Cover Page for SAP

Sponsor name:	Novo Nordisk A/S
NCT number	NCT05723835
Sponsor trial ID:	NN8640 - 4469
Official title of study:	A study evaluating the safety and efficacy of once - weekly dosing of somapacitan in a basket study design in paediatric participants with short stature either born small for gestational age or with Turner syndrome, Noonan syndrome or idiopathic short stature
Document date*	24-June-2022

*Document date refers to the date on which the document was most recently updated.

Statistical Analysis Plan

Protocol Title:
A study evaluating the safety and efficacy of once-weekly dosing of somapacitan in a basket study design in paediatric participants with short stature either born small for gestational age or with Turner syndrome, Noonan syndrome or idiopathic short stature.

Short title:
A research study looking at how safe somapacitan is and how well it works in children who need help to grow – REAL 9

Substance: Somapacitan

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Version History

This Statistical Analysis Plan (SAP) for study NN8640-4469 is based on the protocol version 3.0 dated 21 December 2022.

SAP Version	**Date**	**Change**	**Rationale**
1.0	24 June 2024	Not Applicable	Original version

List of abbreviations

AE	adverse event
BMI	body mass index
DPS	data points set
FAS	full analysis set
FPFV	first patient first visit
GH	growth hormone
GH-INJ-CTB	Growth Hormone Injection - Child Treatment Burden
GH-PPQ	Growth Hormone Patient Preference Questionnaire
HV	height velocity
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein-3
IMP	investigational medical product
ISS	idiopathic short stature
IVSed	end-diastolic interventricular septum thickness
LVIDed	end-diastolic left ventricular internal diameter
LVIDes	end-systolic left ventricular internal diameter
LVPWed	end-diastolic left ventricular posterior wall thickness
MAP	modelling analysis plan
MedDRA	medical dictionary for regulatory activities
MPH	midparental target height
NAH	near adult height
NS	Noonan syndrome
PAS	participant analysis set
PD	pharmacodynamic
PK	pharmacokinetic

SAP	Statistical Analysis Plan
SAS	safety analysis set
SDS	standard deviation score
SGA	small for gestational age
TS	Turner syndrome

1 Introduction

Primary analysis of the primary endpoint addressing the primary estimand was defined in protocol before first patient first visit (FPFV). There are no changes to the analysis described in the protocol.

This SAP is based on the protocol: *A study evaluating the safety and efficacy of once-weekly dosing of somapacitan in a basket study design in paediatric participants with short stature either born small for gestational age or with Turner syndrome, Noonan syndrome or idiopathic short stature*. REAL 9, version 3.0 (dated 21 December 2022). This SAP covers specification of statistical considerations and analyses for efficacy and safety data. SAP 1.0 was created post FPFV.

1.1 Objectives, Endpoints, and Estimands

Table 1 Objectives and endpoints

Objectives	**Endpoints**		
Primary	Title	Time frame	Unit
• To evaluate the safety of once-weekly somapacitan in children, either naïve or non-naïve to GH treatment, within each of the four indications: SGA, TS, NS or ISS.	Primary endpoint:		
	Number of adverse events (AEs)	From baseline (week 0) to week 26	Number of AEs
Secondary	Title	Time frame	Unit
• To evaluate the long-term safety of once-weekly somapacitan in children, either naïve or non-naïve to GH treatment, within each of the four indications: SGA, TS, NS or ISS.	Secondary supportive safety endpoint:		
	Number of adverse events (AEs) possibly or probably related to somapacitan	From baseline (week 0) to week 26	Number of AEs
	Number of adverse events (AEs)	From baseline (week 0) to week 156	Number of AEs
• To evaluate the efficacy of once-weekly somapacitan for in children, either naïve or non-naïve to GH treatment, within each of the four indications: SGA, TS, NS or ISS.	Secondary supportive efficacy endpoints:		
	Height Velocity	From baseline (week 0) to week 26	cm/year
	Change in Height SDS	From baseline (week 0) to week 26	Score*
	Change in Height Velocity SDS	From baseline (week 0) to week 26	Score*
	Change in IGF-1 SDS	From baseline (week 0) to week 26	Score*
	Change in IGFBP-3 SDS	From baseline (week 0) to week 26	Score*
• To evaluate the steady state pharmacokinetics of once-weekly somapacitan in children, either naïve or non-naïve to GH treatment, within each of the four indications: SGA, TS, NS or ISS.	Secondary supportive efficacy endpoint:		
	Weekly average somapacitan concentration (C_{avg}) based on population PK analysis	From baseline (week 0) to week 26	ng/ml

*Positive score indicates that the value is closer to or above the reference population compared to baseline.

