Cover Page for Protocol

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:	19-November-2024

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

Protocol

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

Protocol version number: Version 5.0
Protocol version applicability: Global

Universal Trial Number: U1111-1277-9765

EU CT Number: 2022-501055-87

IND Number: 116327

Study phase: 3a

Protocol amendment and summary of changes table

DOCUMENT HISTORY		
Document version	**Date**	**Applicable in country(-ies) and/or site(s)**
Protocol version 5.0	19 November 2024	All
Protocol version 4.0	30 March 2023	All
Protocol version 3.0	21 December 2022	All
Protocol version 2.0	21 October 2022	All
Original protocol version 1.0	09 September 2022	All

Protocol version 5.0 (19 November 2024)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014[1]

Overall rationale for preparing protocol, version 5.0:

The rationale for amending the protocol is to offer participants that complete the current 3 year study period before somapacitan is available for prescription for children with SGA, TS, NS or ISS in their country to continue in the study in an additional extension period II, during which they will receive treatment with somapacitan until somapacitan is available for prescription in their country or October 2027 at the latest. This will allow for collection of additional clinical data on long-term exposure of somapacitan for safety and clinical efficacy.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis Section 4.1 Overall design	Extension period II was added to offer participants that complete the current 3 year study period before somapacitan is available for prescription for children with SGA, TS, NS or ISS in their country to continue in the study in an additional extension period II, during which they will receive treatment with somapacitan until somapacitan is available for prescription in their country or October 2027 at the latest. Relevant text regarding the same has been updated. Relevant text regarding extension period II (91 weeks) has also been added. Figure 1 Trial design is updated.	To ensure that participants finishing extension period I before somapacitan is available for prescription can continue in the trial (in extension period II) and receive treatment.
Section 1.1 Synopsis Section 5.1 Inclusion criteria	A note was included in the ISS inclusion criteria regarding the specific requirements for normal GH secretion values in Korea.	Clarification
Section 1.2 Flowchart for main and extension period I	Column name ‘End of treatment’ is deleted. Procedures for visits 17, 17A and 18 have been updated.	To accommodate changes due to addition of extension period II

Section # and name	Description of change	Brief rationale
Section 1.3 Flowchart for extension period II	A separate flowchart has been added for the participants entering the extension period II.	To ensure that participants finishing extension period I before somapacitan is available for prescription can continue on treatment.
Section 2.1 Study rationale	Text about clinical study reports and individual DBLs has been modified.	To avoid limitations to DBL and CSR development.
Section 4.3 Justification for dose	Text added to specify the justification for the dose of somapacitan used in extension period II.	Clarification
Section 4.4 End of study definition	'End of study definition' has been updated. Definition of 'For participants continuing in extension period II' has been included.	To accommodate changes due to addition of extension period II
Section 6.1 Study interventions administered	The following text has been deleted: 'The last dose should be administered at least 7 days before End of Treatment visit.'.	Correction
Section 6.1 Study interventions administered	Text included to clarify the dosing information that should be recorded in the diary at each visit during the main and extension period I. Text added to specify the injection site for the most recent dose before each visit should be recorded in the diary in extension period II.	To accommodate changes due to addition of extension period II
Section 6.4 Study intervention compliance	Text added to specify the timing and details of information that should be recorded in the diary until extension period I and during extension period II	To accommodate changes due to addition of extension period II
Section 7.1 Discontinuation of study intervention	Text added to specify what applies if the participant discontinues trial product between visit 7 and visit 17. Text added regarding what visits to perform if the participant discontinues trial product after visit 17.	To accommodate changes due to addition of extension period II
Section 7.2 Participant discontinuation/withdrawal from the study	Text added regarding what visits to perform if a participant withdraws consent before and after visit 17.	To accommodate changes due to addition of extension period II
Section 8 Study assessments and procedures	The amount of blood being collected in the study has been updated to 219 mL for participants born SGA or with TS or ISS and 252 mL for participants with NS.	To accommodate changes due to addition of extension period II
Section 8.1.2 Pubertal status Section 1.2 Flowchart for main and extension period I Section 1.3 Flowchart for extension period II	The following text has been added: 'If a participant reaches Tanner stage 5 during the trial, Tanner staging can be omitted from subsequent visits.' The flowcharts have been updated to reflect this change.	Clarification

Section # and name	Description of change	Brief rationale
8.1.4 Dosing diaries	Text included to specify the dosing information that should be recorded in the diary during the main and extension period I, and that the injection site for the most recent dose before each visit should be recorded in the diary in extension period II.	To accommodate changes due to addition of extension period II
Section 8.3.1 Time period and frequency for collecting AE information	Text has been updated regarding collection of medication errors and injection sites.	To accommodate changes due to addition of extension period II
Section 8.6 Genetics	Text added to specify the need to include special laboratory results in the eCRF	Clarification
Section 9.3.6 Other analyses	The evaluation of near adult height (NAH) was extended up to end of treatment (extension period II).	To ensure NAH data is evaluated until end of treatment.
Section 10.2 Appendix 2: Clinical laboratory tests Table 10-3 Other protocol-required laboratory assessments	The text ‘NS’ added to specify that if genetic texting for NS is not accessible at the local laboratory, the analysis can be conducted by a designated special laboratory.	Clarification
Section 10.2 Appendix 2: Clinical laboratory tests Table 10-4 Timing of visits and blood sampling	Updated to include visits during extension period II.	To accommodate changes due to addition of extension period II
Section 10.8 Dosing Tables	Dose reduction tables were added for somapacitan	Clarification
10.10.2 Visits	The text ‘(Visit 17)’ has been deleted.	To align with the changes made to the study due to addition of extension period II.
Section 10.13 Appendix 13: Protocol amendment history	Text under Protocol version 4.0 ‘Exclusion criteria 10’ has been changed to ‘Exclusion criteria 8’.	Correction
Throughout the Protocol	The term "phase" has been replaced with "period" when referring the main, extension I, and extension II periods.	To ensure consistency through the protocol

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1 Protocol summary

1.1 Synopsis

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 period) in children with short stature in each of the indications: small for gestational age (SGA), Turner syndrome (TS), Noonan syndrome (NS) or idiopathic short stature (ISS). The 26-week main period will be followed by a 130-week extension period (extension period I) with once-weekly dosing of somapacitan 0.24 mg/kg/week to evaluate long-term safety. Further, participants, who complete the extension period I when somapacitan is not available to be prescribed for children with SGA, TS, NS or ISS in their country, can continue treatment in extension period II which will last until somapacitan becomes available for prescription in their country or October 2027 (at the latest). Participants will receive somapacitan 0.24 mg/kg/week. The study is described in this master protocol and includes four sub-studies – one for each of the above listed indications.

Rationale:

The purpose of this phase 3a study is to evaluate safety and efficacy of once weekly subcutaneous (s.c.) treatment with somapacitan in the following four indications of children with short stature: born small for gestational age (SGA) with insufficient catch-up growth by 2 years of age or older, Turner syndrome (TS), Noonan syndrome (NS) or idiopathic short stature (ISS). This study is supportive to the pivotal phase 3a study (NN8640-4467) in prepubertal children with short stature due to SGA, TS, NS or ISS. Based on feedback from Health Authorities, this study is designed to include participants from an older paediatric age-group in each of the four indications that could potentially benefit from somapacitan treatment. All data will be analysed separately for each indication.

Objectives, endpoints and estimands:

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 supportive safety endpoint:		
	Number of adverse events (AEs) possibly or probably related to somapacitan	From baseline (week 0) to week 26	Number of AEs
Secondary	Title	Time frame	Unit
	Secondary supportive safety endpoint:		

Objectives	Endpoints		
• 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.	Number of adverse events (AEs)	From baseline (week 0) to week 156	Number of AEs
• To evaluate the efficacy 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 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) 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 9.3.3.

Overall 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). The main period will consist of 26 weeks of treatment, followed by a 130-week open labelled safety extension period I and a 30-day follow-up period in children with short stature in each of the indications SGA, TS (only females), NS and ISS. Further, participants, who complete the extension period I when somapacitan is not available to be prescribed for children with SGA, TS, NS or ISS in their country, can continue treatment in extension period II which will last until somapacitan becomes available for prescription in their country or October 2027 (at the latest). Participants will receive somapacitan at 0.24 mg/kg/week. A follow-up visit will be conducted 30 days after end of treatment. The study is described in this master protocol and includes four sub-studies – one for each of the above listed indications.

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 period
- a 130-week interventional extension period I
- up to 91-week interventional extension period II
- a 30-day follow-up period

For an overview of the study design please see Section 4.

Study intervention groups and duration:

Children above or equal to 10.0 years (female participants with SGA, TS, NS and ISS) or 11.0 years (male participants with SGA, NS and ISS) and below 18.0 years of age are included in this study.

Eligible participants in all four indications will receive somapacitan 0.24 mg/kg/week. Treatments will be administered s.c. The 26-week main period will be followed by a 130-week extension period I with once-weekly dosing of somapacitan 0.24 mg/kg/week to evaluate long-term safety.

Additionally, participants who remain in the 91-week extension period II will receive somapacitan 0.24 mg/kg/week.

Number of participants:

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 total, at least 40 participants 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.

Participant characteristics:

Key inclusion criteria:

Applicable to children with SGA:

- Born small for gestational age (birth length below -2 SDS OR birth weight below -2 SDS OR both) (according to national standards).
- Age:
  - Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
  - Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
- Open epiphyses; defined as bone age < 14 years for females and bone age < 16 years for males.
- *For GH treatment naïve participants*: Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]

Applicable to children with TS:

- Diagnosis of TS according to local clinical practice.
- Age:
  - Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
- Open epiphyses; defined as bone age < 14 years for females and bone age < 16 years for males.
- *For GH treatment naïve participants:* Impaired height defined as at least 2.0 standard deviation below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]
- *For GH treatment naïve participants:* Confirmed diagnosis of TS by 30-cell (or more) lymphocyte chromosomal analysis *or* confirmation of TS and TS mosaicism using CGH-array.

Applicable to children with NS:

- Diagnosis of NS according to local clinical practice.
- Age:

- Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
- Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.

- Open epiphyses; defined as bone age < 14 years for females and bone age < 16 years for males.
- *For GH treatment naïve participants*: Clinical diagnosis of NS according to van der Burgt score list and genetic test result[3] *OR* confirmed mutation in any of the genes associated with NS before allocation.

Applicable to children with ISS:

- Age:
  - Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
  - Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
- Open epiphyses; defined as bone age < 14 years for females and bone age < 16 years for males.
- *For GH treatment naïve participants:* Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening
- *For GH treatment naïve participants:* Normal GH secretion (GH peak above 7 ng/mL) during GH stimulation test performed within 18 months prior to screening.
  For Korea: Please see local requirements in Appendix 11 (Section 10.11)
- *For GH treatment naïve participants:* Bone age not delayed more than 2 years compared to chronological age at screening.

Key exclusion criteria:

- Children with suspected or confirmed growth hormone deficiency according to local practice.
- Children diagnosed with diabetes mellitus or screening values from the central laboratory of
- Fasting plasma glucose above or equal to 126 mg/dL (7.0 mmol/L) or
- HbA_{1c} above or equal to 6.5%.
- 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 greater than 400 µg/day of inhaled budesonide or equivalent (i.e., 250 µg/day for fluticasone propionate) for longer than 4 consecutive weeks within the last 12 months prior to screening.
- History or known presence of any malignancy, intracranial tumour, or intracranial cyst.

Applicable to children with SGA:

- Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
  - Poorly controlled or uncontrolled hormonal deficiencies.
  - Known chromosomal aneuploidy or significant gene mutations causing medical 'syndromes' with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.

Applicable to children with TS:

- Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
  - Known family history of skeletal dysplasia.

- Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
- Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
- Mosaicism below 10%.
- TS with Y-chromosome mosaicism where gonadectomy has not been performed.
- NYHA class II or above or requiring medication for any heart condition.

Applicable to children with NS:

- Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
  - Known family history of skeletal dysplasia.
  - Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
  - Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
  - Noonan-related disorders including but not limited to: Noonan syndrome with multiple lentigines (formerly called 'LEOPARD' syndrome), Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome (CFC), Costello syndrome, neurofibromatosis type 1 (NF1) and Legius syndrome.

Applicable to children with ISS:

- Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
  - Known family history of skeletal dysplasia.
  - Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
  - Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
  - Poorly controlled or uncontrolled hormonal deficiencies.
  - Known chromosomal aneuploidy or significant gene mutations causing medical 'syndromes' with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.

Data monitoring committee:

Yes.

