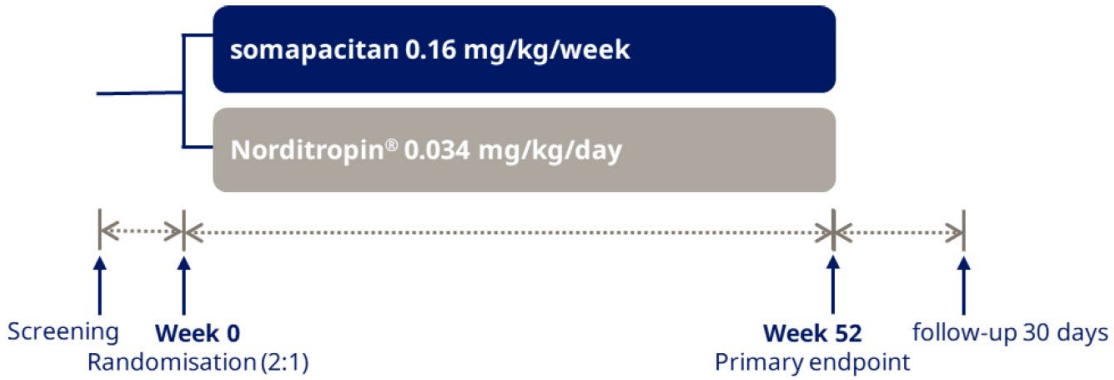
2.3.2. Clinical study

Trial NN840-4468

Description

Trial NN840-4468 was a randomised, multicentre, open-labelled, two arm trial to confirm non-inferiority of efficacy and investigate safety of once weekly s.c. treatment of somapacitan compared to daily s.c. growth hormone (GH) (somatropin) treatment in Chinese prepubertal children with GHD.

Figure 1. Trial design.



Assessor's comment

Chinese prepubertal children with GHD were randomized to receive weekly s.c. treatment of somapacitan or daily s.c. growth hormone (GH) (somatropin) for 52 weeks. The design of the trial strongly resembles the design of the REAL 4 paediatric study which supported the extension of the indication to paediatric patients.

Methods

Study participants

Key inclusion criteria:

1. Informed consent of parent or legally acceptable representative of subject and child assent, as age-appropriate, must be obtained before any trial-related activities.
2. Pre-pubertal children:
    a. Boys: age ≥2 years and 26 weeks and ≤11.0 years at the time of signing informed consent and testis volume < 4 ml.
    b. Girls: age ≥2 years and 26 weeks and ≤10.0 years at the time of signing informed consent. Tanner stage 1, for breast development (no palpable glandular breast tissue).
3. Confirmed diagnosis of growth hormone deficiency determined by two different GH 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.
4. Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and gender according to Chinese general population standards at screening.
5. Impaired height velocity defined as annualised height velocity at screening less than 7 cm/year for subjects between 2.5 and 3 years old and less than 5 cm/year for subjects from 3 years and above calculated over a time span of minimum 3 months and maximum 18 months prior to screening according to Chinese guideline and expert consensus on children with short stature and GH therapy.
6. No prior exposure to GH therapy or IGF-I treatment.

7. Bone age less than chronological age at screening.
8. Body Mass Index >5th and <95th percentile, body mass index-for-age growth charts according to the Chinese general population standards.
9. IGF-I <-1.0 SDS at screening, compared to age and gender normalized range measured at central laboratory.
10. No intracranial tumour confirmed by magnetic resonance imaging or computer tomography scan. An image or scan taken within 9 months prior to screening can be used as screening data if the medical evaluation and conclusion is available.

Key exclusion criteria:

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as randomisation.
3. Receipt of any investigational medicinal product within 3 months before screening or participation in another clinical trial before randomisation.
4. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements (e.g. Turner syndrome, chromosomal aneuploidy, significant spinal abnormalities, congenital abnormalities, family history of skeletal dysplasia).
5. Children born small for gestational age (birth weight 10th percentile of the recommended gender-specific birth weight for gestational age according to national standards in China.
6. Children diagnosed with diabetes mellitus or screening values from central laboratory of fasting plasma glucose ≥126 mg/dl (7.0 mmol/L) or HbA1c ≥6.5%.
7. Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.
8. Children requiring inhaled glucocorticoid therapy at a dose greater than 400 µg/day of inhaled budesonide or equivalents for longer than 4 consecutive weeks within the last 12 months prior to screening.
9. Concomitant administration of other treatments that may have an effect on growth, e.g., but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder.
10. Diagnosis of attention deficit hyperactivity disorder.
11. Prior history or presence of malignancy including intracranial tumours.
12. Prior history or known presence of active Hepatitis B or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B).
13. Any clinically significant abnormal laboratory screening tests, as judged by the investigator.
14. Any disorder which, in the opinion of the investigator, might jeopardize subject's safety or compliance with the protocol.
15. The subject or the parent/legally acceptable representative is likely to be non-compliant in respect to trial conduct, as judged by the investigator.
16. Children with hypothyroidism and/or adrenal insufficiency not on adequate and stable replacement therapy for at least 90 days prior to randomisation.