Primary estimand

The primary clinical question of interest is: What is the incidence of AEs from baseline to week 26 in the four populations (SGA, TS, NS or ISS) in all patients while on treatment regardless of dose reduction?

For the primary objective, the same primary estimand is defined for each of the four populations (SGA, TS, NS or ISS) with 5 attributes:

- The treatment condition of interest is defined as somapacitan regardless of dose reduction
- The population targeted by the clinical question: The treatment effect will be assessed separately for each of the four populations (SGA, TS, NS or ISS)
- Endpoint: Number of adverse events from baseline to 26 weeks
- Remaining intercurrent events:
  - Treatment discontinuation for any reason: Participants data will be included up to 14 days after treatment discontinuation. Data collected 14 days after the intercurrent event will be regarded as not relevant for estimation of the treatment effect
  - Dose reduction due to IGF-I or AE: Is addressed by the treatment condition of interest attribute

  There are no remaining intercurrent events
- Population-level summary: Event rate per 100 patient years

Rationale for estimand: The primary estimand assesses the expected safety profile in relation to incidence of AEs for a future population (SGA, TS, NS or ISS) while on somapacitan treatment for 26 weeks, if no treatment discontinuation occurs for any reason.

Secondary estimands

The supportive secondary safety estimand regarding the incidence of AEs possibly or probably related to somapacitan from baseline up to week 26 of somapacitan treatment will be evaluated in a similar way as the primary endpoint including possibly or probably related to somapacitan in the endpoint attribute.

The supportive secondary safety estimand regarding the incidence of AEs from baseline to week 156 of somapacitan treatment will be evaluated in a similar way as the primary endpoint substituting 156 weeks for 26 weeks.

The supportive secondary efficacy estimands will be specified in Section 4.3.2.

1.2 Study Design

This is an interventional, multi-national, multi-centre, open-labelled, uncontrolled phase 3 study with a basket design. The study is designed to evaluate safety and efficacy of once-weekly dosing of somapacitan 0.24 mg/kg/week during 26 weeks (main phase) in children with short stature in each of the indications SGA, TS, NS and ISS. The 26-week main phase will be followed by a 130-week extension phase with once-weekly dosing of somapacitan 0.24 mg/kg/week to evaluate long-term safety. Study participants will include children with SGA, TS (only females), NS and ISS.

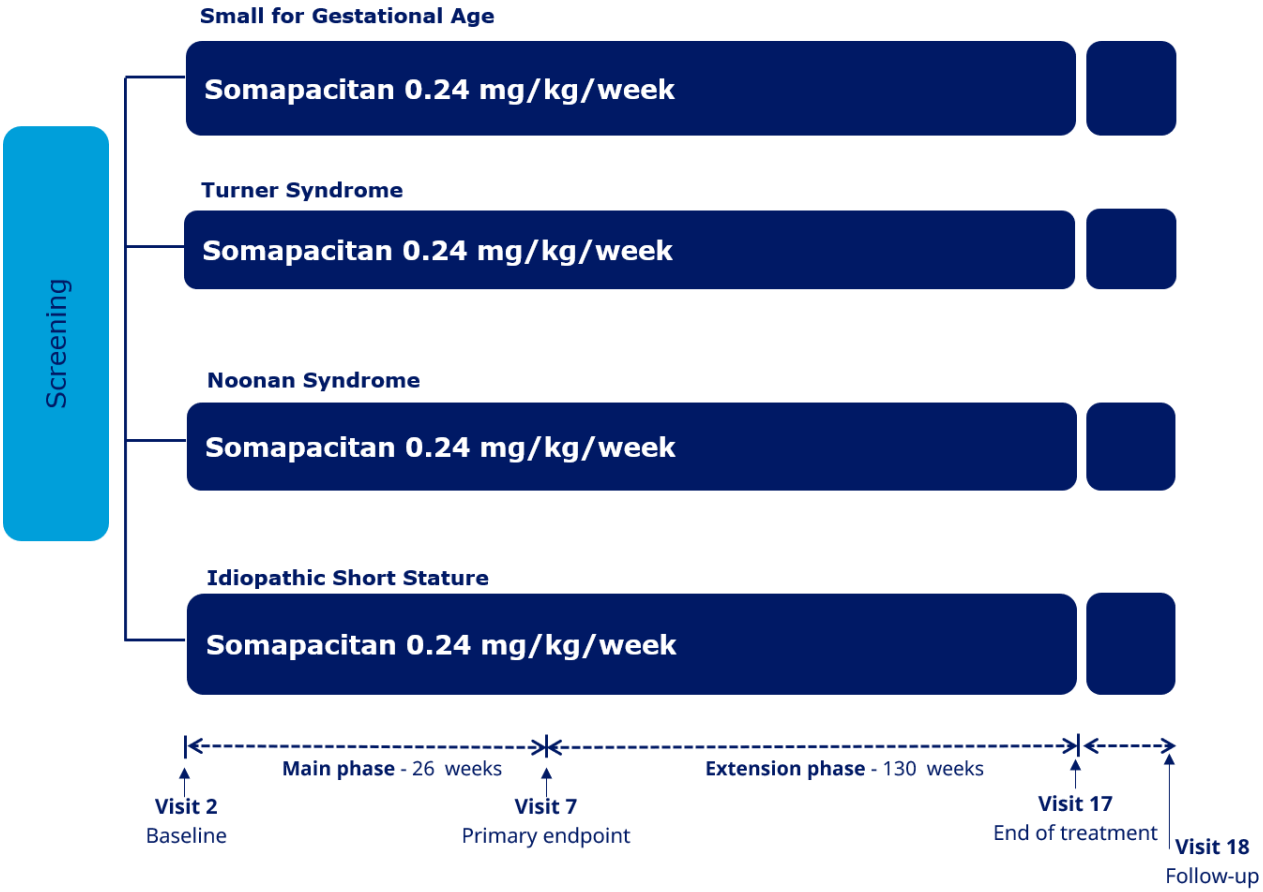
Approximately 60 participants in total are planned to be screened and up to 50 participants in total are planned to be enrolled (planned treated) in this study. In total, at least 40 participants are planned to complete the study. All participants will receive somapacitan 0.24 mg/kg/week.