1.2 Flowchart for main and extension period I

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I										Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			**-2**	**0**	**4 +1d**	**8**	**13 +3d**	**20**	**26 +5d**	**39**	**52 +5d**	**65**	**78**	**91**	**104 +2d**	**117**	**130**	**143**	**156 +5d**		**156 +30d**
Visit window (days)		**Minimum 1 day prior to screening**	**±7[a]**		**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7**	**±7 exactly**	**±7**	**±2**	**±7**	**±7 exactly**	**±7**	**±1**		**+7**
PARTICIPANT RELATED INFORMATION AND ASSESSMENTS																					
Informed consent	10.1.3	X																			
Child assent		X																			
Demography[b]			X																		
Eligibility criteria (Inclusion/exclusion criteria)	5.1 5.2		X	X																	
Discontinuation/ Withdrawal criteria	7				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical history/ Concomitant illness	8.2		X																		

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I									Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			**-2**	**0**	**4 +1d**	**8**	**13 +3d**	**20**	**26 +5d**	**39**	**52 +5d**	**65**	**78**	**91**	**104 +2d**	**117**	**130**	**143**	**156 +5d**		**156 +30d**
Visit window (days)		**Minimum 1 day prior to screening**	**±7[a]**		**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7**	**±7 exactly**	**±7**	**±2**	**±7**	**±7 exactly**	**±7**	**±1**		**+7**
Concomitant medication	6.8		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy test[c]	8.2.6				X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
Pubertal status[n]	8.1.2		X	X			X		X	X	X	x	X	x	X	X	X	X	X	X	
Date of menarche[d]	8.1.2				X		X		X	X	X	X	X	X	X	X	X	X	X	X	X
EFFICACY																					
X-Ray for bone age assessment	8.1.3		X								X				X				X	X[e]	
Body Measurements	8.1.1																				
Height			X	X			X		X	X	X	X	X	X	X	X	X	X	X	X	

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I									Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			**-2**	**0**	**4 +1d**	**8**	**13 +3d**	**20**	**26 +5d**	**39**	**52 +5d**	**65**	**78**	**91**	**104 +2d**	**117**	**130**	**143**	**156 +5d**		**156 +30d**
Visit window (days)		**Minimum 1 day prior to screening**	**±7[a]**		**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7**	**±7 exactly**	**±7**	**±2**	**±7**	**±7 exactly**	**±7**	**±1**		**+7**
Body weight			X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	
Sitting height (TS & ISS)			X						X		X				X				X	X	
Pharmacodynamics	8.5																				
IGFBP-3				X	X	X	X	X	X	X	X		X		X		X		X	X	
IGF-I				X	X	X	X	X	X	X	X		X		X		X		X	X	
Bioactive IGF-I				X	X		X		X	X	X		X		X		X		X	X	
Pharmacokinetics	8.4																				
Somapacitan				X	X	X	X	X	X	X	X		X		X		X		X		

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I										Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			-2	0	4 +1d	8	13 +3d	20	26 +5d	39	52 +5d	65	78	91	104 +2d	117	130	143	156 +5d		156 +30d
Visit window (days)		**Minimum 1 day prior to screening**	±7[a]		±1	±7 exactly	±1	±7 exactly	±1	±7 exactly	±1	±7	±7 exactly	±7	±2	±7	±7 exactly	±7	±1		+7
Clinical Outcome Assessments	8.1.5																				
Growth Hormone Injection - Child Treatment Burden - Child (GH-INJ-CTB-Child)[h]							X														
Growth Hormone Patient Preference Questionnaire - Child (GH-PPQ-Child)[h]							X														
SAFETY																					
Physical examination[f]	8.2.1		X						X		X		X		X		X		X	X	
Vital signs	8.2.2		X						X		X		X		X		X		X	X	

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I										Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			**-2**	**0**	**4 +1d**	**8**	**13 +3d**	**20**	**26 +5d**	**39**	**52 +5d**	**65**	**78**	**91**	**104 +2d**	**117**	**130**	**143**	**156 +5d**		**156 +30d**
Visit window (days)		**Minimum 1 day prior to screening**	**±7[a]**		**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7**	**±7 exactly**	**±7**	**±2**	**±7**	**±7 exactly**	**±7**	**±1**		**+7**
Electrocardiogram (ECG) (SGA & ISS)	8.2.3		X						X		X				X				X	X	
Electrocardiogram (ECG) (TS & NS)	8.2.3		X						X		X		X		X		X		X	X	
Transthoracic echocardiogram (TTE) (TS)	8.2.4		X						X		X				X				X	X	
Transthoracic echocardiogram (TTE) (NS)	8.2.4		X						X		X		X		X		X		X	X	
Adverse Event	8.3		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory safety assessments	8.2.5 10.2																				
Haematology			X						X		X		X		X		X		X	X	

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I										Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			**-2**	**0**	**4 +1d**	**8**	**13 +3d**	**20**	**26 +5d**	**39**	**52 +5d**	**65**	**78**	**91**	**104 +2d**	**117**	**130**	**143**	**156 +5d**		**156 +30d**
Visit window (days)		**Minimum 1 day prior to screening**	**±7[a]**		**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7**	**±7 exactly**	**±7**	**±2**	**±7**	**±7 exactly**	**±7**	**±1**		**+7**
Biochemistry				X					X		X		X		X		X		X	X	
Glucose metabolism			X						X		X		X		X		X		X	X	
Lipids				X					X		X				X				X	X	
Hormones			X						X		X				X				X	X	
Antibodies				X			X			X			X				X			X	X
Coagulation parameters (NS)					X					X		X		X		X		X		X	
TRIAL MATERIAL																					
Dispensing of trial product	6.3			X	X		X		X	X	X	X	X	X	X	X	X	X	X[l]		

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I										Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			**-2**	**0**	**4 +1d**	**8**	**13 +3d**	**20**	**26 +5d**	**39**	**52 +5d**	**65**	**78**	**91**	**104 +2d**	**117**	**130**	**143**	**156 +5d**		**156 +30d**
Visit window (days)		**Minimum 1 day prior to screening**	**±7[a]**		**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7 exactly**	**±1**	**±7**	**±7 exactly**	**±7**	**±2**	**±7**	**±7 exactly**	**±7**	**±1**		**+7**
OTHER ASSESSMENTS																					
Karyotype determination/CGH (TS)[i]	8.6		X																		
Genetic testing (NS)[i]	8.6		X																		
REMINDERS																					
Attend visit fasting[g]	5.3.1		X						X		X		X		X		X		X	X	
Handout ID card	8		X																		
Training in trial product and pen handling	6.1			X	X					X				X							
Hand out direction for use	6.1			X																	

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I									Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			-2	0	4 +1d	8	13 +3d	20	26 +5d	39	52 +5d	65	78	91	104 +2d	117	130	143	156 +5d		156 +30d
Visit window (days)		**Minimum 1 day prior to screening**	±7[a]		±1	±7 exactly	±1	±7 exactly	±1	±7 exactly	±1	±7	±7 exactly	±7	±2	±7	±7 exactly	±7	±1		+7
Handout and instruct in dosing diary	8.1.4			X	X		X		X	X	X	X	X	X	X	X	X	X			
Dosing diary review	8				X		X		X	X	X	X	X	X	X	X	X	X	X	X	
End of treatment																			X[m]	X[m]	
End of study																					X[m]

[a]For participants with Turner syndrome and Noonan syndrome the visit window for Visit 1 can be extended to -28/+7 days in case it is needed in order to acquire the results from the karyotype determination/CGH or genetic testing, respectively.
[b]Demography consists of date of birth, sex, ethnicity and race (according to local regulation). Race and ethnicity must be self-reported by the participant or participant's parent(s)/participant's LAR.
[c]Pregnancy test should be performed at every visit after menarche for female participants, if applicable. See Appendix 2 (Section 10.2) and Appendix 4 (Section 10.4) for more information.
[d]Only applicable for female participants.
[e]To be performed at premature discontinuation unless performed within the past 6 months prior to discontinuation visit.
[f]**United States:** Please see local requirement in Appendix 11 (Section 10.11).
[g]Fasting time is 6 hours.
[h]Only to be collected from participants or parent(s)/LAR of participants switching to somapacitan from daily GH treatment.

Procedure	Protocol section	Information	Screening	Baseline	Main period					Extension period I										Discontinuation of treatment	Follow up
Visit		**V0**	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**	**V11**	**V12**	**V13**	**V14**	**V15**	**V16**	**V17[j]**	**V17A**	**V18[k]**
Timing of visit (weeks)			-2	0	4 +1d	8	13 +3d	20	26 +5d	39	52 +5d	65	78	91	104 +2d	117	130	143	156 +5d		156 +30d
Visit window (days)		**Minimum 1 day prior to screening**	±7[a]		±1	±7 exactly	±1	±7 exactly	±1	±7 exactly	±1	±7	±7 exactly	±7	±2	±7	±7 exactly	±7	±1		+7

[i]Only applicable for treatment naïve participants.
[j]visit 17 is the end of treatment visit for participants who will end the trial at visit 17. Participants who continue in extension period II will have an end of treatment visit according to the flowchart for extension period II (Section 1.3)
[k]This follow-up visit is only applicable for participants ending the trial after extension period I. See the flowchart for extension period II (Section 1.3) for follow-up visit for participants continuing in extension period II. Follow-up visit 18 should also be performed after visit 17A for participants who discontinue treatment before visit 17. The follow-up visit should take place 30 days after last treatment.
[l]Only for participants continuing in extension period II.
[m]Only for participants ending the trial at visit 17 or 17A.
[n]After reaching Tanner stage 5, pubertal status assessment can be discontinued.

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1.3 Flowchart for extension period II

Procedure	Protocol Section	Extension period II							Discontinuation of treatment	Follow up
Visit		**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V98**	**V99[a]**
Timing of visit (weeks)		**169**	**182**	**195**	**208+2d**	**221**	**234**	**247**		**V98 +30d**
Visit window (days)		±7	**±7 exactly**	±7	±2	±7	**±7 exactly**	±7		+5
PARTICIPANT RELATED INFORMATION AND ASSESSMENTS										
Discontinuation/Withdrawal criteria	7	X	X	X	X	X	X	X	X	
Concomitant medication	8.2	X	X	X	X	X	X	X	X	X
Pregnancy Test[b]	8.2.6	X	X	X	X	X	X	X	X	X
Pubertal status[g]	8.1.2		X		X		X		X	
Date of menarche[c]	8.1.2	X	X	X	X	X	X	X	X	X
EFFICACY										
X-Ray for bone age assessment	8.1.3				X				X[f]	
Body Measurements	8.1.1									
Height		X	X	X	X	X	X	X	X	

Procedure	Protocol Section	Extension period II							Discontinuation of treatment	Follow up
Visit		**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V98**	**V99[a]**
Timing of visit (weeks)		**169**	**182**	**195**	**208+2d**	**221**	**234**	**247**		**V98 +30d**
Visit window (days)		±7	±7 **exactly**	±7	±2	±7	±7 **exactly**	±7		+5
Body weight		X	X	X	X	X	X	X	X	
Sitting height (Turner syndrome & ISS)					X				X	
Pharmacodynamics	8.5									
IGFBP-3			X		X		X		X	
IGF-I			X		X		X		X	
Bioactive IGF-I			X		X		X		X	
Pharmacokinetics	8.4									

Procedure	Protocol Section	Extension period II							Discontinuation of treatment	Follow up
Visit		**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V98**	**V99[a]**
Timing of visit (weeks)		**169**	**182**	**195**	**208+2d**	**221**	**234**	**247**		**V98 +30d**
Visit window (days)		±7	**±7 exactly**	±7	**±2**	±7	**±7 exactly**	±7		**+5**
Somapacitan			X		X		X		X	
SAFETY										
Physical Examination[d]	8.2.1		X		X		X		X	
Vital Signs	8.2.2		X		X		X		X	
Electrocardiogram (ECG) (SGA & ISS)	8.2.3				X				X	
Electrocardiogram (ECG) (Turner- & Noonan syndrome)	8.2.3		X		X		X		X	
Transthoracic echocardiogram (TTE) (Turner syndrome)	8.2.4				X				X	
Transthoracic echocardiogram (TTE) (Noonan syndrome)	8.2.4		X		X		X		X	

Procedure	Protocol Section	Extension period II							Discontinuation of treatment	Follow up
Visit		**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V98**	**V99[a]**
Timing of visit (weeks)		**169**	**182**	**195**	**208+2d**	**221**	**234**	**247**		**V98 +30d**
Visit window (days)		±7	**±7 exactly**	±7	±2	±7	**±7 exactly**	±7		+5
Adverse Event	8.3	X	X	X	X	X	X	X	X	X
Laboratory safety assessments	8.2.5 10.2									
Haematology			X		X		X		X	
Biochemistry			X		X		X		X	
Glucose metabolism			X		X		X		X	
Lipids					X				X	
Hormones					X				X	
Antibodies			X				X		X	X

Procedure	Protocol Section	Extension period II							Discontinuation of treatment	Follow up
Visit		**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V98**	**V99[a]**
Timing of visit (weeks)		**169**	**182**	**195**	**208+2d**	**221**	**234**	**247**		**V98 +30d**
Visit window (days)		±7	**±7 exactly**	±7	**±2**	±7	**±7 exactly**	±7		**+5**
Coagulation parameters (Noonan syndrome)			X		X		X		X	
TRIAL MATERIAL										
Dispensing of trial product	6.3	X	X	X	X	X	X	X		
REMINDERS										
Attend Visit Fasting[e]	5.3.1		X		X		X		X	
Training in trial product and pen handling	6.1		X		X		X			
Handout and instruct in dosing diary	8.1.4	X	X	X	X	X	X	X		
Dosing Diary review	8	X	X	X	X	X	X	X	X	
End of treatment									X	
End of study										X

Procedure	Protocol Section	Extension period II							Discontinuation of treatment	Follow up
Visit		**V19**	**V20**	**V21**	**V22**	**V23**	**V24**	**V25**	**V98**	**V99[a]**
Timing of visit (weeks)		**169**	**182**	**195**	**208+2d**	**221**	**234**	**247**		**V98 +30d**
Visit window (days)		±7	±7 **exactly**	±7	±2	±7	±7 **exactly**	±7		+5

[a]The follow-up visit should take place 30 days after last treatment in extension period II. This means that the follow-up visit should also be performed for participants who discontinue treatment during this period. The follow-up visit can be performed as a phone visit.