Assessor's comment

This study included growth hormone treatment-naïve paediatric patients aged between 2.5 years and 10 for girls and 11 years for boys, with a confirmed diagnosis of GHD defined as a peak growth hormone level of ≤10.0 ng/ml.

GHD is a rare endocrine disorder, and it is assumed that there is no apparent racial difference in the incidence of GHD. However, most epidemiological studies are performed in Europe and global population-based registries are lacking (Mameli et al, Endocrine 2024).

Treatments

The treatments administered are described in Table 1.

Table 1. Treatments administered provided by Novo Nordisk A/S

Treatment	**Somapacitan**	**Norditropin®**
Trial product name	Somapacitan	Somatropin (INN name)
Trial product type	IMP, test product	IMP, reference therapy
Pharmaceutical form	Solution for injection	Solution for injection
Route of administration	Subcutaneous	Subcutaneous
Medical device	Pen injector PDS290	Pen injector PDS290 (FlexPro®)
Trial product strength	5 mg/1.5 ml 10 mg/1.5 ml 15 mg/1.5 ml	10 mg/1.5ml
Dose and dose frequency	0.16 mg/kg, once weekly	0.034 mg/kg once daily
Dosing instructions and administration	Subjects (and parent/LAR) were trained according to the directions for use in how to handle the PDS290 somapacitan pen-injector when handed out the first time. Training was documented and repeated during the trial at regular intervals to ensure correct use of the PDS290 somapacitan pen-injector	Subjects (and parent/LAR) were trained according to the directions for use in how to handle the Norditropin® FlexPro® when handed out the first time. Training was documented and repeated during the trial at regular intervals to ensure correct use of Norditropin® FlexPro®

Abbreviations: IMP = investigational medicinal product; INN = international non-proprietary name; LAR = legally acceptable representative

The total trial duration for a subject was up to 70 weeks approximately. The trial duration included a variable 14 weeks of screening period, 52 weeks treatment period and minimum 30 days of follow-up.

If IGF-I SDS exceeds +2.5 SDS at two consecutive visits the investigator will be informed by Novo Nordisk. Dose reduction must then be done by a 25% of the current dose.

Assessor's comment

Dosing in the study is conform the SmPC. However, the SmPC states regarding elevated IGF-I SDS, that in case of IGF-I (SDS) > 2 it should be reassessed after a subsequent somapacitan administration. If the value remains > 2, reducing the dose by 0.04 mg/kg/week is recommended.

Objective(s)

Table 2. Objectives and endpoints

Objectives	**Endpoints**		
	Title	**Time frame**	**Unit**
Primary To compare efficacy of somapacitan vs somatropin on longitudinal growth in Chinese children with GHD.	**Primary**:		
	Height Velocity	Height Velocity (annualized) at week 52	cm/year
	Supportive secondary:		
	Efficacy:		
	Change in bone age	From visit 1 to week 52	Years
	Change in Height Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10
	Change in Height Velocity Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10
	Pharmacodynamics:		
	Change in IGF-I Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10
	Change in IGFBP-3 Standard Deviation Score	From baseline (week 0) to week 52	-10 to +10
Secondary To compare safety of somapacitan vs somatropin in Chinese children with GHD.	**Supportive secondary**:		
	Safety:		
	Change in fasting plasma glucose	From baseline (week 0) to week 52	mmol/L
	Change in HbA_{1c}	From baseline (week 0) to week 52	%

Abbreviations: GHD = growth hormone deficiency; IGF-I = insulin-like growth factor I; IGFBP3 = insulin-like growth factor binding protein 3; HbA1c = glycated haemoglobin.

Assessor's comment

The objective of Trial N840-4468 was to confirm non-inferiority of efficacy and investigate safety of somapacitan compared to somatropin in Chinese prepubertal children with GHD.

Outcomes/endpoints

See Table 2 above.

Sample size

A total of 110 subjects were randomly assigned to trial product. The sample size calculation was based on the primary estimand. It was expected that the proportion of subjects with no landmark visit data or who discontinued randomised treatment before landmark visit to be 10% with similar withdrawal reasons in the two treatment groups. It was expected that subjects who discontinued their randomised treatment would start on ancillary treatment, if no medical reasons were prohibited. Thus, data assessed after discontinuation of the randomised treatment was not used for the primary analysis of the primary endpoint based on the primary estimand. Assuming the same proportions of subjects with no landmark visit and subjects discontinuing randomised treatment but have landmark visit data in the two groups leads to the following sample size calculation.