The total treatment duration for each participant is scheduled to be 3 years. The treatment period is followed by a safety follow-up period of 30 days.

The study consists of:

- an up to 3-week screening period for participants in the indications SGA and ISS
- an up to 6-week screening period for participants in the indications TS and NS
- a 26-week interventional main phase
- a 130-week interventional extension phase
- a 30-day follow-up period

Figure 1 Study design



2 Statistical Hypothesis

No hypotheses are planned to be tested in the study.

2.1 Multiplicity Adjustment

Not applicable.

3 Analysis Sets

The following participant analysis sets are defined within each sub-study:

Participant analysis set (PAS)	Description
Full analysis set (FAS)	All participants assigned to study intervention.
Safety analysis set (SAS)	All participants who are exposed to study intervention.

The full analysis set will be used to analyse endpoints related to the efficacy objectives and the safety analysis set will be used to analyse the endpoints and assessments related to safety.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

The following data points sets are defined:

Defined data points set (DPS)	Description
In-study	All observations from assignment to study intervention date up until visit 7 or last study contact, whichever comes first.
On-treatment	All observed data from first study intervention and up until visit 7, last study contact, or 14 days after last administration, whichever comes first.

The on-treatment data point sets represent data collected in the period in which a participant is considered exposed to IMP.

FAS and In-study are used to estimate the supportive secondary efficacy estimands for Height velocity, Change in Height SDS and Change in Height Velocity SDS.

FAS and On-treatment are used to present the supportive secondary efficacy estimands for Change in IGF-I SDS and Change in IGFBP-3 SDS.

Safety analysis set and On-treatment are used to present the primary estimand for the primary objective and all other safety data.

4 Statistical Analyses

4.1 General Considerations

Descriptive statistics will be performed as described in the sections 4.2 and 4.3.

4.2 Primary Endpoint/Estimand Analysis

The primary endpoint number of adverse events will be used to support the primary objective of evaluating safety of once-weekly somapacitan during 26 weeks of treatment in children with SGA, TS, NS or ISS based on the primary estimand corresponding to the on-treatment data points set.

To support the primary estimand descriptive statistics (Number and percentage of participants who experienced adverse events, the number of events) will be derived in addition to the event rate per 100 patient years of exposure. The primary endpoint will be summarised for each indication, SGA,TS, NS or ISS. All adverse events with onset after the first administration of trial product and up until end of treatment or 14 days after last trial product administration, whichever comes first, will be included in the analysis. The adverse events will be summarised by MedDRA (Medical Dictionary for Regulatory Activities) system organ class and MedDRA preferred term. Adverse events with onset 14 days or more after last trial product administration will be reported in a separate listing.