[b]Pregnancy test should be performed at every visit after menarche for female participants, if applicable. See Appendix 2 (Section 10.2) and Appendix 4 (Section 10.4) for more information.

[c]Only applicable for female participants.

[d]United States: Please see local requirement in Appendix 11 (Section 10.11).

[e]Fasting time is 6 hours.

[f]To be performed at discontinuation visit unless performed within the past 6 months prior to discontinuation visit.

[g]After reaching Tanner stage 5, pubertal status assessment can be discontinued.

2 Introduction

Throughout the protocol, the term participant refers to the paediatric participant in this study. There may also be referred to the parent or legally acceptable representative (LAR), if applicable, depending on the age and the capability of the participant to perform the required study procedures.

In this study, participants either naïve or non-naïve to growth promoting therapy can be included. Participants are considered 'non-naïve' if they have received ≥1 dose of growth promoting therapy prior to screening.

2.1 Study rationale

The purpose of this phase 3a study is to evaluate safety and efficacy of once weekly s.c. treatment with somapacitan in the following four indications of children with short stature: born small for gestational age (SGA) with insufficient catch-up growth by 2 years of age or older, Turner syndrome (TS), Noonan syndrome (NS) or idiopathic short stature (ISS). This study is supportive to the pivotal phase 3a study (NN8640-4467) in prepubertal children with short stature due to SGA, TS, NS or ISS. Based on feedback from Health Authorities, this study is designed to include participants from an older paediatric age-group in each of the four indications that could potentially benefit from somapacitan treatment. All data will be analysed separately for each indication.

Growth disorders exist across a continuum of GH–IGF-I axis defects ranging from severe GH deficiency, where GH secretion is very low and responsiveness to treatment is high, to extreme GH resistance (Laron syndrome), where GH secretion is high and response to administered GH is very low or non-existent. Conditions in-between these extremes include SGA, TS, NS and ISS where GH secretion is slightly reduced or normal and where GH sensitivity is decreased.[4, 5] Therefore, in children with non-GH-deficient causes of growth failure, and initially normal IGF-1 SDS, elevated IGF-1 levels associated with higher GH doses may be required to achieve an acceptable height gain. The underlying reason for treating children with SGA, TS, NS and ISS with GH is the same for all four indications; namely to treat short stature, which is due to either idiopathic causes (ISS), due to environmental and/or genetic factors (SGA) or specific genetic modifications (NS and TS). In order to evaluate the safety and efficacy of somapacitan within each of the four indications of children with short stature, and as key design elements across these four indications are similar, an overarching master protocol with a basket study design is applied. Importantly, indication-specific elements of study conduct are clearly specified throughout sections within this master protocol. Regulatory authorities or independent ethics committees/institutional review boards have the opportunity to only approve the study for some of the indications to be conducted in a particular country/site. In that case, the relevant site or country is exempted from participation in the non-approved sub-study/sub-studies.

Reporting may occur on a per indication basis, thus, individual database locks may be performed and separate clinical study reports may be issued for the four indications covered in this master protocol.

The basket study design provides advantages for the investigators who are able to apply a single master protocol while enrolling patients within all four indications (SGA, TS, NS and ISS). The implementation of a basket study design will best ensure the quality of clinical development of

somapacitan, taking the limited number of patients with SGA, TS, NS and ISS into consideration. The concept of using basket studies and master protocols has been recognised by regulatory authorities to optimise drug development.[6-8]

2.2 Background

2.2.1 Short stature

Short stature can be due to various aetiologies and the cause may be a primary or secondary growth disorder, or idiopathic.[9] Primary growth disorders are intrinsic to the growth plate and include clinically defined syndromes and factors that result in being born small for gestational age (SGA). Secondary growth disorders are believed to change the milieu of the growth plate and include GH deficiency, disorders of the IGF-I axis including IGF-I deficiency or resistance, endocrine and metabolic disorders, organ system disorders, malnutrition, psychosocial disorders, and iatrogenic conditions. A combined approach of systematic phenotyping, targeted genetic testing and whole-exome sequencing allows the identification of the underlying cause of ISS in at least 33% of cases.[10] The majority, however, have no identified cause. The condition is very heterogeneous and may be either familial or non-familial. While the list of secondary growth disorders has hardly changed over the last decades, the number of primary growth disorders has considerably increased due to the expanding use of novel genetic techniques.[11]

2.2.2 Treatment of short stature

GH increases growth by both a direct action on the growth plates as well as by stimulating IGF-1 secretion, mainly in the liver. Human GH (hGH) also has important effects on the metabolism of proteins, lipids and carbohydrates, not only during childhood, but also throughout adult life. It is critically important to maximize height with GH therapy before the onset of puberty. The earlier GH is commenced, the more likely the child is to achieve a height that is appropriate for the target height.[12]

In children who have a deficiency of endogenous GH (GHD), the use of GH replacement therapy stimulates linear growth and increases growth rate. In 1985, when biosynthetic GH became available on a large-scale, a large number of clinical studies investigating the effect of GH in various indications associated with short stature and normal GH secretion were initiated. In the years that followed, recombinant human GH (rhGH) treatment was approved for use in various other indications. It was first approved for treatment of children with chronic renal insufficiency in 1993, Turner syndrome (TS) in 1990, Prader-Willi syndrome (PWS) in 2000, short children born small for gestational age (SGA) in 2001, children with idiopathic short stature (ISS) in 2003, and children with Noonan syndrome (NS) in 2007.[13] The rationale for this treatment is based on the empirical observation of growth acceleration in response to GH administration, rather than on a pathophysiological approach.[14]

2.2.3 Included populations

The current protocol includes four indications associated with short stature and indicated for pharmacological treatment with GH.

Throughout the protocol the following abbreviations and definitions are used for the indications:

- SGA: Small for Gestational Age: Children born small for gestational age with insufficient catch-up growth by 2 years of age or older
- TS: Turner Syndrome
- NS: Noonan Syndrome
- ISS: Idiopathic Short Stature

2.2.3.1 Small for Gestational Age: Children born small for gestational age with insufficient catch-up growth by 2 years of age or older

SGA is a heterogenous condition which is a result of impaired foetal growth due to environmental as well as genetic factors, not yet clearly identified. SGA refers to the size of an infant at birth and is defined as a birth length and/or birth weight of at least 2 Standard Deviation Scores (SDS) below the mean for gestational age and sex.[15] The prevalence of SGA has been reported to be between 3.1% and 15.3% depending on the geographical area investigated.[16-19] The variation might be influenced by regional differences in diagnostic practice. Most children born SGA have sufficient GH secretion and IGF-I levels and show spontaneous catch-up growth to a normal height and weight above 2 SDS by 2 years of age. However, approximately 10% of the children do not catch up despite sufficient GH and IGF-I levels and therefore have a markedly reduced final adult height compared to predicted height.[20, 21]

2.2.3.2 Turner Syndrome

TS is a chromosomal disorder occurring in approximately 50 per 100,000 live born girls.[22, 23] Monosomy X is present in about half of the cases. The remaining cases present a structural X-chromosome aberration or a mosaic karyotype, consisting of a 45X cell line in combination with at least one of the following: 46XX, isochromosome, ring chromosome or marker X, 47XXX, or a whole or partial Y-chromosome. Phenotypic features vary widely in Turner syndrome. Cardinal features include short stature and gonadal failure. Congenital and acquired cardiovascular disease, diabetes, hypothyroidism, impaired hearing, scoliosis, renal abnormalities and neurocognitive disorders are frequently associated diseases.[24] Patients with deletions of the distal segment of the short arm of X chromosome (Xp-) including haploinsufficiency of the SHOX (short stature homeobox) have, more often, short stature, skeletal abnormalities, and hearing impairments.[25]

2.2.3.3 Noonan Syndrome

NS is a relatively common, with widely quoted prevalence of 1 in 1,000–2,500 live births,[26] clinically variable and genetically heterogeneous developmental disorder characterized by postnatally reduced growth, distinctive facial dysmorphism, congenital heart defects or hypertrophic cardiomyopathy and variable cognitive deficits. Other associated features include ectodermal and skeletal defects, cryptorchidism, lymphatic dysplasias, bleeding tendency, and, rarely, predisposition to hematologic malignancies during childhood.[27, 28] NS is regarded as a disorder of upregulated RAS-MAPK signalling.[29] NS is nearly always an autosomal-dominant condition, although recently there have been reports of autosomal recessive forms.[30] Two-thirds of patients are the first affected person in their family due to a de novo pathogenic variant.[31] Despite advances in molecular testing of NS an underlying genetic mutation is not identified in 20%–30% of patients. Short stature affects 50–70% of patients with NS.[28] At birth the height and weight of the patient are

within the reference range but growth retardation involving height, weight and bone development shows during childhood. The height and weight are usually below -2 SDS for the population.[32]

2.2.3.4 Idiopathic Short Stature

ISS describes short children with normal GH secretion. ISS is a condition in which the height of the individual is more than 2 standard deviations (SD) below the corresponding mean height for a given age, sex and population, without evidence of systemic, endocrine, nutritional or chromosomal abnormalities.[33] The prevalence of ISS is approximately 2%.[34] Due to global treatment guidance differences, the inclusion criteria for the present study will be an impaired height more than 2.5 SD below the corresponding mean height for a given age, sex and population.

2.2.4 Study Intervention

2.2.4.1 Somapacitan

Somapacitan is a long acting rhGH derivative with a single substitution in the amino acid backbone to which a non-covalent albumin binding moiety has been attached. This facilitates reversible binding to endogenous albumin after injection which in turn decreases the clearance and increases the in vivo half-life 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 is intended for once-weekly s.c. administration with the aim of reducing treatment burden and improving treatment adherence by reducing injection frequency, and ultimately to improve clinical outcome.[35] As for hGH, the mechanism of action of somapacitan on longitudinal growth is mainly via IGF-I. The receptor potency and pharmacokinetic (PK) profile of somapacitan has been assessed to be suitable for once-weekly administration in humans and it is expected to have at least as good an efficacy and safety profile as daily administered GH.[36] Currently, somapacitan is approved for the treatment of Adult GHD in USA, Japan and EU, and is under development for the treatment of children with GHD. For further information, please refer to the Investigator's Brochure (IB).

2.2.4.2 Somapacitan nonclinical data

No safety issues were identified during the nonclinical development of somapacitan which would prevent administration of the compound in humans. Nonclinical data supports once-weekly administration in humans and further development in phase 3.

Further details on the nonclinical findings are described in the IB.

2.2.4.3 Somapacitan clinical data

Overall, the safety profile of somapacitan is similar to the well-known safety profile of daily growth hormone products e.g., Norditropin® and no new safety concerns have been found during the conduct of the somapacitan study program. Clinical data obtained from both adults and children continue to support the further development of somapacitan into phase 3 in children with GHD, SGA, TS, NS and ISS.

2.3 Benefit-risk assessment

The main benefits and risks related to participation in the study are described in the below sections. More detailed information about the known and expected benefits and risks and reasonably expected adverse events of somapacitan may be found in the IB.

2.3.1 Risk assessment

Table 2-1 Risk assessment

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Study interventions (somapacitan)		
Allergic reaction	Allergic hypersensitivity may occur with the administration of somapacitan. Acute generalised hypersensitivity reactions are generally known to occur within the first few hours after the injection and may include headache, nausea, vomiting, dizziness, sweating, flushing, change in blood pressure and difficulties in breathing.	Patients with known or suspected hypersensitivity to study product, any constituents of the product or related products will not be enrolled in the study (see exclusion criteria in Section 5.2). Signs of allergic hypersensitivity will be monitored closely throughout the study. The first dose of somapacitan will be administered at the study site, and the participants are therefore monitored very closely after first dosing. Allergic type hypersensitivity should be treated as per local practice at the investigator's discretion.
Diabetes mellitus	Treatment with GH may decrease insulin sensitivity, particularly at higher doses in susceptible patients. Consequently, hyperglycaemia may occur in participants with inadequate insulin secretory capacity.	Glucose levels should be monitored periodically in all patients treated with GH, especially in those with risk factors for diabetes mellitus, such as obesity, or a family history of diabetes mellitus. Patients with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose tolerance are excluded from participation in the study. The doses of anti-hyperglycaemic medicinal products may require adjustment when GH therapy is instituted in these patients.