The sample size was determined using a non-inferiority margin of -2.0 cm/year for growth velocity and a one sided two-group t-test with a significance level of 2.5% for a 2:1 randomisation ratio between somapacitan and somatropin.

Randomisation and blinding (masking)

Eligible subjects were randomised in a 2:1 manner to receive either somapacitan or somatropin. The randomisation was stratified by age (<6 versus ≥6 years), gender (boys versus girls) and GH peak (< 7 versus ≥ 7 ng/ml) to minimize bias on the primary endpoint.

This was an open study, no blinding procedures were in place.

Statistical Methods

The following analysis sets were defined in the protocol and the SAP, prior to unblinding:

- Full analysis set (FAS): All subjects randomised. Exclusion of data from analyses was used restrictively, and normally no data was to be excluded from the FAS. Subjects were analysed according to the randomised treatment.
- Safety analysis set (SAS): All subjects randomly assigned to trial treatment and who took at least 1 dose of trial product. Subjects were analysed according to the treatment they actually received.
- Per protocol analysis set (PP): Subjects from FAS who had not violated any inclusion/exclusion criteria and had used the randomised treatment for at least 47 weeks (for subjects receiving somapacitan) or 329 days (for subjects receiving somatropin) corresponding to 90% of the planned exposure. Subjects were analysed according to the treatment they actually received.

All efficacy endpoints were analysed using FAS and all safety endpoints were analysed using SAS. The primary endpoint was additionally analysed using PP as a support to the results achieved using FAS under the hypothetical strategy.

Two observation periods were defined:

- on-treatment: from first administration and up until last trial contact, visit 7 or 14 days after last administration, whichever came first
- in-trial: from first administration and up until last trial contact or visit 8, whichever came first

Analysis based on the 'in-trial' observation period was to be viewed as supplemental analysis to the analysis based on the 'on-treatment' analysis.

Analysis of efficacy endpoints

Height Velocity = (height at 52 weeks visit - height at baseline)/(time from baseline to 52 weeks visit in years).

Hypothesis testing for the primary endpoint was done by testing H0: D≤−2 cm/year vs HA: D>-2 cm/year, where D was the mean treatment difference (somapacitan – somatropin). Non-inferiority of somapacitan was considered confirmed if the lower boundary of the two-sided 95% confidence interval was above -2 cm/year.

Height SDS was derived using Chinese general population standards[1] and HV SDS will be derived using Prader standards[2] as reference data. The formula to calculate height SDS is as below:

Height SDS = ((Height / M)**L-1) / (L*S)

[1] LI Hui, JI Cheng-ye, ZONG Xin-nan, ZHANG Ya-qin. Height and weight standardized growth charts for Chinese children and adolescents aged 0 to18 years. Chinese Journal of Pediatrics,2009,47(7):487-492
[2] 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.

Height: height at the time of assessment, L: The sex and age-specific power in the Box-Cox transformation, M: The sex and age-specific median, S: The sex and age-specific generalized coefficient of variation.

For bone age assessment, X-rays of left hand and wrist was made for bone age assessment according to the Greulich and Pyle atlas. Bone age was analysed using an ANCOVA model on bone age/chronological age assessed at week 52 and the model included treatment, sex, age group, GH peak group and sex by age group interaction term as factors and baseline bone age/chronological age as a covariate. The treatment difference estimate was reported with corresponding 95% CI and p-value.

IGF-I and IGFBP-3 was used to evaluate the pharmacodynamics (PD) of somapacitan and somatropin. All samples were drawn prior to trial product administration.

The following Patient reported outcome questionnaires were collected in the trial:

- GHD-CIM (Growth Hormone Deficiency – Child Impact Measure)
- GHD-CTB (Growth Hormone Deficiency – Child Treatment Burden)
- GHD-PTB (Growth Hormone Deficiency – Parent Treatment Burden)

Analysis of safety endpoints

The safety endpoints were analysed using descriptive statistics based on the 'on –treatment' observation period and the 'in-trial' observation period. All AEs and SAEs were collected from the first trial-related activity after obtaining informed consent and until the follow up visit/the end of trial visit.

All anti-drug antibody (ADA) samples were drawn prior to trial product administration if trial product administration was planned on the sampling day. Confirmed anti-somapacitan antibody positive samples were further tested for cross-reactivity to hGH.

Assessor's comment

The assessments are considered adequate and relevant for the determination of efficacy on longitudinal growth and safety of somapacitan compared to somatropin.