4.2.1 Definition of Endpoint

Number of adverse events (AEs) from baseline (week 0) to week 26.

4.2.2 Main Analytical Approach

Safety analysis set and On-treatment are used to present the primary estimand for the primary objective.

4.2.3 Sensitivity Analysis

Not applicable.

4.2.4 Supplementary Analysis

Not applicable.

4.3 Secondary Endpoints/Estimands Analysis

4.3.1 Confirmatory Secondary Endpoints

Not applicable.

4.3.2 Supportive Secondary Endpoints/Estimands

4.3.2.1 Supportive secondary safety endpoints/estimands

The supportive secondary safety estimand regarding the incidence of AEs possibly or probably related to somapacitan from baseline up to week 26 of somapacitan treatment will be evaluated in a similar way as the primary endpoint including AEs possibly or probably related to somapacitan in the endpoint attribute.

The supportive secondary safety estimand regarding the incidence of AEs from baseline up to week

156 of somapacitan treatment will be evaluated in a similar way as the primary endpoint substituting 156 weeks for 26 weeks.

4.3.2.2 Supportive secondary efficacy endpoints/estimands

Table 1 Supportive secondary efficacy endpoints

Title	Time frame	Unit
Height velocity	From baseline (week 0) to visit 7 (week 26)	cm/year
Change in Height SDS	From baseline (week 0) to visit 7 (week 26)	Score[a]
Change in Height Velocity SDS	From baseline (week 0) to visit 7 (week 26)	Score[a]
Change in IGF-I SDS	From baseline (week 0) to visit 7 (week 26)	Score[a]
Change in IGFBP-3 SDS	From baseline (week 0) to visit 7 (week 26)	Score[a]
Weekly average somapacitan concentration (C_{avg}) based on population PK analysis	From baseline (week 0) to visit 7 (week 26)	ng/ml

[a]Positive score indicates that the value is closer to or above the reference population compared to baseline.

Height velocity, Change in Height SDS and Change in Height Velocity SDS

The clinical question of interest for the supportive secondary efficacy endpoints Height velocity, Change in Height SDS and Change in Height Velocity SDS are: What is the mean Height velocity, Change in Height SDS or Change in Height Velocity SDS after 26 weeks of somapacitan treatment for each group of previously treated (yes/no) in the four populations (SGA, TS, NS or ISS) regardless of dose reduction due to IGF-I or AE, regardless of treatment discontinuation for any reason and regardless of initiation of ancillary therapy or medication with a special focus?

The supportive secondary estimands are defined for each of the four populations (SGA, TS, NS or ISS) with five attributes:

- The treatment condition of interest is defined as somapacitan treatment with or without ancillary therapy or medication with a special focus (treatment policy strategy).
- The population targeted by the clinical question: The treatment effect will be assessed separately for each group of previously treated (yes/no) in the four populations (SGA, TS, NS or ISS).
- Endpoints:
- Height velocity from baseline (week 0) to visit 7 (week 26)
- Change in Height SDS from baseline (week 0) to visit 7 (week 26)
- Change in Height Velocity SDS from baseline (week 0) to visit 7 (week 26)

Remaining intercurrent events: The 4 intercurrent events ‘dose reduction due to IGF-I or AE’, ‘treatment discontinuation for any reason’, ‘initiation of ancillary therapy’ and ‘medication with a special focus’, are all addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.

- Population-level summary: Mean change

Rationale for estimands: The estimands assess the expected benefit a future population (SGA, TS, NS or ISS) can achieve if prescribed somapacitan. By not placing any restrictions on treatment adherence, these estimands aim to obtain a difference as close as possible to the one that can be expected in clinical practice, provided that the dose reduction, treatment adherence and use of ancillary therapy in the study reflects what would be seen in clinical practice.

The supportive secondary estimands will be evaluated based on all participants where both baseline and week 26 data are collected. To support the supportive secondary estimands SD, median, min and max values will also be derived for the supportive secondary endpoints.

Change in IGF-I SDS and Change in IGFBP-3 SDS

The clinical question of interest for the supportive secondary efficacy endpoints Change in IGF-I SDS and Change in IGFBP-3 SDS from baseline (week 0) to visit 7 (week 26) are: What is the mean change after 26 weeks of somapacitan treatment within each group of previously treated (yes/no) in the four populations (SGA, TS, NS or ISS) patients while on treatment regardless of dose reduction due to IGF-I or AE or medication with a special focus?