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Intracranial hypertension	Patients with intracranial hypertension are at increased risk of worsening of the condition by treatment with GH, because a major adverse effect of GH treatment is fluid retention.	In the event of severe or recurrent headache, visual symptoms, nausea, and/or vomiting, a fundoscopic examination for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and if appropriate the GH treatment should be discontinued. If GH treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.
Adrenocortical insufficiency	Introduction of GH treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with GH, previously undiagnosed central (secondary) hypoadrenalism may be unmasked.	Glucocorticoid replacement may be required in this population. Patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of GH treatment.
Hypothyroidism	GH increases the extrathyroidal conversion of T4 to T3 and may as such unmask incipient hypothyroidism.	As hypothyroidism interferes with the response to GH therapy, patients should have their thyroid function tested regularly, and should receive replacement therapy with thyroid hormone when indicated.
Medication errors	A medication error covers unintended administration of wrong drug and/or use of wrong device, wrong route of administration (such as intramuscular instead of subcutaneous) and accidental overdose. For details, see Section 10.3.3. .	The following risk minimisation measures were implemented to prevent medication errors: The investigator is responsible for communicating the dose and training the participants on how to use the pen. Dispensing of trial product is controlled by an electronic system to ensure that the correct number of pens are provided, counting of returned trial product at each visit, review of dosing diaries, alerts if a dose is forgotten. Novo Nordisk closely follows medication errors, which are reported through the EDC by the site.
Study procedures		

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Injection site reaction	Somapacitan will be injected subcutaneously.	Participants will be trained to do the injections themselves. The participants will be trained to rotate injection site. This will reduce the risk of injection site reactions. Injection site reactions will be monitored closely throughout the study. For more details see Section 8.3.
X-Ray for bone age assessment	No risks are expected to be associated with the procedure. The risks are related to the total dose of radiation received.	The burden of this assessment is reduced by the possibility of using an X-Ray performed up to 13 weeks prior to screening. In case of premature treatment discontinuation, an X-Ray should only be performed if this has not been performed within the past 6 months. The frequency of the X-Ray examination is similar to normal clinical practice to limit the total dose of radiation received.
Electrocardiogram (ECG)	The procedure involves placing adhesive skin surface electrodes on the body. This procedure does not incur any risks. Burdens may include discomfort and fear.	The number and frequency of ECGs have been critically evaluated and limited to the extent possible. In case of premature treatment discontinuation, an ECG should only be performed if this has not been performed within the past 6 months.
Transthoracic echocardiogram (TTE) (only relevant for Turner Syndrome and Noonan Syndrome)	No risks are expected to be associated with the procedure. Burdens may include discomfort and fear.	The number and frequency of TTEs have been critically evaluated and limited to the extent possible. In case of premature treatment discontinuation, a TTE should only be performed if this has not been performed within the past 6 months.
Peripheral venepuncture	Risks include vasovagal reactions, minor bleeding, and vessel damage. Burdens include moderate pain and possibly fear and distress.	Peripheral venous access is widely used for taking blood samples. Pain can be reduced with use of local anaesthetic agents. In this study investigators are encouraged to use numbing cream according to local practice. To avoid that too much blood is sampled during the study, blood sampling volume limits have been implemented.[37]

Potential risk of clinical significance	Summary of data/rationale for risk	Mitigation and monitoring strategy
Fundoscopic examination (can be performed in case of severe headache at the investigator's discretion. See Section 8.3.3. **United States:** Please see local requirement in Appendix 11 (Section 10.11)).	Risks have not been identified, but if a medicine is used to dilate the pupils, risks include increased intraocular pressure, disturbance of vision, dry mouth, neurological symptoms and nausea. Burdens may include fear, discomfort, and, when a medicine is used, distress with its repeated application and hour-long vision changes.	The number of fundoscopic examinations should be kept to a minimum and should only be performed at the discretion of the investigator to follow up on AEs (see Section 8.3.3). In USA, it is mandatory to perform fundoscopic examination at baseline and therefore this has been implemented as a local requirement in USA (see Appendix 11 (Section 10.11)).
Other		
Risk of COVID-19 infection in relation to participation in the study	Participants may be exposed to COVID-19 transmission and infection in relation to site visits if an outbreak is ongoing in the given country.	The risk of COVID-19 transmission in relation to site visits is overall considered to be low, however this may vary between geographical areas. Testing in case of any symptoms compatible with COVID-19 is strongly recommended.
Concomitant administration of COVID-19 vaccines.	Administration of COVID-19 approved vaccines is not considered to pose a risk to participants treated with somapacitan.	Non-approved COVID-19 vaccines under investigation are not allowed during participation in this study since such vaccines may have an unknown safety profile.
Physical examination and body measurements including Tanner pubertal staging	No risks are expected to be associated with standard physical examination. Burden (embarrassment, discomfort, distress) associated with examinations that are related to sexual development (e.g., Tanner staging) can be expected.	As these assessments are performed by physicians familiar with the participants the burden is expected to be low.
Fasting prior to blood sampling	Risks may include mild to moderate hypoglycaemia (usually subclinical). Burdens may include hunger and distress, increasing with duration of fasting and generally with younger age.	The number of fasting visits and length of the fasting period are reduced to the extent possible.

Risk assessment has been conducted for the PDS290 pen-injector for somapacitan 15 mg/1.5 mL in compliance with ISO 14971:2019[38]. A device risk assessment has been performed to ensure safe and accurate handling and dosing of somapacitan when using the PDS290 pen-injector in the study population (children born SGA, or with TS, NS or ISS). All identified risks (see the IB) associated with using the PDS290 pen-injector for somapacitan 15 mg/1.5 mL for the population in the clinical study, when used according to the clinical procedures specified in this protocol, have been reduced as far as possible and are acceptable, taking into account the current state of the art. The overall

conclusion is that the use of the PDS290 pen-injector for somapacitan 15 mg/1.5 mL in this study is safe and effective for the study participants.

2.3.2 Benefit assessment

Information gained from this study will support the development of a growth hormone product with clinical advantages over currently available products to children with SGA, TS, NS and ISS.

For most of the participating children the administration of study intervention during the study most likely reduces the treatment burden compared to current available therapy as somapacitan is administered once weekly.

It is expected that many participating treatment naïve children will experience increased height velocity compared to pre-study experience.

Participating children might benefit from the increased attention during the participation of the study which might lead to an increase in treatment adherence.

2.3.3 Overall benefit-risk conclusion

Overall, the safety profile of somapacitan is similar to the well-known safety profile of daily growth hormone products e.g., Norditropin® and no new safety concerns have been found during the conduct of the somapacitan study program.

There are well known risks associated with administration of injectable medication[36] as well as procedural risks as described in Table 2-1. In this study the risks associated with administration of trial product as well as the risks associated with the study procedures are expected to be comparable to what is seen in routine clinical practice.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AE) of somapacitan may be found in the IB.

Taking into account the measures taken to minimise risk and burden to children participating in this study, the potential risks identified in association with somapacitan are justified by the anticipated benefits that may be afforded to children with SGA, TS, NS and ISS.

3 Objectives, endpoints and estimands

Table 3-1 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 supportive safety endpoint:		
	Number of adverse events (AEs) possibly or probably related to somapacitan	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)	From baseline (week 0) to week 156	Number of AEs
• To evaluate the efficacy 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 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 9.3.3.

4 Study design

4.1 Overall 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 period) in children with short stature in each of the indications SGA, TS, NS and ISS. The 26-week main period will be followed by a 130-week extension period I with once-weekly dosing of somapacitan 0.24 mg/kg/week to evaluate long-term safety. Further, participants, who complete the extension period I when somapacitan is not available to be prescribed for children with SGA, TS, NS or ISS in their country, can continue treatment in extension period II which will last until somapacitan becomes available for prescription in their country or October 2027 (at the latest). Participants will receive somapacitan at 0.24 mg/kg/week. Study participants will include children with SGA, TS (only females), NS and ISS.

Children above or equal to 10.0 years (female participants with SGA, TS, NS, and ISS) or 11.0 years (male participants 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 Health Authorities, this age group will be investigated in this study NN8640-4469.

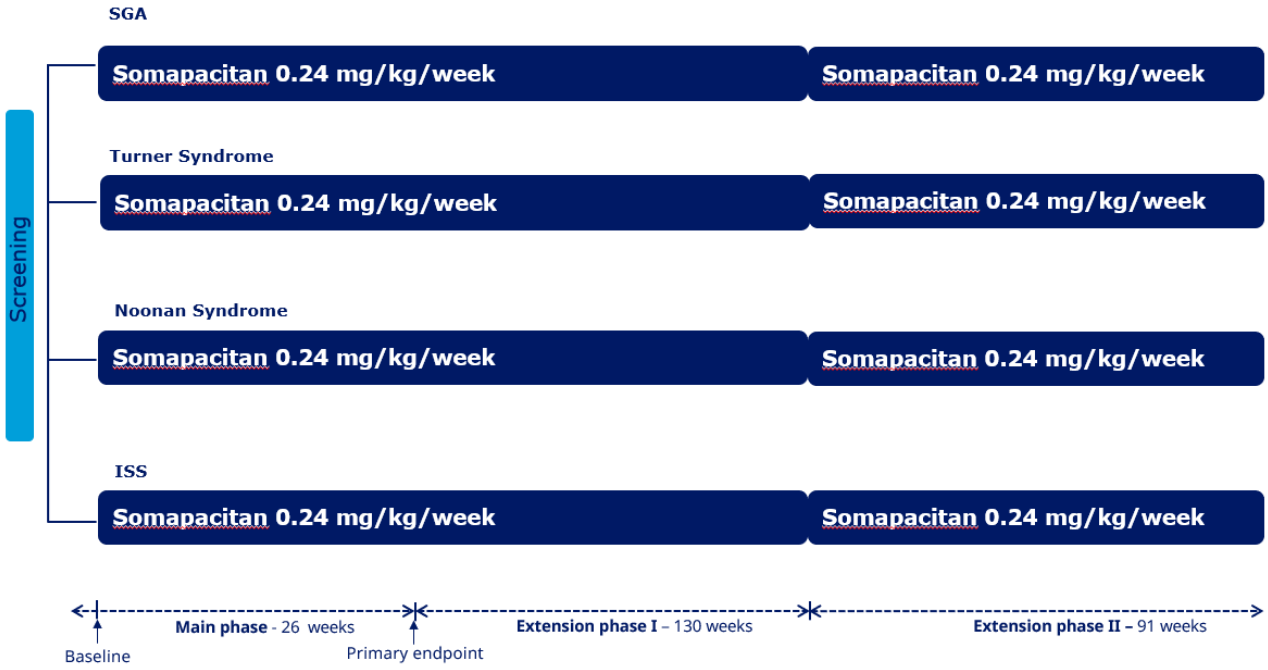
Approximately 60 participants in total are planned to be screened and up to 50 participants in total are planned to be enrolled (planned treated) in this study. In total, at least 40 participants are planned to complete the study. All participants will receive somapacitan 0.24 mg/kg/week.

The total treatment duration for participants in the study, up to the end of the extension period I, is scheduled to be 3 years. For participants who remain on treatment in the extension period II, the total study duration will be up to 5 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 period
- a 130-week interventional extension period I
- up to 91-week interventional extension period II
- a 30-day follow-up period

Figure 4-1 Study design



4.2 Scientific rationale for study design

GH treatment is generally regarded as safe with no major adverse effects being recorded in any condition. Recombinant human GH has been in use for over 30 years, and its indications have gradually expanded from replacement therapy in GHD to pharmacological therapy in patients with normal GH secretion.

The study is designed to evaluate the safety and efficacy of once-weekly somapacitan in non-growth hormone-deficient children. It includes children in all four indications (SGA, TS, NS and ISS), in order to support study NN8640-4467 in collecting evidence of the effects of somapacitan within the paediatric age-range.

The supportive role of this study is also the reason there is no control or comparator group. It is evaluated unethical to treat the age group with placebo. Based on data from previous studies with somapacitan as well as daily GH, 26 weeks collection of safety data is evaluated sufficient to support study NN8640-4467.

While safety evaluation is the primary objective, efficacy assessments will be used to support the clinical evaluation of weekly growth hormone treatment, since daily growth hormone treatment has shown to increase the height velocity and final height in children with the four proposed indications.[15, 24, 39-41]

The study is open-labelled.

The four sub-studies covered in this master protocol are designed in alignment with the objectives (Section 3) to evaluate safety and efficacy of once-weekly somapacitan during 26 weeks.

Both GH treatment-naïve and GH treatment-non-naïve children with short stature either born SGA, or with TS, NS and ISS are the target populations. Both female and male participants will be

enrolled in the study (although only female participants in the sub-study for TS) in order to obtain information on safety and efficacy in both sexes and the study is conducted globally, to ensure a representative patient population.[42]

A basket study design has been applied in this master protocol, as the key design elements for this study are the same for all four indications, including primary and secondary endpoints, the majority of in- and exclusion criteria, most assessments, study duration and visit structure. Similar safety monitoring between the four indications will be applied, with additional monitoring implemented for patients enrolled with TS and NS to ensure cardiovascular safety.

If a safety issue occurring in one of the sub-studies is evaluated relevant for the other sub-studies the necessary actions will be implemented for all relevant sub-studies.

Furthermore, all four indications are often treated by the same medical specialists. Therefore, the clinical study sites are likely to cover more or all indications. A well-recognised principle in clinical studies is, that having a reasonable number of patients enrolled in a study at each clinical study site will best ensure the quality of study conduct by the clinical study site staff having more practice, as compared to having very few patients, as would be the case if the indications would be investigated under separate protocols using separate data systems. Furthermore, handling one protocol is most likely less burdensome to the clinical study site staff than handling four individual protocols. The potential advantages of applying a basket study design are supported by a recent review.[7] Thus, the implementation of a basket study design will optimise the use of operational resources as it will allow for the best utilisation of the expertise by the investigators and the number of sites will be reduced compared to conducting individual studies for the four indications.