Results

Participant flow

In total, 242 children were screened and 110 (100%) children with GHD were randomised and exposed to treatment. There were 132 children considered screen failures. The main reason for screen failure was violation of inclusion criteria number 9.

Study conduct

Protocol deviations (PDs) were categorised as important or non-important and into different categories according to a set of pre-specified categories and subcategories. Important PDs were deviations that could significantly impact the completeness, accuracy and/or reliability of the trial data or that could significantly affect the subject's rights, safety or well-being.

The cut-off date (i.e., the database lock date) for inclusion of important PDs in the CTR is 05 February 2024.

Important PDs comprised 18 site-level PDs and 58 subject-level PDs. There were no trial-level PDs reported. There were no important differences in the number or type of important PDs reported between sites or subjects. A substantial proportion of the PDs in the category trial procedures/assessments were related to the COVID-19 pandemic. Based on the totality of the important PDs, the important PDs were not considered to have an overall impact on trial conduct, patient safety or data interpretation.

Recruitment

Trial subjects were screened, randomised, and assigned to treatment at 20 sites in China.

Initiation date was 22 July 2021 and the primary completion date was 17 November 2023. The trial completion date: 18 December 2023. The results presented reflect the data available in the clinical database as of 05 February 2024.

Baseline data

At baseline, demographics were similar between the somapacitan and somatropin groups (Table 3). Baseline height, body weight, GH peak, HV, HVSDS, HSDS and IGF-I SDS were similar between the somapacitan and somatropin groups (Table 4 and Table 5).

Table 3. Summary of demographics – full analysis set

	Norditropin		somapacitan		Total	
	N	(%)	N	(%)	N	(%)
Number of subjects	36		74		110	
Age group						
N	36	(100.0)	74	(100.0)	110	(100.0)
< 6 years	18	(50.0)	36	(48.6)	54	(49.1)
>= 6 years	18	(50.0)	38	(51.4)	56	(50.9)
Sex						
N	36	(100.0)	74	(100.0)	110	(100.0)
Female	6	(16.7)	9	(12.2)	15	(13.6)
Male	30	(83.3)	65	(87.8)	95	(86.4)
Race						
N	36	(100.0)	74	(100.0)	110	(100.0)
Asian	36	(100.0)	74	(100.0)	110	(100.0)
Peak GH level(ng/ml)						
N	36	(100.0)	74	(100.0)	110	(100.0)
< 7	18	(50.0)	40	(54.0)	58	(52.7)
>= 7	18	(50.0)	34	(46.0)	52	(47.3)
GHD cause						
N	36	(100.0)	74	(100.0)	110	(100.0)
Idiopathic	33	(91.7)	72	(97.3)	105	(95.5)
Organic	2	(5.6)	2	(2.7)	4	(3.6)
Missing*	1	(2.8)	0		1	(0.9)

N: Number of subjects, %: Percentage, GHD: Growth hormone deficiency
*Subject with a genetic variant known to cause GHD, who could not be classified as idiopathic or organic.

Table 4. Summary of baseline characteristics – full analysis set

	Norditropin	somapacitan	Total
Number of subjects	36	74	110
Age (yrs)			
N	36	74	110
Mean (SD)	6.5 (2.3)	6.6 (2.1)	6.5 (2.2)
Median	6.0	6.0	6.0
Min ; Max	2.6 ; 10.7	2.5 ; 10.9	2.5 ; 10.9
Height (cm)			
N	36	74	110
Mean (SD)	106.3 (13.8)	107.4 (12.1)	107.1 (12.6)
Median	105.8	104.8	105.4
Min ; Max	83.7 ; 127.5	82.7 ; 129.6	82.7 ; 129.6
Body weight (kg)			
N	36	74	110
Mean (SD)	17.7 (5.1)	17.7 (4.2)	17.7 (4.5)
Median	16.8	17.5	17.2
Min ; Max	9.5 ; 28.7	10.0 ; 30.5	9.5 ; 30.5
BMI (kg/m^2)			
N	36	74	110
Mean (SD)	15.4 (1.1)	15.2 (1.1)	15.2 (1.1)
Median	15.3	15.1	15.1
Min ; Max	13.5 ; 18.8	13.5 ; 19.5	13.5 ; 19.5
GH peak (ug/L)			
N	36	74	110
Mean (SD)	6.4 (2.6)	6.2 (2.6)	6.3 (2.6)
Median	7.0	6.9	7.0
Min ; Max	0.6 ; 9.9	0.1 ; 10.0	0.1 ; 10.0

N: Number of subjects, BMI: Body mass index, GH: Growth hormone, SD: Standard deviation, yrs: Years

Number analysed

Of the 110, 74 children were exposed to somapacitan and 36 to somatropin. Of the 110 randomised subjects, 103 (93.6%) subjects completed both the treatment and the trial period. Three children in the somapacitan group and 4 children in the somatropin group discontinued trial treatment prematurely and were withdrawn from the trial. Of these, 1 child in the somapacitan group discontinued trial treatment due to an AE of adenoidal hypertrophy. In total, 4 children in the somapacitan group and 1 child in the somatropin group were randomised in violation of inclusion or exclusion criteria.