The supportive secondary estimands are defined for each of the four populations (SGA, TS, NS or ISS) with five attributes:

- The treatment condition of interest is defined as somapacitan regardless of dose reduction or medication with a special focus.
- The population targeted by the clinical question: The treatment effect will be assessed separately for each group of previously treated (yes/no) in the four populations (SGA, TS, NS or ISS)
- Endpoints:
  - Change in IGF-I SDS from baseline week 0 to week 26
  - Change in IGFBP-3 SDS from baseline week 0 to week 26
- Remaining intercurrent events:
  - Treatment discontinuation for any reason: Participant's data will be included up to 14 days after treatment discontinuation. Data collected 14 days after the intercurrent event will be regarded as not relevant for the estimation of the treatment effect.
  - Initiation of medication with a special focus: Addressed by the treatment condition of interest attribute.
  - Dose reduction due to IGF-I or AE: Addressed by the treatment condition of interest attribute. There are no remaining intercurrent events.
- Population-level summary: Mean change

Rationale for estimand: The supportive secondary estimand assesses the expected benefit a future population (SGA, TS, NS or ISS) can achieve if prescribed somapacitan if no treatment discontinuation had occurred.

The supportive secondary estimands will be evaluated based on all participants where both baseline and week 26 data are collected. To support the supportive secondary estimands SD, median, min and max values will also be derived for the supportive secondary endpoints.

FAS and In-study are used to estimate the supportive secondary efficacy estimands for Height velocity, Change in Height SDS and Change in Height Velocity SDS.

FAS and On-treatment are used to present the supportive secondary efficacy estimands for Change in IGF-I SDS and Change in IGFBP-3 SDS.

Pharmacokinetic and/or pharmacodynamic modelling

Pharmacokinetic (PK) and pharmacodynamic (PD) modelling based on the somapacitan concentration and IGF-I data from the study will be performed.

The objective of the PK/PD modelling analysis is to characterise the weekly PK/PD profile, weekly average exposure (C_{avg}) and weekly IGF-I average levels following somapacitan treatment in SGA, TS, NS and ISS.

A more technical and detailed elaboration of the PK/PD modelling will be given in a modelling analysis plan (MAP), which will be prepared prior to database lock. Weekly average exposure (C_{avg}) based on population PK/PD modelling will be reported as a secondary endpoint. Other PK/PD modelling results will be reported in a separate modelling report, which will not be part of the CSR. The individual somapacitan concentration data will be tabulated in the bioanalytical report.

4.4 Exploratory Endpoints Analysis

Not applicable.

4.5 Other Safety Analysis

Safety laboratory assessments

Safety laboratory assessments (biochemistry, haematology, glucose metabolism, coagulation parameters (NS), and lipids) will be summarised by time of assessment for each indication, SGA, TS, NS or ISS. All abnormal values will be listed.

Vital signs

Vital signs (electrocardiogram, transthoracic electrocardiogram (TS, NS)) will be summarised by time of assessment for each indication, SGA, TS, NS or ISS. The investigator's evaluation of vital signs will be tabulated by time of assessment for each indication, SGA, TS, NS or ISS.

Antibodies

For confirmed anti-somapacitan antibody positive samples, the anti-somapacitan positive crossreactivity to hGH antibodies and in vitro neutralising effect will be tabulated by time of assessment for each indication, SGA, TS, NS or ISS.

4.5.1 Extent of Exposure

Not applicable.

4.5.2 Adverse Events

Adverse events will be displayed as per the primary and secondary endpoints.

4.5.3 Additional Safety Assessments

Not applicable.

4.6 Other Analysis

4.6.1 Other parameters

Table 2 Overview of other parameters

Title	Time frame	Unit
Child treatment burden measure: GH-INJ-CTB-Physical[e]	Visit 5	Score[a]
Child treatment burden measure: GH-INJ-CTB-Emotional Well-being[e]	Visit 5	Score[a]
Child treatment burden measure: GH-INJ-CTB-Interference[e]	Visit 5	Score[a]
Child treatment burden measure: GH-INJ-CTB-Overall treatment burden[e]	Visit 5	Score[a]
Patient Preference: GH-PPQ-Child[e]	Visit 5	Categorical response
Near adult height (NAH)	18 months prior to screening to visit 18 (week 156)	Yes/No
Change in height SDS at the visit when NAH is reached	From baseline (week 0) to the visit NAH is reached	Score[b]
Midparental target height (MPH)	Screening (visit 1)	cm
MPH SDS	Screening (visit 1)	Score[c]
Index of genetic height potential	From baseline (week 0) to the visit NAH is reached	Score[d]
Change in interventricular Septum end diastole (IVSed) SDS	From baseline (week 0) to visit 7 (week 26)	Score[b]
Change in left ventricle posterior wall end diastole (LVPWed) SDS	From baseline (week 0) to visit 7 (week 26)	Score[b]
Change in left ventricle inner dimension end diastole (LVIDed) SDS	From baseline (week 0) to visit 7 (week 26)	Score[b]
Change in left ventricle inner dimension end systole (LVIDes) SDS	From baseline (week 0) to visit 7 (week 26)	Score[b]
Change in sitting height/height (SH/H)	From baseline (week 0) to visit 7 (week 26)	Ratio
Change in sitting height/height SDS (SH/H SDS)	From baseline (week 0) to visit 7 (week 26)	Ratio
Change in bone age/chronological age	From screening (visit 1) to visit 9 (week 52)	Ratio