To ensure that differences in study conduct between the four indications are recognisable and apparent, the following measures are implemented:

- Thorough study specific training of site staff is conducted by Novo Nordisk before initiation as well as during the study.
- Thorough monitoring of participant data by Novo Nordisk staff to support correct allocation as well as indication-specific protocol compliance. See Section 10.1.8.2.
- Appropriate measures during the screening process e.g., automatic system prompts to ensure participants are allocated correctly into the relevant sub-study. See Section 6.3.
- Participant numbers are indication-specific, so that site staff should be able to easily recognise what indication a given participant belongs to.
- Indication-specific data are entered in indication-specific eCRF pages.
- Indication-specific procedures are clearly outlined and easily identified throughout this master protocol.
- Trial product and -labelling will be identical to minimise mistakes.

4.2.1 Patient input into design

Patient input to study design has not been applied for this confirmatory phase 3 study, but rather adopted earlier in the development programme for somapacitan as per clinical guideline.[43, 44]

4.3 Justification for dose

Main period and extension period I

For all four indications, a somapacitan dose of 0.24 mg/kg/week is chosen. The selected dose is based on the results of the phase 2 dose-finding study (NN8640-4245) that investigated three somapacitan dose levels of 0.16, 0.20 and 0.24 mg/kg/week in children with short stature born SGA for 26 weeks.

A consistent dose response on height increase was demonstrated across all dose levels (0.16-0.24 mg/kg/week) in study NN8640-4245. As expected, the highest levels of somapacitan exposure and increases in IGF-I SDS levels were obtained in the somapacitan 0.24 mg/kg/week arm. Exposure-response analyses indicated that the highest improvements in HV were correlated with the highest somapacitan exposures and highest changes in IGF-I-SDS. Thus, the totality of evidence on improvements in height combined with exposure-response analyses suggests that somapacitan 0.24 mg/kg/week is the most efficacious dose level within the dose range explored in study NN8640-4245. Furthermore, the IGF-I SDS levels obtained with somapacitan 0.24 mg/kg/week were in line with what has been observed in clinical practice and clinical studies with daily GH treatment.[45, 46] No safety issues were identified across treatment arms up to somapacitan 0.24 mg/kg/week, including in participants obtaining IGF-I SDS levels above +3, and no safety issues were identified as compared to daily GH treatment. Studies with daily GH support that treatment leading to supraphysiological IGF-I SDS levels in some patients in the non-replacement indications is needed to be efficacious[45] and that treatment with daily GH doses above 0.040 mg/kg/day is not associated with higher long-term safety risks compared to lower GH doses.[47, 48] Therefore, no safety issues are anticipated for somapacitan 0.24 mg/kg/week in this phase 3 study. Novo Nordisk will carefully monitor the safety of all participants in our active safety surveillance program. Furthermore, participant safety will be monitored by an independent, external data monitoring committee (DMC).

Extension period II

In the extension period I, participants will continue receiving somapacitan 0.24 mg/kg/week based on the same rationale outlined above for main and extension period I.

4.4 End of study definition

The end of the study is defined as the date of the last participant's last visit in the sub-study to finish last.

For all participants in the study

A participant is considered to have completed the study if he/she has completed all periods of the main and extension period I of the study including visit 18.

The primary endpoint is evaluated from visit 2 to visit 7 for each indication/sub-study. The primary completion date (PCD) is defined as the date of visit 7 (week 26) on which the last participant in the first indication to complete the main period has an assessment for the primary endpoint. If the last participant is withdrawn early, the PCD is considered the date when the last participant in the first indication to complete the main period would have completed visit 7.

For participants continuing in extension period II

Participation in this extension period II will be offered to continue treatment with somapacitan until somapacitan becomes available for prescription for treatment of SGA, TS, NS or ISS or until October 2027 at the latest. Therefore, there is no predefined specific period that must be completed.

5 Study population

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Pre-screening is defined as review of the patient medical records, including handing out participant information, as well as database review. Any pre-screening activities must be documented on site by the investigator.

5.1 Inclusion criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Informed consent of parent or legally acceptable representative of participant and child assent, as age appropriate must be obtained before any study-related activities. Study-related activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. Thyroid hormone replacement therapy should be adequate and stable for at least 90 days prior to allocation, if applicable.
3. Open epiphyses; defined as bone age < 14 years for females and bone age < 16 years for males.
4. Historical height measured 6-18 months prior to screening.

Applicable to children with SGA:

5. Born small for gestational age (birth length below -2 SDS OR birth weight below -2 SDS OR both) (according to national standards).
6. Age:
    a. Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
    b. Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
7. *For GH treatment naïve participants*: Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]

Applicable to children with TS:

8. Diagnosis of TS according to local clinical practice.
9. Age:
    a. Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
10. *For GH treatment naïve participants:* Impaired height defined as at least 2.0 standard deviation below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]
11. *For GH treatment naïve participants:* Confirmed diagnosis of TS by 30-cell (or more) lymphocyte chromosomal analysis *or* confirmation of TS and TS mosaicism using CGH-array.

Applicable to children with NS:

12. Diagnosis of NS according to local clinical practice.

13. Age:
    a. Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
    b. Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
14. *For GH treatment naïve participants*: Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]
15. *For GH treatment naïve participants*: Clinical diagnosis of NS according to van der Burgt score list and genetic test result[3] *OR* confirmed mutation in any of the genes associated with NS before allocation.

Applicable to children with ISS:

16. Age:
    a. Male participants: Age equal to or above 11.0 years and below 18.0 years at screening.
    b. Female participants: Age equal to or above 10.0 years and below 18.0 years at screening.
17. *For GH treatment naïve participants:* Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.[2]
18. *For GH treatment naïve participants:* Normal GH secretion (GH peak above 7 ng/mL) during GH stimulation test performed within 18 months prior to screening.
    For Korea: Please see local requirements in Appendix 11 (Section 10.11)
19. *For GH treatment naïve participants:* Bone age not delayed more than 2 years compared to chronological age at screening.

5.2 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous allocation into same sub-study in this study.
3. Receipt of any investigational medicinal product within 3 months before screening or participation in another clinical study at the time of allocation.
4. Children with suspected or confirmed growth hormone deficiency according to local practice.
5. Children diagnosed with diabetes mellitus or screening values from the central laboratory of
    a. fasting plasma glucose above or equal to 126 mg/dL (7.0 mmol/L) or
    b. HbA_{1c} above or equal to 6.5%.
6. Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.
7. Children requiring inhaled glucocorticoid therapy at a dose greater than 400 µg/day of inhaled budesonide or equivalent (i.e., 250 µg/day for fluticasone propionate) for longer than 4 consecutive weeks within the last 12 months prior to screening.
8. History or known presence of any malignancy, intracranial tumour, or intracranial cyst.
9. 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).

10. Any disorder, which in the investigator's opinion, might jeopardise participant's safety or compliance with the protocol.
11. The participant or the parent/legally acceptable representative is likely to be non-compliant in respect to study conduct, as judged by the investigator.
12. Female who is pregnant, breast-feeding or intends to become pregnant or is of childbearing potential and not using adequate contraceptive method, as defined in Appendix 4 (Section 10.4).
13. Male of reproductive age who, or whose female partner(s), is not using an adequate contraceptive method, as defined in Appendix 4 (Section 10.4).

Applicable to children with SGA:

14. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
    d. TS (including mosaicism).
    e. NS.
    f. Poorly controlled or uncontrolled hormonal deficiencies.
    g. Children who are small due to malnutrition defined as -2 standard deviations according to World Health Organisation 2007 Body Mass Index.
    h. Known chromosomal aneuploidy or significant gene mutations causing medical 'syndromes' with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.

Applicable to children with TS:

15. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
    d. NS.
    e. Mosaicism below 10%.
    f. TS with Y-chromosome mosaicism where gonadectomy has not been performed.
    g. NYHA class II or above or requiring medication for any heart condition.
    h. Coeliac disease where participant is not stable on gluten free diet for the previous 12 months prior to screening.
    i. Children who are small due to malnutrition defined as -2 standard deviations according to World Health Organisation 2007 Body Mass Index.

Applicable to children with NS:

16. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
    d. TS (including mosaicism).
    e. Noonan-related disorders including but not limited to: Noonan syndrome with multiple lentigines (formerly called 'LEOPARD' syndrome), Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome (CFC), Costello syndrome, neurofibromatosis type 1 (NF1) and Legius syndrome.
    f. Coeliac disease where participant is not stable on gluten free diet for the previous 12 months prior to screening.
    g. Children who are small due to malnutrition defined as -2 standard deviations according to World Health Organisation 2007 Body Mass Index.

Applicable to children with ISS:

17. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with height, such as, but not limited to:
    a. Known family history of skeletal dysplasia.
    b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
    c. Any other disorder that can cause short stature such as, but not limited to nutritional disorders, chronic systemic illness and chronic renal disease.
    d. TS (including mosaicism).
    e. NS.
    f. Poorly controlled or uncontrolled hormonal deficiencies.
    g. Born small for gestational age (defined as birth length below -2 SDS OR birth weight below -2 SDS OR both) (according to national standards).
    h. Known chromosomal aneuploidy or significant gene mutations causing medical 'syndromes' with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.
    i. Children who are small due to malnutrition defined as -2 standard deviations according to World Health Organisation 2007 Body Mass Index.

5.3 Lifestyle considerations

5.3.1 Meals and dietary restrictions

Participants should be fasting (only water is allowed) for 6 hours prior to blood sampling for glucose metabolism.

5.4 Screen failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently eligible for participation according to the inclusion/exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet requirements from regulatory authorities. Minimal information includes informed consent date, demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

A screen failure must be registered in the Randomisation and Trial Supplies Management system (RTSM).

Individuals who do not meet the criteria for participation in this study may not be rescreened. If the participant has failed one of the inclusion criteria or fulfilled one of the exclusion criteria related to laboratory parameters, re-sampling is not allowed. However, in case of technical issues (e.g., haemolysed or lost sample), re-sampling is allowed for the affected parameter(s).

Individuals who have been enrolled into a wrong sub-study due to technical issues, may be rescreened to the correct sub-study and are required to sign a new informed consent form, if applicable. Rescreening must be registered in the RTSM.

5.5 Randomisation criteria

Not applicable.

6 Study interventions and concomitant therapy

Study intervention is defined as all pre-specified investigational and auxiliary medicinal products, medical devices and other intervention(s) (e.g., surgical and behavioural) intended to be administered to a study participant during the study conduct according to the study protocol.

Investigational interventions are a subset of study interventions that are being tested or used as a control (e.g., placebo or active control).

The term 'Trial product' is used in the protocol when referring to specific actions to be taken, that only apply for these products. In this study, 'trial products' comprise investigational medicinal products (IMPs).

6.1 Study interventions administered

The investigator must document that directions for use were given to the participant verbally and in writing as a directions for use (DFU) document at the first dispensing visit (as specified in the flowchart, Section 1.2).

Investigational medicinal products (IMP)

Table 6-1 provides an overview of the study interventions.

Table 6-1 Study interventions

Intervention/Arm name	**Somapacitan**
Intervention name	Somapacitan
Intervention type	IMP, test product
Investigational or non-investigational	Investigational intervention
Pharmaceutical form	Solution for injection
Route of administration	Subcutaneous
Medical Device[a]	Trial product provided in PDS290 somapacitan pen-injector
Trial product strength	Somapacitan 15 mg/1.5 mL
Dose and dose frequency	0.24 mg/kg/week
Dosing instructions and administration	Somapacitan can be injected any time during the dosing day.
Sourcing	Manufactured and/or supplied by Novo Nordisk A/S

Intervention/Arm name	Somapacitan
Packaging and labelling	• Labelled and packaged by Novo Nordisk A/S • Labelled in accordance with Annex VI,[49] local regulations and study requirements • Trial product is provided in PDS290 somapacitan pen-injector
Authorisation status	Somapacitan (trade name Sogroya®) is currently approved for treatment of adult growth hormone deficiency in USA, Japan, EU, UK, Australia, and Saudi Arabia. The indications to be studied in this trial are outside the terms of the marketing authorisation for Sogroya®.

Notes:

[a]The medical device PDS290 is used within its approved intended use and indication for use in all study countries.

Pen-injectors with somapacitan 15 mg/1.5 mL will be used in this study. The relevant dose can be determined using the dosing table in Appendix 8 (Section 10.8).

Time of somapacitan injection:

- First dose of somapacitan should be administered at site.
- Somapacitan can be injected any time during the dosing day.
- If a dose is not administered on the planned dosing day, the dose must be administered as soon as possible.
- If the dose cannot be administered within 3 days after the planned dosing day, the dose should be skipped. The next dose should be taken on the originally planned weekday.
- If it is known that a dose cannot be administered on the planned dosing day, the dose can be administered 1 or 2 days before the planned dosing day. The next dose should be taken on the originally planned weekday.
- Visits with blood sampling should be scheduled to match the required timing of the actual dose (See Table 10-4). If a blood sample is planned on the dosing day, the blood sample should be taken before dosing.

Participants switching at baseline from alternative GH treatment to somapacitan:

When switching from other growth-promoting treatment to somapacitan, the participant should administer the first dose of somapacitan at least 1 day after the last daily growth-promoting treatment dose, depending on the participant's preferred day of weekly dosing.