Efficacy results

Height velocity

Non-inferiority for somapacitan versus somatropin for the primary endpoint HV at week 52 was confirmed for hypothetical strategy estimand. Estimated HV at week 52 was similar for somapacitan (0.16 mg/kg/week) and somatropin (0.034 mg/kg/day) corresponding to 11.0 cm/year and 10.4 cm/year, respectively. The estimated treatment difference was 0.6 cm/year [−0.2; 1.3] 95% CI (Table 5).

T

Mean HVSDS and mean HSDS increased in somapacitan and somatropin groups from baseline to week 52. No statistically significant differences in HVSDS or HSDS were found between the treatment groups at week 52 (Table 5).

No statistical differences in advancement of bone age from baseline to chronological age were observed between both treatment groups at week 52 (Table 5).

Table 5. Observed mean HV, HVSDS, HSDS and bone age and change from baseline to week 52 for HVSDS, HSDS and bone age - on-treatment

	Somatropin	Somapacitan
Observed mean		
HV (cm/year), baseline	3.3 (n=36)	3.5 (n=74)
HV (cm/year), week 52	10.5 (n=32)	11.0 (n=71)
HVSDS, baseline	-3.25 (n=36)	-3.12 (n=74)
HVSDS, week 52	5.04 (n=32)	5.75 (n=69)
HSDS, baseline	-2.91 (n=36)	-2.73 (n=74)
HSDS, week 52	-1.78 (n=32)	-1.48 (n=69)
Bone age (years), baseline	4.4 (n=36)	4.3 (n=74)
Bone age (years), week 52	5.6 (n=32)	5.5 (n=68)
Observed mean change from baseline		
Change in HVSDS, week 52	8.34 (n=32)	8.96 (n=69)
Change in HSDS, week 52	1.13 (n=32)	1.21 (n=69)
Change in bone age, week 52	1.3 (n=32)	1.2 (n=68)

IGF-I SDS and IGFBP-3 SDS

The mean IGF-I SDS and IGFBP-3 SDS increased during the trial in both treatment groups.

Mean IGF-I SDS was similar between somapacitan and somatropin at week 52 and within normal range (-2 to +2) (Table 6).

No statistically significant differences in change from baseline in IGF-I SDS or IGFBP-3 SDS between somapacitan and somatropin at week 52.

Table 6. Observed mean IGF-I SDS and change in IGF-I SDS from baseline to week 52 – on-treatment

	Somatropin	Somapacitan
Observed mean		
IGF-I SDS, baseline	-1.61 (n=36)	-1.58 (n=74)
IGF-I SDS, week 52	0.15 (n=32)	0.53 (n=67)
Observed mean change from baseline		
Change in IGF-I SDS, week 52	1.73 (n=32)	2.09 (n=67)

Note: Week 52 visit was scheduled 4-6 days after last dosing.

Assessor's comment

Primary objective was to compare efficacy of somapacitan vs somatropin on longitudinal growth in Chinese children with GHD. Non-inferiority of somapacitan was considered confirmed if the lower boundary of the two-sided 95% confidence interval was above -2 cm/year. The estimated HV at week 52 was 11.0 cm/year for somapacitan (0.16 mg/kg/week) and 10.4 cm/year for somatropin (0.034 mg/kg/day). Non-inferiority of somapacitan relative to somatropin was confirmed for the

hypothetical estimand as the lower bound of the 95% confidence interval (-0.2 cm/year) was higher than the predefined non-inferiority margin of -2 cm/year.

The mean change from baseline in height velocity SDS and height SDS at week 52 was comparable for somapacitan and somatropin.

There is no difference between the two treatments in bone age at baseline and after 52 weeks of treatment. Chronological age was also comparable between the two groups at baseline; 6.6 years (range: 2.5-10.9 years) in the somapacitan group and 6.5 years (range: 2.6-10.7 years) in the somatropin group.