[a]Negative score indicates that treatment burden is less compared to baseline.
[b]Positive score indicates that the value is closer to or above the reference population compared to baseline.
[c]Negative values indicate that the values are lower than the reference population.
[d]Negative values indicate that the NAH is below the genetic height potential.
[e]Only to be collected from participants switching to somapacitan from daily GH treatment.

Height Velocity at visit 9 (week 52), Change in Height SDS from baseline (week 0) to visit 9 (week 52), Change in Height Velocity SDS from baseline (week 0) to visit 9 (week 52), Change in IGF-1 SDS from baseline (week 0) to visit 9 (week 52) and Change in IGFBP-3 SDS from baseline (week 0) to visit 9 (week 52) will derived as parameters in the same way as the corresponding secondary endpoints at visit 7 (week 26).

The parameters will be summarised for relevant indications, SGA, TS, NS or ISS.

4.6.2 Subgroup Analysis

Not applicable.

4.7 Interim Analysis

Not applicable.

4.8 Changes to Protocol-planned Analysis

There are no changes to the protocol-planned analysis.

5 Sample size determination

No formal sample size calculation was performed in the four populations (SGA, TS, NS or ISS). The number of participants reflects what is expected feasible to enroll to provide adequate safety information in each indication.

Children above or equal to 10.0 years (girls with SGA, TS, NS and ISS) or 11.0 years (boys with SGA, NS and ISS) and below 18.0 years are not included in the pivotal study NN8640-4467. Based on a recommendation from the FDA, this age group will be investigated in study NN8640-4469.

Up to 50 participants are planned to be enrolled in this study. In total, at least 10 participants in each indication are planned to complete the study, as outlined below:

- **SGA:** Ten (10) female and male participants equal to or above 10.0 and 11.0 years, respectively, and below 18.0 years at screening.
- **TS:** Ten (10) female participants equal to or above 10.0 years and below 18.0 years at screening.
- **NS:** Ten (10) female and male participants equal to or above 10.0 and 11.0 years, respectively, and below 18.0 years at screening.
- **ISS:** Ten (10) female and male participants equal to or above 10.0 and 11.0 years, respectively, and below 18.0 years at screening.

6 Supporting Documentation

6.1 Appendix 1: Definition and calculation of endpoints, assessments and derivations

Type	Title	Time frame	Unit	Details
Supportive secondary efficacy endpoint	Height velocity	From baseline (week 0) to visit 7 (week 26).	cm/year	Derived as: HV at week 26 = (height at 26 weeks visit – height at baseline)/(time from baseline to 26 weeks visit in years).
Supportive secondary efficacy endpoint	Change in Height SDS	From baseline (week 0) to visit 7 (week 26).	Score[b]	Derived as the Height SDS value at baseline week 0 subtracted from the Height SDS value at week 26 (visit 7). Height SDS is derived as: $$\text{Height SDS}_i = \frac{\left(\frac{\text{Height}_i}{\text{population median}}\right)^{\text{Skewness}} - 1}{\text{Skewness} * \text{population SD}}$$ where i indicates the visit. The population median and standard deviation are the ones corresponding to the age at visit i. The population median and standard deviation and skewness are based on reference data.[1]
Supportive secondary efficacy endpoint	Change in Height Velocity SDS	From baseline (week 0) to visit 7 (week 26).	Score[b]	Derived as the Height Velocity SDS value at baseline week 0 subtracted from the Height Velocity SDS value at week 26 (visit 7). Height Velocity SDS is derived as: $$\text{HV SDS}_i = \frac{\text{HV}_i - \text{population mean HV}}{\text{population SD}}$$ where i indicates the visit. The population mean and standard deviation corresponding to the age at visit i. The population mean and standard deviation are based on reference data.[1, 2]
Supportive secondary efficacy endpoint	Change in IGF-I SDS	From baseline (week 0) to visit 7 (week 26).	Score[b]	Derived as the IGF-I SDS value at baseline week 0 subtracted from the IGF-I SDS value at week 26 (visit 7). IGF-I SDS is derived as: $$\text{IGF} - \text{I SDS}_i = \frac{\left(\frac{\text{IGF} - \text{I}_i}{\text{population median}}\right)^{\text{Skewness}} - 1}{\text{Skewness} * \text{population SD}}$$ where i indicates the visit. The population median and standard deviation are the ones corresponding to the age at visit i. The population median and standard deviation and skewness are based on reference data.[3]
Supportive secondary efficacy endpoint	Change in IGFBP-3 SDS	From baseline (week 0) to visit 7 (week 26).	Score[b]	Derived as the IGFBP-3 SDS value at baseline week 0 subtracted from IGFBP-3 SDS value at week 26 (visit 7). IGFBP-3 SDS is derived as: $$\text{IGFBP} - 3\ \text{SDS}_i = \frac{\left(\frac{\text{IGFBP} - 3_i}{\text{population median}}\right)^{\text{Skewness}} - 1}{\text{Skewness} * \text{population SD}}$$ where i indicates the visit. The population median and standard deviation are the ones corresponding to the