When switching from weekly growth-promoting treatment to somapacitan, the participant should administer the first dose of somapacitan at least 7 days after the last growth-promoting treatment dose.

Other study supplies including non-investigational medical device(s)

Needles:

- Only needles provided by Novo Nordisk must be used for administration of trial product. Needle lengths between 4 and 6 mm will be used.

PDS290:

- Information about the use of the pre-filled PDS290 pen-injector for somapacitan can be found in the DFU.
- The participants and the participant's parent/participant's LAR must be trained according to the DFU in the use of the PDS290 somapacitan pen-injector when handed out the first time. Training is the responsibility of the investigator or a delegate and must be repeated during the study as outlined in the flowchart (Section 1.2) to ensure correct use of the pen-injectors. The following should be emphasised:
  - Always use a new needle for each injection as this will prevent contamination and ensure correct dosage.
  - In-use conditions of the pen-injector including the in-use time and storage. Relevant details can be found on the trial product label and in the Trial Materials Manual (TMM).
  - Injection site should be rotated at each injection. Participant's parent/participant's LAR will be asked to record the injection site for each injection in the dosing diary for main period and extension period I.
  - Participant's parent/participant's LAR will be asked to record the injection site for the most recent dose before each visit in extension period II.
  - Injections can be given s.c. in the following body locations:
    - Upper leg (thigh)
    - Buttocks
    - Upper arm
    - Abdomen

6.2 Preparation, handling, storage and accountability

Only participants enrolled in the study may use study intervention and only delegated site staff may supply study intervention.

Each site will be supplied with sufficient study intervention for the study on an ongoing basis according to recruitment and allocation to sub-study/indication.

For selected countries and if permitted by local regulations, the investigator may offer to send study intervention from the study site or pharmacy to the participant's home by courier service. The process for sending study intervention from the study site or pharmacy to a participant's home is described in the "Study site/pharmacy instruction for shipment of trial product to participants' homes" document. This document contains detailed instructions for preparing, packaging and setting up the pick-up of study intervention, handover of study intervention from the study site or pharmacy staff to the courier, required temperature monitoring of study intervention, delivery to and receipt of study intervention by the participant. The process for returning study intervention to the study site or pharmacy by courier is also described in this document. Investigators, study site/pharmacy staff and participants who will be involved in shipment of study intervention to the participant's home will be adequately trained in this process.

The investigator or designee must confirm that appropriate temperature conditions have been maintained during transit for all trial products received, and that any discrepancies are reported and resolved before use of the trial products.

All trial products must be stored in a secure, controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and delegated site staff.

The investigator must inform Novo Nordisk immediately if any trial product has been stored outside specified conditions. The trial product must not be dispensed to any participant before it has been evaluated and approved for further use by Novo Nordisk. Additional details regarding handling of temperature deviations can be found in the Trial Materials Manual (TMM).

The investigator or designee is responsible for trial product accountability and record maintenance (i.e., receipt, accountability and final disposition records).

The investigator or designee must instruct the participant in what to return at next visit. In this study, the participant should bring all trial product back at every visit, if not otherwise instructed.

The investigator or designee must instruct the participant on how to manage the in-use time of the dispensed products.

Drug accountability is performed on Kit ID level.

Destruction of trial products can be performed on an ongoing basis and will be done according to local procedures after accountability is finalised by the site and/or reconciled by the monitor, if not otherwise agreed at the site selection.

All returned (used or un-used), expired or damaged trial products (for technical complaint samples, see Appendix 9 (Section 10.9)) must be stored separately from non-allocated trial products. No temperature monitoring is required.

Non-allocated trial products, including expired or damaged products, must be accounted by the site and/or reconciled by the monitor, at the latest at closure of the site.

Korea: Please see local requirements in Appendix 11 (Section 10.11).

6.3 Measures to minimise bias: Randomisation and blinding

All participants will be screened and centrally allocated using the RTSM system and assigned by diagnosis to the relevant treatment according to the allocation schedule. Trial product will be allocated by the RTSM and dispensed by the investigator at the study visits summarised in the flowchart.

All screened participants will receive a unique subject ID at the screening visit using RTSM. The subject ID will be assigned to the participant throughout the study. The subject ID will reflect the sub-study to which the participant has been allocated.

This is an open-label one-armed study with no blinding at site level.

6.4 Study intervention compliance

Drug treatment compliance

Throughout the study, the investigator will remind the participants to follow the study procedures and requirements to encourage participant compliance.

When participants are dosed at the site, they will receive trial product directly from the investigator or designee, under medical supervision. The date and time of each dose administered at the site will be recorded in the source documents.

When participants are dosed at home, compliance with trial product administration will be assessed, and the assessment documented in source documents at each visit where information is available. If any suspicion of non-compliance arises, the site must enter into a dialogue with the participant, re-emphasizing the importance of compliance and uncover barriers to compliance. This dialogue must be documented. Compliance will be assessed by cross checking the following sources and comparing these to the expected use:

- Accountability information; counting returned trial product, comparing number of returned pens with number of dispensed pens, compare number of used pens with the planned dose, visual inspection of pens
- Review of dosing diaries
- Questioning of participants

Trial product injection date, time, dose and injection location will be recorded in the dosing diary until visit 17 (extension period I). From visit 19 to visit 25 and the discontinuation visit (visit 98) (extension period II) trial product injection date, time, dose and injection site of the most recent dose before each visit will be recorded in the dosing diary.

6.5 Dose modification

The dose will be calculated by the investigator at each visit based on the participant's body weight measured at the visit. This dose will be injected until the next visit. The dosing table in Appendix 8 (Section 10.8) must be used for calculation of the dose and selection of pen strength.

The investigator will communicate the prescribed dose to the participant's parent(s)/participant's LAR.

Modifications to the calculated dose should only be performed as described in Section 6.5.1. Dose titration is not allowed.

6.5.1 Dose reduction criteria

If adverse events (AEs) with a probable relationship to the trial product are severe but allow continuation in the study, as judged by the investigator, a dose reduction can be considered at the investigator's discretion. A reduction of the dose leading to a 25% reduction of the current exposure level is recommended (See Table 6-2). If the AE persists after the first dose reduction, a second dose reduction may be considered. If the AE is not resolved after two dose reductions the participant's treatment may be discontinued according to treatment discontinuation or withdrawal

criteria (see Section 7). Treatment with a reduced dose should be for at least 4 weeks before dose can be resumed to the original planned dose at the investigator's discretion.

In the present study, dose will, furthermore, be reduced, if two consecutive IGF-I measurements confirmed by a re-test are above +3.0 SDS, if it is confirmed that the IGF-I sample is taken according to protocol. If IGF-I SDS exceeds +3.0 SDS at two consecutive visits the investigator will be contacted by Novo Nordisk and requested to reach out to the participant as soon as possible. The participant should be invited for a re-test within 4 weeks to confirm persistent IGF-I levels above +3.0 SDS. Blood samples for the confirmatory measurement of IGF-I should be collected at the end of the dosing interval (day 7 post-dose).

If IGF-I is still elevated above +3.0 SDS in the additional confirmatory measurement, dose reduction to a lower dose level will be required. Treatment with a reduced dose should be for at least 4 weeks before a subsequent IGF-1 determination can result in further dose reduction. If the next scheduled visit is less than 4 weeks after the dose reduction was effectuated, the IGF-1 result at that visit must NOT be used for evaluation of an additional dose reduction. At the next visit (or at an extra, unscheduled visit which complies with the 4 weeks minimum period), IGF-1 will be re-tested.

Details about dose reduction are included below.

In the extension periods of the study, if the IGF-I level is below 1 SDS following dose reduction, the dose can be increased to the previous (higher) dose level.

First dose reduction

The first dose-reduction should be from 0.24 mg/kg/week to 0.21 mg/kg/week (See Table 6-2). This dose reduction step is expected to provide at least 25% reduction in somapacitan exposure considering the non-linear PK of somapacitan.

Second dose reduction

If, after first dose reduction, IGF-1 exceeds +3.0 SDS at two (2) consecutive visits and is confirmed by re-test following the above described process, somapacitan dose should be reduced from 0.21 mg/kg/week to 0.18 mg/kg/week (See Table 6-2). This dose reduction step is expected to provide an additional 25% reduction in somapacitan exposure considering the non-linear PK of somapacitan.

Continuous persistently elevated IGF-I after two dose reductions

If, after second dose reduction, IGF-I exceeds +3.0 SDS at two (2) consecutive visits and is confirmed by re-test following the above-described process, the participant should be offered individual medical advice by the investigator.

In case of dose reduction, relevant dosing tables must be requested from Novo Nordisk.

Table 6-2 Dose reduction for somapacitan

Original dose (mg/kg/week)	Dose after first reduction (mg/kg/week)	Dose after second reduction (mg/kg/week)
0.24	0.21	0.18

6.5.2 Rationale for dose reduction criteria

In studies including children born SGA, IGF-I levels have been found to range up to +5.6 SDS with 0.067 mg/kg daily GH treatment (n=31)[45] and up to +5.0 SDS with mean daily GH dose of 0.06 mg/kg (n=23)[50]. Furthermore, in the phase 2 study NN8640-4245 in children born SGA, the IGF-I levels following Norditropin® 0.067 mg/kg/day ranged up to +4.2 SDS (n=13). These studies are conducted with use of approved daily GH doses, and based on the safety outcome of the studies, Novo Nordisk finds it reasonable to suggest the described dose reduction criteria.

6.6 Continued access to study intervention after end of study

When discontinuing trial product, the participant should be transferred to a suitable marketed product at the discretion of the investigator.

If a participant discontinues trial product during the study and is transferred to a marketed product this should be recorded as ancillary therapy according to Section 6.8.1.

6.7 Treatment of overdose

Novo Nordisk does not recommend specific treatment for an overdose of somapacitan. In the event of an overdose appropriate supportive treatment should be initiated according to local practice.

Accidental overdose must be reported as a medication error. Intentional overdose must be reported as misuse and abuse, please refer to Section 8.3 and Appendix 3 (Section 10.3) for further details.

In the event of an overdose, the investigator should closely monitor the participant for overdose-related AEs/SAEs.

For more information on overdose, also consult the somapacitan investigator's brochure (IB).

6.8 Concomitant therapy

Changes in concomitant medication must be recorded at each visit. If a change is due to an AE/SAE, then this must be reported according to Section 6.8.1.

From visit 2 onwards, initiation of treatment that may affect growth is not recommended. Relevant medication not recommended during the study is listed in Section 6.8.2. However, medical judgement should always be according to the investigator's discretion.

Any medication or vaccine (including over-the-counter or prescription medicines, recreational drugs, vitamins, and/or herbal supplements) other than the trial product, that the participant is receiving at the time of the screening visit or receives during the study must be recorded along with:

- Trade name or generic name
- Primary indication

- Start and stop dates
- Frequency
- Dose

Changes in concomitant medication or therapy must be recorded at each visit. If a change is due to an AE, then this must be reported according to Section 8.3.

All previous growth promoting treatment must be recorded until visit 2.

6.8.1 Ancillary therapy

Ancillary therapy is defined as any GH treatment (other than trial product) and IGF-I medication that the participant receives. Ancillary therapy is not allowed, but participants who discontinue trial product can start treatment with a marketed GH product as outlined in Section 6.6.

Any ancillary therapy must be recorded along with:
- Trade name or generic name
- Start and stop dates

6.8.2 Medication with a special focus

Medication with a special focus is defined as medication that can potentially impact the evaluation of the primary endpoint, due to either directly growth promoting or -inhibiting effects.

In the present protocol these are defined:
- ADHD medication (ATC code: N06BA04; methylphenidate)
- Glucocorticoid therapy: (ATC code: H02AB)
- Sex steroids (ATC code: G03A; G03C; G03F) and aromatase inhibitors (ATC code: L02BG)
- Insulin treatment (ATC code: A10A)

Any medication with a special focus must be recorded along with:
- Trade name or generic name
- Primary indication
- Start and stop dates
- Frequency
- Dose

7 Discontinuation of study intervention and participant discontinuation/withdrawal

Discontinuation of specific sites or of the study as a whole is detailed in Appendix 1 (Section 10.1.11).

7.1 Discontinuation of study intervention

Study intervention may be discontinued at any time during the study at the discretion of the participant or at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

Efforts should be made to have the participants who discontinue study intervention attend visit 7 to collect the required data for the analysis of the primary endpoint. Only participants who withdraw consent will be considered as withdrawn from the study. Participants must be informed about the continued scientific importance of their data, even if they discontinue study intervention.

The study intervention must be discontinued, if any of the following applies for the participant:
1. Pregnancy.
2. Intention of becoming pregnant.
3. Simultaneous use of an approved or non-approved investigational medicinal product in another clinical study.
4. Tumour development.
5. Near adult height is reached (Near adult height (NAH) is defined as HV below 2 cm/year calculated over a period of at least 9 months AND for males: have reached a bone age of above or equal to 16 years; for females: have reached a bone age of above or equal to 14 years). If bone age is not available, then NAH is defined as HV below 2 cm/year calculated over a period of at least 9 months AND a chronological age of ≥17 years for males and a chronological age of ≥ 15 years for females.
6. Evidence of closure of the epiphysial growth plates.