Mean IGF-I SDS increased upon 52 weeks of treatment with somapacitan and somatropin (to 0.53 and 0.15, respectively). Levels remained within normal limits and there were no significant differences in change from baseline in IGF-SDS between the two treatments at week 52. To minimalize the excursions to unsafe IGF-I levels (>2 SDS) the treatment goal should be 0 SDS. However, there were n=10 patients who had IGF-I SDS values ≥ +2 after 52 weeks of somapacitan treatment, of which n=5 had IGF-I SDS values ≥ +3. These are values above the safety limit. For all but two patients this elevation was measured at week 52 and not at the previous administrations. Two male paediatric patients (4.8 and 4.5 years of age) had elevated levels at week 39 and at week 52 (IGF-I SDS values of 2.5 and 2.3 at week 39 and 3.0 for both at week 52). Study protocol states that in case the IGF-I SDS level exceeds +2.5 SDS at two consecutive visits that the dose must be reduced by 25%. Week 39 and week 52 were two consecutive visits, but the level of 2.5 was not exceeded at both visits. Week 52 was also the end of the study. Somapacitan dose was not adjusted. According to the SmPC, in case IGF-I SDS is >2 after two consecutive administrations of somapacitan, the dose should be decreased. Thus, safety measures are in place and therefore this issue is not further pursued.

These efficacy results are in line the previously observed effects of somapacitan compared to somatropin treatment in treatment-naïve paediatric patients with GHD in the REAL 4 study.

Patient reported outcome (PRO)

The Growth Hormone Deficiency – Child Treatment Burden (GHD-CTB) and the Growth Hormone Deficiency – Parent Treatment Burden (GHD-PTB) questionnaires evaluated treatment burden at week 52 and showed lower scores in somapacitan group, representing lower treatment burden for somapacitan relative to somatropin. Moreover, the interference score and total score in GHD-PTB at week 52 showed statistical significance in favour of somapacitan. The Growth Hormone Deficiency – Child Impact Measure (GHD-CIM) questionnaire demonstrated similarity (small and statistically non-significant differences) between somapacitan and somatropin groups for all domain scores (physical health, emotional well-being, social well-being) as well as the overall total score at week 52.

Assessor's comment

In line with previous observations, the treatment burden questionnaire results tended to be more favourable for somapacitan as compared to somatropin at week 52. The child impact measure questionnaire showed similarity between the two treatments.

Safety results

The results and conclusions are based on the safety analysis set including all children exposed (110 children, 100%).

- The safety profile of somapacitan 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.
- Similar adverse event (AE) reporting rates were observed for somapacitan (368.0 AEs/100 per patient-years of exposure (PYE)) and somatropin (398.0 AEs/100 PYE). In total, 91.9% of the children experienced AEs in the somapacitan group compared with 86.1% in the somatropin group (Table 7).
- Two (2) AEs (gastritis and upper gastrointestinal haemorrhage) in 1 child were classified as severe. Both events were assessed as unlikely related to trial product. All remaining events in trial were classified as mild or moderate.
- Eleven (11) serious adverse events (SAEs) were reported in 8 children in the somapacitan group. Of these 11 SAEs, 1 SAE of oedema was assessed by the investigator as possibly related to trial product and considered as a suspected unexpected serious adverse reaction (SUSAR). The event was of mild severity and full recovery was reported. The remaining 10 SAEs were assessed as unlikely related to trial product. Two (2) SAEs (gastritis and upper gastrointestinal haemorrhage) in 1 child in the somapacitan group were classified as severe by the investigator. Remaining all AEs reported in the trial were classified as mild or moderate in severity. One (1) SAE was reported in 1 child in the somatropin group, and the event was assessed as unlikely related to trial product.
- No deaths were reported in the trial.
- One (1) AE of adenoidal hypertrophy in the somapacitan group led to premature discontinuation of trial product. The event was non-serious, of mild severity and assessed by the investigator as possibly related to trial product.
- The most frequent AEs (≥10%) in the somapacitan group were events commonly observed in children including (by proportion) upper respiratory tract infection, pyrexia, cough, COVID-19, respiratory tract infection and bronchitis.
- In total, 10.8% of the children experienced AEs considered possibly or probably related to trial product by the investigator in the somapacitan group compared with 19.4% in the somatropin group (somapacitan: 21.1 AEs/100 PYE; somatropin: 43.9 AEs/100 PYE). All possibly or probably related AEs were of mild or moderate severity.
- Based on the clinical experience with somapacitan, GH drug class effects and regulatory feedback and requirements, the safety focus areas were defined as being of special interest in the evaluation of the safety of somapacitan. Generally low numbers of AEs were reported within each safety focus areas. No noteworthy differences were identified between somapacitan and somatropin groups.