				age at visit i. The population median and standard deviation and skewness are based on reference data.[4]
Other parameter	Child treatment burden measure: GH-INJ-CTB-Physical[e]	Visit 5	Score[a]	GH-INJ-CTB-Physical score at week 13 (visit 5). GH-INJ-CTB – Physical score is derived as the sum of the 4 items (0=Not at all, 1=A little, 2=Some, 3=A lot, 4=Extreme) normalised to a 0-100-point scale as: Physical (question 1-4): (Sum/16)*100
Other parameter	Child treatment burden measure: GH-INJ-CTB-Emotional Well-being[e]	Visit 5	Score[a]	GH-INJ-CTB-Emotional Well-being score at week 13 (visit 5). GH-INJ-CTB – Emotional Well-being score is derived as the sum of the 4 items (0=Not at all, 1=A little, 2=Some, 3=A lot, 4=Extreme) normalised to a 0-100-point scale as: Emotional Well-being (question 5-10): (Sum/24)*100
Other parameter	Child treatment burden measure: GH-INJ-CTB-Interference[e]	Visit 5	Score[a]	GH-INJ-CTB-Interference score at week 13 (visit 5). GH-INJ-CTB – Interference score is derived as the sum of the 4 items (0=Not at all, 1=A little, 2=Some, 3=A lot, 4=Extreme) normalised to a 0-100-point scale as: Interference: (question 11-14): (Sum/16)*100
Other parameter	Child treatment burden measure: GH-INJ-CTB-Overall treatment burden[e]	Visit 5	Score[a]	GH-INJ-CTB-Overall treatment burden score at week 13 (visit 5). GH-INJ-CTB – Overall treatment burden score is derived as the mean of the GH-INJ-CTB – Physical score, GH-INJ-CTB- Emotional Well-being score and GH-INJ-CTB –Interference score.
Other parameter	Patient Preference: GH-PPQ-Child[e]	Visit 5	Categorical response	Patient Preference GH-PPQ-Child at week 13 (visit 5) (Previous treatment, Current treatment, No preference).
Other parameter	Near adult height (NAH)	18 months prior to screening to visit 18 (week 156)	Yes/No	Near adult height (NAH) will be derived. NAH is defined as HV < 2 cm/year calculated over a period of at least 9 months, males have reached a bone age of ≥16 years and females has reached a bone age of ≥14 years. If bone age is not available, then males have reached a chronological age of ≥17 years and females have reached a chronological age of ≥15 years. Historical height measurements collected at screening will be included in the derivation.
Other parameter	Change in height SDS at the visit when NAH is reached	From baseline (week 0) to the visit NAH is reached	Score[b]	Derived as the Height SDS value at baseline week 0 subtracted from the Height SDS value at the visit where NAH is reached.
Other parameter	Midparental target height (MPH)	Screening (visit 1)	cm	Derived as: Girls TH: (mother's height + father's height-13)/2.[5] Boys TH: (mother's height + 13 + father's height)/2.[5]
Other parameter	MPH SDS	Screening (visit 1)	Score[c]	MPH SDS is derived as: $\text{MPH SDS} = \frac{\text{Fathers height SDS} + \text{mothers height SDS}}{2}$