See the flowchart for data to be collected at the time of study intervention discontinuation (early discontinuation visit) and follow-up and for any further evaluations that need to be completed.

At visit 17A/98 (Discontinuation visit) the following assessments are not applicable if performed within the last 6 months:
- X-ray for bone age assessment
- ECG
- TTE

The primary reason for discontinuation of study intervention must be specified in the CRF, and final trial product accountability must be performed. Discontinuation of treatment must be registered in RTSM.

Trial product discontinuation prior to visit 7

If a participant discontinues treatment prior to visit 7, the discontinuation visit (Visit 17A) should be performed at least 7 days after the last dose of trial product and prior to starting treatment with a

marketed product. The follow up visit (Visit 18) should be performed a minimum of 30 days after the last dose of trial product.

Although the treatment has been discontinued, the participant should continue to follow the planned visit schedule until the visit 7 (26 weeks) in order to collect data for the primary endpoint and should then be withdrawn.

If the participant or participant's parent(s)/participant's LAR refuses to attend the planned visit schedule, then visit 7 is of utmost importance to attend. Visit 7 should be performed on planned visit date compared to baseline.

At visits after visit 17A (Discontinuation visit) the following assessments are not applicable for participants that discontinue trial product:

- Study intervention
- Drug accountability (when completed for the participant)
- PK sampling
- Collection of technical complaints
- Injection site reactions
- Medication errors
- COA questionnaires

Trial product discontinuation between visit 7 and visit 17

If a participant discontinues treatment at or between visit 7 and visit 17 the treatment discontinuation visit (Visit 17A) should be performed at least 7 days after the last dose of trial product and prior to starting treatment with a marketed product.

The follow-up visit should be performed a minimum 30 days after the last dose of trial product and the participant should then be withdrawn from the study.

Trial product discontinuation after visit 17

If a participant discontinues treatment after visit 17, the treatment discontinuation visit (visit 98) should be performed at least 7 days after the last dose of trial product and prior to starting treatment with a marketed product. The follow-up visit should be performed a minimum 30 days after the last dose of trial product and the participant should then be withdrawn from the trial.

7.1.1 Temporary discontinuation of study intervention

If treatment is temporarily discontinued due to an AE, treatment can be resumed in accordance with Section 6.5.1.

7.1.1.1 Hepatic events requiring temporary discontinuation of study intervention

Temporary discontinuation of study intervention is required for hepatic events, defined as:

- ALT (or AST) ≥ 3 x upper limit of normal (ULN) and total bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or ALT (or AST) ≥ 3 x ULN and international normalised ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (potential Hy's law)**

- ALT (or AST) ≥ 3 x ULN with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%).

**Please note that such an event must be reported as a SAE using the important medical event criterion if no other seriousness criteria are applicable (as described in Appendix 3 (Section 10.3)).

Temporary discontinuation of study intervention is also required in case of abnormal liver laboratory values not meeting protocol-specified discontinuation criteria, if the investigator deems that it is in the best interest of the participant.

Study intervention can be restarted only if an alternative aetiology is definitively identified, and liver blood parameters have returned to pre-event levels. If an alternative aetiology is not definitively defined and/or liver blood parameters have not returned to pre-event levels, drug-induced liver injury (DILI) cannot be excluded, and study intervention must be permanently discontinued.

Please see Appendix 6 (Section 10.6) for follow-up information on hepatic safety.

Please also see the criteria for an AE and Hepatic Event form in Appendix 3 (Section 10.3.3).

7.2 Participant discontinuation/withdrawal from the study

A participant may be discontinued from the study at any time at the discretion of the investigator for safety, behavioural, compliance or administrative reasons.

A participant may withdraw consent at any time at his/her own request or at the request of the participant's parent(s)/participant's LAR.

If a participant withdraws consent or is withdrawn by the investigator prior to receipt of study intervention, he/she will not be asked to have any follow-up assessments performed. The following data must be collected: Demography, eligibility criteria, date of informed consent, date of screening and the date when participant's participation ended. The end of study form must be completed.

If a participant withdraws consent or is withdrawn by the investigator after receipt of study intervention before visit 17, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to visit 17A. Furthermore, the investigator must ask the participant if he/she is willing to come for a follow up visit (Visit 18) a minimum of 30 days after last dose of trial product. See the flowchart (Section 1.2) for data to be collected.

If a participant withdraws consent after visit 17, the investigator must ask the participant if he/she is willing, as soon as possible, to have assessments performed according to visit 98 and the follow-up visit (visit 99). See the flowchart (Section 1.3) for data to be collected.

Final trial product accountability must be performed even if the participant is not able to come to the site. Discontinuation of treatment must be registered in RTSM.

If the participant withdraws consent, Novo Nordisk may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research.

If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the medical record.

Although a participant is not obliged to give his/her reason(s) for withdrawing, the investigator must make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights. Where the reasons are obtained, the primary reason for withdrawal must be specified in the CRF.

7.2.1 Replacement of participants

If a participant discontinues study intervention, withdraws consent or is withdrawn by the investigator, he/she will not be replaced.

7.3 Lost to follow-up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the site.
The following actions must be taken if a participant fails to return to the site for a required visit:

- The site must attempt to contact the participant or the participant's parent(s)/participant's LAR and reschedule the missed visit as soon as possible and counsel the participant or the participant's parent(s)/participant's LAR on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant or the participant's parent(s)/participant's LAR (where possible, at least three telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's source document.
- Should the participant or the participant's parent(s)/participant's LAR continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of 'lost to follow-up'.
- Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants allocated. Public sources may be searched for vital status information. If vital status is determined as deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

8 Study assessments and procedures

The following sections describe the assessments and procedures, while their timing is summarised in the flowchart.

Informed consent must be obtained before any study-related activity, see Appendix 1 (Section 10.1.3).

All screening evaluations must be completed and reviewed to confirm that potential participants meet all inclusion criteria and none of the exclusion criteria.

The investigator will maintain a screening log to record details of all participants screened (and rescreened) and to confirm eligibility or record reason for screen failure, as applicable.

At screening, participants will be provided with a card stating that they are participating in a study and giving contact details of relevant site staff that can be contacted in case of emergency.

Adherence to the study design requirements, including those specified in the flowchart, is essential and required for study conduct.

Review of diaries, PRO instruments, ECGs, TTEs, laboratory reports, etc., must be documented in the source documents or the participant's medical record. If clarification of entries or discrepancies in the diary or PRO instruments is needed, the participant must be questioned, and a conclusion made in the participant's source documents. Care must be taken not to bias the participant. In case of detection of an AE, this should be reported as applicable.

Local standards and requirements for calibration of equipment used for assessments in the study should be followed unless otherwise specified.

Blood sampling

The maximum amount of blood collected from each participant over the duration of the study will not exceed 219 mL for participants born SGA, or with TS or ISS, and will not exceed 252 mL for participants with NS. If genetic testing for NS at the engaged special laboratory is applicable, an additional 5 mL will be drawn.

An approximate total blood volume in children of 80 mL/kg is applied and specific blood sample volume limits are required.[37] Please refer to Appendix 2 (Section 10.2) and the laboratory manual for additional information. Any additional blood sampling for local tests should be taken into account.

If study intervention is dosed during a visit (at site), blood samples should be taken pre-dose.

Repeat samples may be taken for technical issues and unscheduled samples or assessments may be taken for safety reasons. Please refer to Appendix 2 (Section 10.2) for further details on laboratory samples.

8.1 Efficacy assessments

Planned time points for all efficacy assessments are provided in the flowchart (Section 1.2).

8.1.1 Body measurements

Height

For height measurements, European Medicines Agency (EMA) guideline[51] should be followed.

A manual for height measurement prepared by Novo Nordisk will be provided to the sites.

Standing height should be measured:
- by a trained person (preferably the same person throughout the study)
- preferably by using the same stadiometer
- at the same time (± 2 hours, compare to baseline (Visit 2))
- without shoes
- with 3 consecutive measurements
- in centimetres with one decimal to the nearest 1 mm or in inches with one decimal

Confirmation that height measurements have been performed by a trained person should be documented.

A tool to evaluate if a child of a certain height is eligible to the study, is provided in Appendix 7 (Section 10.7). The evaluation tool must be used to evaluate the height eligibility criteria at the screening visit (Visit 1). This must be documented in the participant's medical record.

Sitting height

Sitting height measurements should be performed for participants with ISS and TS. Sitting height should be measured:
- with the child sitting on a sitting height stadiometer, on an anthropometric box/chair, or on the floor
- once per relevant visit (according to flowchart (Section 1.2))
- in centimetres with one decimal to the nearest 1 mm or in inches with one decimal

The same sitting height measurement method should be used throughout the study for a given participant.

Body weight

Body weight may be measured in kilos (kg) or pounds (lb) with one decimal without shoes and wearing only light clothing.

Body weight should be measured preferably at the same time of the day and by using the same scale throughout the study, if possible.

8.1.2 Pubertal status

Pubertal status according to Tanner staging will be assessed.[52] If a participant reaches Tanner stage 5 during the trial, Tanner staging can be omitted from subsequent visits.

The date of menarche will be collected for girls, when applicable.

Female participants becoming of childbearing potential and male participants becoming of reproductive age during the study should be given age-appropriate sexual counselling and instructed to use adequate contraceptive methods (see Appendix 4, Section 10.4) according to local regulations throughout the study, if applicable.

8.1.3 X-ray for bone age assessment

X-rays of left hand and wrist for bone age assessment according to the Greulich and Pyle atlas[51] will be performed. Right hand and wrist will only be imaged if the left hand/wrist cannot be imaged at screening. All participants who have the right hand/wrist imaged at screening will continue to have the right hand/wrist imaged at any post-baseline imaging visit.

The X-ray images will be sent to a central imaging laboratory for evaluation. An X-ray performed within 13 weeks prior to screening can be used instead of the X-ray at screening, if the image is acquired according to the required standards defined by the central imaging laboratory and available to be sent to the central imaging laboratory.

The overall process for imaging is described in a manual prepared by the central imaging laboratory.

8.1.4 Dosing diaries

Dosing diaries should be completed by the participants or the participant's parent(s)/participant's LAR.

Paper dosing diaries will be used in this trial and will be handed out for the first time at visit 2. The investigator or delegated site staff must train the participants and the participant's parent(s)/participant's LAR in dosing diary completion, as applicable.

Information about the injection of trial product will be recorded in the dosing diary and will be collected at every visit following visit 2. In main and extension period I, participant's parent/participant's LAR will be asked to record the dosing information for each dose, while in extension period II they will be asked to record the dosing information for the most recent dose before each visit. The investigator must ensure that the dosing diary data is reviewed and transcribed to the CRF.

8.1.5 Clinical outcome assessments

Clinical outcome assessment (COA) questionnaires should be completed by participants at visits specified in the flowchart (Section 1.2). An overview of COAs relevant for the study is outlined in Table 8-1.

The COAs should only be collected from participants switching to somapacitan from daily GH treatment.

COA questionnaires will be available as paper copies. The investigator or delegated site staff must train the participants in COA questionnaire completion, as applicable.

The investigator must ensure that the COA questionnaires are reviewed and transcribed to the CRF.

Table 8-1 Clinical outcome assessment questionnaires

COA questionnaire	Estimated time to complete the individual questionnaire
Growth Hormone Injection – Child Treatment Burden – Child (GH-INJ-CTB-Child)	3 min
Growth Hormone Patient Preference Questionnaire - Child (GH-PPQ-Child)	3 min

8.1.6 Clinical efficacy laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the flowchart and the laboratory manual.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the flowchart.

Medical history is a medical event that the participant experienced prior to the time point from which AEs are collected.

A **concomitant illness** is any illness that is already present at the time point from which AEs are collected or found as a result of a screening procedure or other study procedures performed before exposure to study intervention under clinical investigation.

In case of an abnormal and clinically significant finding fulfilling the definition of medical history or concomitant illness, the investigator must record the finding on the medical history/concomitant illness form.

Information related to children with SGA:

- Birth related information
- Height data
  - Standing height measured minimum 6 and maximum 18 months prior to screening must be provided. If more than one height measurement has been performed during this period, the most recent measurement should be used. Standing height should be reported in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- Parental height: Standing height for both biological parents in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- GH status, if available
  - Type of GH stimulation test and result of peak GH values.

Information related to children with TS:

- Degree of mosaicism *OR* Complete karyotype, if available. Mandatory for GH treatment naïve children.
- Height data

- Standing height measured minimum 6 and maximum 18 months prior to screening must be provided. If more than one height measurement has been performed during this period, the most recent measurement should be used. Standing height should be reported in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- Parental height: Standing height for both biological parents in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- GH status, if available
  - Type of GH stimulation test and result of peak GH values.

Information related to children with NS:

- Clinical diagnosis of NS according to van der Burgt score list (see Table 8-2)[3], if available. Mandatory for GH treatment naïve children without confirmed mutation in any of the genes associated with NS.
- Identified gene mutation
  - Presence or absence of 17 NS related gene mutations, if known.
- Height data
  - Standing height measured minimum 6 and maximum 18 months prior to screening must be provided. If more than one height measurement has been performed during this period, the most recent measurement should be used. Standing height should be reported in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- Parental height: Standing height for both biological parents in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- GH status, if available
  - Type of GH stimulation test and result of peak GH values.