Table 7. Overview of adverse events - on-treatment – safety analysis set

	Norditropin				somapacitan				Total			
	N	(%)	E	R	N	(%)	E	R	N	(%)	E	R
Number of subjects	36				74				110			
Total patient years at risk	36.4				75.8				112.2			
All adverse events	31	(86.1)	145	398.0	68	(91.9)	279	368.0	99	(90.0)	424	377.7
Serious adverse events												
Yes	1	(2.8)	1	2.7	8	(10.8)	11	14.5	9	(8.2)	12	10.7
No	31	(86.1)	144	395.2	67	(90.5)	268	353.5	98	(89.1)	412	367.1
Severity												
Mild	30	(83.3)	137	376.0	68	(91.9)	254	335.0	98	(89.1)	391	348.3
Moderate	5	(13.9)	8	22.0	13	(17.6)	23	30.3	18	(16.4)	31	27.6
Severe	0				1	(1.4)	2	2.6	1	(0.9)	2	1.8
Causality												
Probable	1	(2.8)	1	2.7	2	(2.7)	2	2.6	3	(2.7)	3	2.7
Possible	6	(16.7)	15	41.2	6	(8.1)	14	18.5	12	(10.9)	29	25.8
Unlikely	29	(80.6)	129	354.1	67	(90.5)	263	346.9	96	(87.3)	392	349.2
Missing	0				0				0			
Action taken to trial product due to AE												
Drug interrupted	13	(36.1)	26	71.4	6	(8.1)	6	7.9	19	(17.3)	32	28.5
Drug withdrawn	0				1	(1.4)	1	1.3	1	(0.9)	1	0.9
Dose reduced	0				1	(1.4)	2	2.6	1	(0.9)	2	1.8
Dose increased	0				0				0			
Dose not changed	29	(80.6)	115	315.6	65	(87.8)	264	348.2	94	(85.5)	379	337.6
Not applicable	4	(11.1)	4	11.0	5	(6.8)	6	7.9	9	(8.2)	10	8.9
Unknown	0				0				0			
Missing	0				0				0			
Related to technical complaint												
Yes	0				2	(2.7)	2	2.6	2	(1.8)	2	1.8
No	31	(86.1)	145	398.0	68	(91.9)	277	365.4	99	(90.0)	422	376.0
Injection site reaction*												
Yes	6	(16.7)	13	35.7	2	(2.7)	4	5.3	8	(7.3)	17	15.2
No	31	(86.1)	132	362.3	68	(91.9)	275	362.7	99	(90.0)	407	362.6
Outcome												
Recovered/resolved	30	(83.3)	135	370.5	66	(89.2)	264	348.2	96	(87.3)	399	355.5
Recovering/resolving	1	(2.8)	1	2.7	0				1	(0.9)	1	0.9
Recovered/resolved with sequelae	0				0				0			
Not recovered/not resolved	6	(16.7)	9	24.7	10	(13.5)	12	15.8	16	(14.6)	21	18.7
Fatal	0				0				0			
Unknown	0				3	(4.0)	3	4.0	3	(2.7)	3	2.7
Missing	0				0				0			
Treatment discontinuations due to adverse events	0				1	(1.4)	1	1.3	1	(0.9)	1	0.9

N: Number of subjects, %: Percentage, E: Number of events, R: Event rate per 100 patient years at risk, MedDRA version 26.1, AE: Adverse event
AE causality is based on judgement of investigators.
On treatment: Measurement after first administration of trial product and up until 14 days after last trial drug administration for withdrawn subjects, and up until week 52 or 14 days after last trial drug administration, which ever comes first, for all other subjects.
*Based on information entered by the investigator in the CRF.

- There were no apparent clinically relevant changes from baseline to week 52 in physical examination, vital signs, electrocardiogram (ECG), or clinical laboratory assessments for any of the treatment groups.
- No differences between the treatment groups were observed in mean fasting plasma glucose and glycated haemoglobin (HbA1c) up to week 52.
- Mean IGF-I SDS were within normal range (-2 to +2) during the 52 weeks and no specific AEs related to IGF-I SDS above +2 were observed.
- Antibodies were detected in 17 (23.0%) somapacitan treated children and 7 (19.4%) children treated with somatropin. Of these, 5 (6.8%) children in the somapacitan group and 3 (8.3%) children in the somatropin group had at least 2 consecutive positive antibody samples.

Assessor's comment

The safety analysis set included all 110 paediatric patients.

There were 11 SAE's in the somapacitan group. One case of oedema was assessed as possibly related and led to a dose reduction. Peripheral oedema is a known side effect of somapacitan treatment. Other SAE's (two cases of pneumonia, and two cases of bronchitis, gastritis, upper gastrointestinal haemorrhage, adenovirus infection, tonsillar hypertrophy, tonsillitis and inguinal hernia) all recovered the same day or within a couple of days. All were assessed by the investigator as unlikely related to the treatment, which is supported.