				Where parental height SDS is derived as: $\text{Parental height SDS} = \frac{\text{Height} - \text{population mean}}{\text{population SD}}$ The population mean and standard deviation comes from reference data.[6]
Other parameter	Index of genetic height potential	From baseline (week 0) to the visit NAH is reached	Score[d]	Derived as NAH SDS – MPH SDS
Other parameter	Change in interventricular Septum end diastole (IVSed) SDS	From baseline (week 0) to visit 7 (week 26)	Score[b]	Derived as the IVSed SDS value at baseline week 0 subtracted from IVSed SDS value at week 26 (visit 7) for Turner syndrome. IVSed SDS is derived as: $\text{IVSed SDS}_i = \frac{\ln(\text{IVSed SDS})_i - \text{intercept} + \ln(\text{Weight}_i * \text{slope})}{\text{SD residual}}$ where i indicates the visit. The intercept, slope and SD residuals are the ones corresponding to the age at visit i. The intercept, slope and SD residuals are based on reference data.[7]
Other parameter	Change in left ventricle posterior wall end diastole (LVPWed) SDS	From baseline (week 0) to visit 7 (week 26)	Score[b]	Derived as the LVPWed SDS value at baseline week 0 subtracted from LVPWed SDS value at week 26 (visit 7) forTurner syndrome. LVPWed SDS is derived as: $\text{LVPWe SDS}_i = \frac{\ln(\text{LVPWe SDS})_i - \text{intercept} + \ln(\text{Weight}_i * \text{slope})}{\text{SD residual}}$ where i indicates the visit. The intercept, slope and SD residuals are the ones corresponding to the age at visit i. The intercept, slope and SD residuals are based on reference data.[7]
Other parameter	Change in left ventricle inner dimension end diastole (LVIDed) SDS	From baseline (week 0) to visit 7 (week 26)	Score[b]	Derived as the LVIDed SDS value at baseline week 0 subtracted from LVIDed SDS value at week 26 (visit 7) for Turner syndrome. LVIDed SDS is derived as: $\text{LVIDed SDS}_i = \frac{\ln(\text{LVIDed SDS})_i - \text{intercept} + \ln(\text{Weight}_i * \text{slope})}{\text{SD residual}}$ where i indicates the visit. The intercept, slope and SD residuals are the ones corresponding to the age at visit i. The intercept, slope and SD residuals are based on reference data.[7]
Other parameter	Change in left ventricle inner dimension end systole (LVIDes) SDS	From baseline (week 0) to visit 7 (week 26)	Score[b]	Derived as the LVIDes SDS value at baseline week 0 subtracted from LVIDes SDS value at week 26 (visit 7) for Turner syndrome. LVIDes SDS is derived as:

				$\text{LVIDes SDS}_i = \frac{\ln(\text{LVIDes SDS})_i - \text{intercept} + \ln(\text{Weight}_i * \text{slope})}{\text{SD residual}}$ where i indicates the visit. The intercept, slope and SD residuals are the ones corresponding to the age at visit i. The intercept, slope and SD residuals are based on reference data.[7]
Other parameter	Change in sitting height/height (SH/H)	From baseline (week 0) to visit 7 (week 26)	Ratio	Derived as SH/H at baseline week 0 subtracted from SH/H at week 26 (visit 7) for **TS & ISS**.
Other parameter	Change in sitting height/height SDS (SH/H SDS)	From baseline (week 0) to visit 7 (week 26)	Ratio	Derived as SH/H SDS at baseline week 0 subtracted from SH/H SDS at week 26 (visit 7) for **TS & ISS**. SH/H SDS is derived as: $\text{SH/H SDS}_i = \frac{\left(\frac{\text{SH/H}_i}{\text{population median}}\right)^{\text{Skewness}} - 1}{\text{Skewness} * \text{population SD}}$ where i indicates the visit. The population median and standard deviation are the ones corresponding to the age at visit i.
Other parameter	Change in bone age/chronological age	From screening (visit 1) to visit 9 (week 52)	Ratio	The bone age/chronological age value at screening (visit 1) subtracted from the bone age/chronological age value at week 52 (visit 9).

[a]Negative score indicates that treatment burden is less compared to baseline.
[b]Positive score indicates that the value is closer to or above the reference population compared to baseline.
[c]Negative values indicate that the values are lower than the reference population.
[d]Negative values indicate that the NAH is below the genetic height potential.
[e]Only to be collected from participants switching to somapacitan from daily GH treatment.

7 References

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