The most frequent AEs, such as respiratory tract infections, pyrexia and cough are not listed in the SmPC, but most likely reflect common cold and the flu symptoms frequently observed in paediatric patients.

There were 7 subjects who discontinued study treatment prematurely. Lost to follow-up (1), withdrawal by parent/guardian (3) and 'other' (3) were the reasons withdrawal. Among these 7, one patient had a non-severe AE adenoidal hypertrophy which led to discontinuation.

There were no deaths reported.

There were no clinically relevant changes from baseline in the mean fasting glucose and HbA_{1c}.

Mean IGF-I SDS were within normal range during the 52 weeks however, individual IGF-SDS values were not always within normal range (see discussion above). However, no specific AEs related to IGF-I SDS were reported. Which supports the approach to not pursue this issue.

Antibodies were detected in a substantial number of patients; in 23.0% of somapacitan treated children and in 19.4% of children treated with somatropin. However, the formation of anti-drug antibodies had no impact on PK, PD, efficacy and safety. This in line with previous observations. A warning on antibodies is in the SmPC and thus sufficiently covered.

All in all, the safety data gathered in this paediatric study are in line with previous observations from the REAL-4 study.

2.3.3. Discussion on clinical aspects

Trial NN840-4468 was a randomised, multicentre, open-labelled, two arm trial to confirm non-inferiority of efficacy and investigate safety of once weekly s.c. treatment of somapacitan compared to daily s.c. growth hormone (GH) (somatropin) treatment in Chinese prepubertal children with GHD. The design of the trial strongly resembles the design of the REAL 4 paediatric study which supported the extension of the indication to the paediatric patients in Europe. This confirmatory trial in Chinese children with GHD was performed for a market authorisation application within this indication in China.

This study included 110 children; 74 were exposed to somapacitan and 36 to somatropin. The primary objective was to compare efficacy of somapacitan vs somatropin on longitudinal growth in Chinese children with GHD. The estimated height velocity at week 52 was 11.0 cm/year for somapacitan (0.16 mg/kg/week) and 10.4 cm/year for somatropin (0.034 mg/kg/day). Non-inferiority of somapacitan relative to somatropin was confirmed for the hypothetical estimand as the lower bound of the 95% confidence interval (-0.2 cm/year) was higher than the predefined non-inferiority margin of -2 cm/year. Furthermore, change from baseline in height velocity SDS and height SDS at week 52 were comparable between the two treatments. There was also no difference between both treatments in bone age at baseline and at week 52. The patient reported outcome questionnaires tended to be in favour of somapacitan. Which is in line with previous observations in paediatric patients.

Mean IGF-I SDS increased upon 52 weeks of treatment with somapacitan and somatropin (from -1.58 and -1.61 to 0.53 and 0.15, respectively), as could be expected. There were no significant differences in change from baseline in IGF-SDS between the two treatments at week 52. However, there were some patients (n=10) who had IGF-I SDS values ≥ +2 after 52 weeks of somapacitan treatment, of which n=5 had IGF-I SDS values ≥ +3. These values are above the safety limit. Two male paediatric patients (4.8 and 4.5 years of age) had elevated levels (IGF-I SDS values of 2.5 and 2.3 at week 39 and 3.0 for both at week 52). Study protocol dictates that in case IGF-I SDS exceeds +2.5 SDS at two consecutive visits the dose must be reduced by a 25% of the current dose. Somapacitan dose was not

adjusted. According to the SmPC, in case IGF-I SDS is >2 in after two consecutive administrations of somapacitan, the dose should be decreased by 0.04 mg/kg/week. Multiple reductions might be required. Thus, safety measures are in place and therefore this issue is not further pursued.

There were no new safety signals reported in the study. Similar AE reporting rates were observed in both groups. There were 11 SAE's in the somapacitan group. One case of oedema was assessed as possibly related and led to a dose reduction. Peripheral oedema is a known side effect of somapacitan treatment. All other SAE's recovered the same day or within a couple of days. All were assessed by the investigator as unlikely related to the treatment, which is supported.

There were no clinically relevant changes from baseline in the mean fasting glucose and HbA_{1c}.

Antibodies were detected in a substantial number of patients; in 23.0% of somapacitan treated children and in 19.4% of children treated with somatropin. However, the formation of anti-drug antibodies had no impact on PK, PD, efficacy and safety. This in line with previous observations. A warning on antibodies in the SmPC and thus sufficiently covered.

The MAH is of opinion that no additions to the SmPC are warranted. This is supported.

3. Rapporteur's overall conclusion and recommendation

In conclusion, the efficacy data gathered in this paediatric study are in line with previous observations from the REAL-4 study. No new safety signals were identified.

The B/R remains positive.

No changes to the SmPC are considered necessary.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Not applicable.