Information related to children with ISS

- Height data
  - Standing height measured minimum 6 and maximum 18 months prior to screening must be provided. If more than one height measurement has been performed during this period, the most recent measurement should be used. Standing height should be reported in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- Parental height: Standing height for both biological parents in centimetres with one decimal to the nearest 1 mm or in inches with one decimal.
- GH status
  - Type of GH stimulation test and result of peak GH values.

Table 8-2 Diagnostic criteria for Noonan syndrome* (van der Burgt score list)

Feature	A = major	B = minor
1 Facial	• Typical face	• Suggestive face
2 Cardiac	• Pulmonary valve stenosis and/or typical ECG[b]	• Other defect
3 Height	• <3rd centile (-1.88 SDS)	• <10th centile (-1.28 SDS)

Feature	A = major	B = minor
4 Chest wall	• Pectus carinatus/excavatum	• Broad thorax
5 Family history	• First degree relative definite Noonan syndrome	• First degree relative suggest Noonan syndrome
6 Other	• All 3 (males): mental retardation, cryptorchidism, lymphatic dysplasia	• One of mental retardation, cryptorchidism, lymphatic dysplasia

Notes:

*Definite Noonan syndrome: 1A plus one of 2A-6A or two of 2B-6B; 1B plus two of 2A-6A or three of 2B-6B.
[a]The typical face anomalies consists of a broad forehead, hypertelorism, ptosis, down-slanting palpebral fissures, micrognathia, apparently lowset, posteriorly angulated ears with a thick helix and a broad short neck.
[b]The typical ECG is characterised by an abnormal R/S ratio over the left precordial leads, wide QRS complexes, left-axis deviation and a giant Q wave.

8.2.1 Physical examinations

A physical examination will include assessments of the cardiovascular, respiratory, gastrointestinal and musculoskeletal systems, as well as of the central and peripheral nervous system. Furthermore, it will include lymph node palpation and assessment of the skin, head, ears, eyes, nose, throat and neck. **United States:** Please see local requirements in Appendix 11 (Section 10.11).

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital signs

Blood pressure and pulse rate measurements will be assessed sitting with a completely automated device. Manual techniques must be used only if an automated device is not available.

8.2.3 Electrocardiograms

12-lead ECG will be obtained according to local practice.

The investigator or a qualified specialist will evaluate the ECG recordings and classify them as either: “normal”, “abnormal, not clinically significant” or “abnormal, clinically significant”.

If the ECG is evaluated as “abnormal, clinically significant” at screening, and judged by the investigator not to be relevant for exclusion from the study, the finding will be recorded as a concomitant illness.

8.2.4 Transthoracic echocardiogram

A transthoracic echocardiogram (TTE) will be performed for participants with TS or NS.

Any TTE performed within a month prior to screening can be used as baseline data, if the TTE is performed according to the required standards and all relevant parameters are available.

The investigator or a qualified specialist will evaluate the findings from the TTE examination and classify them as either: “normal”, “abnormal, not clinically significant” or “abnormal, clinically significant”. The evaluation and classification will be based on both morphologic and dynamic parameters, as per local practice. Common morphologic parameters are: Left ventricular internal diameter at the end of diastole (LVIDed), Left ventricular internal diameter at the end of systole (LVIDes), End-diastolic interventricular septal thickness (IVSed), End-diastolic left ventricular posterior wall thickness (LVPWed), Left ventricular outflow tract (LVOT) diameter, or right ventricular internal diameter at the end of diastole (RVIDed), whereas dynamic parameters commonly address cardiac output, ejection fraction, and diastolic function.

For the participants with NS, the parameters of interest outlined in Table 8-3 will be recorded in the eCRF.

Table 8-3 Echocardiographic measures to be collected for children with NS

Echocardiographic measures to be collected (NS)	Unit
End-diastolic interventricular septal thickness (IVSed)	mm
End-diastolic left ventricular posterior wall thickness (LVPWed)	mm
Left ventricular internal diameter at the end of diastole (LVIDed)	mm
Left ventricular internal diameter at the end of systole (LVIDes)	mm
Left ventricular mass	g
Left ventricular outflow tract (LVOT) peak gradient	mmHG

8.2.5 Clinical safety laboratory assessments

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the protocol flowchart.

8.2.6 Pregnancy testing

Woman of childbearing potential (WOCBP) should only be included after a negative, highly sensitive urine pregnancy test. Please refer to Appendix 2 (Section 10.2) for additional information.

Pregnancy testing should be performed whenever a menstruation is missed or when pregnancy is otherwise suspected.

Additional pregnancy testing should be performed during the treatment period, if required locally, refer to Appendix 11 (Section 10.11).

Netherlands, Poland and Spain: Please see local requirements in Appendix 11 (Section 10.11).

8.3 Adverse events and other safety reporting

The investigator is responsible for detecting, documenting, recording and following up on events that meet the definition of an AE or SAE.

The definition of AEs and SAEs can be found in Appendix 3 (Section 10.3), along with a description of AEs requiring additional data collection.

Some AEs require additional data collection on a specific event form. The relevant events are listed below in Table 8-4.

Table 8-4 AEs requiring additional data collection

Event type	AE requiring additional data collection
Medication error	X
Misuse and abuse	X
Injection site reactions	X
Hepatic events	X

Definitions and reporting timelines for the events mentioned in the above table can be found in Appendix 3 (Section 10.3).

8.3.1 Time period and frequency for collecting AE information

All AEs and SAEs must be collected from the first study-related activity after obtaining informed consent and until the follow-up visit in accordance with the flowchart (Section 1.2) or whenever, within the above time period, the site becomes aware of an AE or SAE.

Information regarding medication errors and injection site reactions must be collected at every visit from baseline until end of treatment.

Conditions present prior to the timepoint from which AEs are collected and anticipated day-to-day fluctuations of these conditions, including those identified during screening or during other study-related procedures performed before exposure to study intervention under clinical investigation, will be recorded as medical history/concomitant illness.

AE and SAE reporting timelines can be found in Appendix 3 (Section 10.3). All SAEs must be recorded and reported to Novo Nordisk without undue delay but not later than within 24 hours of obtaining knowledge of the events. Similarly, the investigator must submit any updated SAE data to Novo Nordisk without undue delay but not later than within 24 hours of obtaining knowledge of the information.

Investigators are not obligated to actively seek for AE or SAE in former study participants. However, if the investigator learns of any SAE with a suspected causal relationship to the IMP or to study participation, occurring after a participant has discontinued/completed the study, the investigator must notify Novo Nordisk without undue delay.

8.3.2 Method of detecting AEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care should be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about events.

8.3.3 Follow-up of AEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs should be followed until final outcome of the event or until the participant is lost to follow-up as described in Section 7.3. Further information on follow-up and final outcome of events is given in Appendix 3 (Section 10.3).

In participants with severe headache, a fundoscopic examination should be performed at the investigator's discretion to rule out intracranial hypertension.

8.3.4 Regulatory reporting requirements for SAEs

Prompt notification by the investigator to Novo Nordisk of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation is met.

Novo Nordisk has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Novo Nordisk will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. This also includes suspected unexpected serious adverse reactions (SUSAR).

An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from Novo Nordisk will review and then file it along with the investigator's brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

Details of pregnancies in female participants and female partners of male participants will be collected between first study related activity after obtaining informed consent and until the follow up visit (Visit 18). For details regarding collection and reporting of pregnancy information, please refer to Appendix 4 (Section 10.4).

8.3.6 Technical complaints

Technical complaints will be collected for all products listed on the technical complaint form on a continuous basis.

Instructions for reporting technical complaints can be found in Appendix 9 (Section 10.9).

In order for Novo Nordisk to perform a complete investigation of reported SAEs, Novo Nordisk might ask the investigator to complete a technical complaint form.

8.4 Pharmacokinetics

Samples will be used to evaluate the PK of somapacitan. All samples must be drawn prior to trial product administration if this is planned on a sampling day. The bioanalysis of somapacitan PK samples will be performed by a special laboratory.

The exact methods and the results will be described in bioanalytical reports.

8.5 Pharmacodynamics

IGF-I, IGFBP-3 and bioactive IGF-I will be used to evaluate the pharmacodynamics (PD) of somapacitan. All samples must be drawn prior to trial product administration if this is planned on a sampling day. The analyses of samples for PD parameters will be performed by a special laboratory. The analysis of bioactive IGF-I is exploratory.

8.6 Genetics

For TS:
For treatment naïve children with TS, a 30-cell (or more) lymphocyte chromosomal analysis result OR TS mosaicism CGH-array analysis result must be available prior to baseline (Visit 2) in the study. If analysis results are already available from previous analysis, the results from this analysis can be used. Otherwise, the analysis must be performed locally. The result will be collected as part of the Turner syndrome related information in the eCRF.

For NS:
If a genetic diagnosis is already available for a treatment-naïve child with NS prior to baseline (Visit 2), this result can be used for enrolment and no further testing is needed.

If a positive genetic test result for NS is not available, the analysis can be performed locally on the relevant genes listed in Table 10-6. In this case, the result will be collected as part of the NS-related information in the eCRF. If genetic testing is not available at the local laboratory, the analysis must be performed by the engaged special laboratory, which will be providing the investigator with the result. The special laboratory results obtained should also be added in eCRF.

Once a relevant gene mutation has been identified, no further testing is required.

If all genes in Table 10-6 have been tested and no genetic variant was identified, the participant can still be eligible if all remaining inclusion criteria and no exclusion criteria are fulfilled, as the participant may have a de-novo mutation associated with NS.

In the event of sample handling failure, a replacement genetic blood sample may be requested from the participant.

8.7 Biomarkers

No biomarkers are collected in this study.

8.8 Immunogenicity assessments

All anti-drug antibody (ADA) samples must be drawn prior to trial product administration if trial product administration is planned on the sampling day.

A tiered approach including screening of samples, confirmation of ADA as well as characterisation of cross-reactivity towards endogenous hGH and in vitro neutralising activity against the trial product will be used. To evaluate the impact of antibody formation, results of antibody analyses will be compared to PK and PD markers.

The investigator will not be able to review the results of the antibody measurements in relation to AEs as the results will not be available to the investigator.

ADA samples will be analysed no later than at end of study or if presence of neutralising ADA are suspected by investigator or sponsor. Participants who have had a positive in vitro neutralising antibody test result at the last visit will be offered an appropriate follow-up period until the antibody response remains unchanged, is decreasing or until the investigator or the sponsor decides that no further follow-up is warranted. The participants may be requested to have additional blood samples collected for follow-up analyses. If deemed relevant, i.e., due to an antibody relevant AE, unexpected low PK, or per request from the safety committee, specific samples may be analysed at other time-points during the study. The results may be reported as an amendment to the CSR.

8.8.1 Anti-somapacitan antibodies

Determination of antibodies against somapacitan will be performed by a special laboratory using a validated antibody assay. Confirmed anti-somapacitan antibody positive samples will be further tested for cross-reactivity to hGH and for in vitro neutralising effect in a validated neutralising antibody assay and by correlating to PK/PD.

8.8.2 Assessment in case of suspicion of severe systemic hypersensitivity

In the event of a severe local and/or systemic hypersensitivity reaction possible or probably related to trial product, blood sampling for assessment of anti-somapacitan IgE antibodies as well as binding antibodies should be performed in relation to the reaction and no later than 1-2 weeks after the event.

In the event of a severe systemic hypersensitivity reaction to trial product it is recommended also to analyse a sample collected within 3 hours of the reaction for tryptase (total and/or mature tryptase) at the local laboratory. Moreover, a baseline tryptase measurement is necessary 1-2 weeks after the immediate severe hypersensitivity reaction due to individual variation in tryptase baseline concentration.

A follow up visit should be conducted 3-4 weeks after the allergic reaction with repeated blood sampling for assessment of anti-somapacitan IgE antibodies as well as binding antibodies and, if possible, also at a visit 3 months post the hypersensitivity reaction for assessing the persistence of the IgE response. Tryptase measurements are not required at the follow up visits.

9 Statistical considerations

If necessary, a statistical analysis plan (SAP) may be written in addition to the protocol, including a more technical and detailed elaboration of the statistical analysis. The SAP will be finalised before first participant first visit (FPFV).

9.1 Statistical hypotheses

No hypotheses are planned to be tested in the study.

9.1.1 Multiplicity adjustment

Not applicable.

9.2 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.

9.3 Statistical analyses

9.3.1 General considerations

Descriptive statistics will be performed as described in the sections 9.3.2 and 9.3.3.

9.3.2 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.

9.3.3 Secondary endpoints/estimands analysis

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.

Supportive Secondary efficacy endpoints/estimands

Table 9-1 Overview of supportive secondary Efficacy endpoints

Title	Time frame	Unit	Details
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).

Title	Time frame	Unit	Details
Change in Height SDS	From baseline (week 0) to visit 7 (week 26).	Score[a]	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.[2]
Change in Height Velocity SDS	From baseline (week 0) to visit 7 (week 26).	Score[a]	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: $$HV\ SDS_i = \frac{\text{HV}_i - population\ mean\ \text{HV}}{population\ \text{SD}}$$ 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.[2, 53]
Change in IGF-I SDS	From baseline (week 0) to visit 7 (week 26).	Score[a]	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: $$IGF\text{-}I\ SDS_i = \frac{\left(\frac{IGF\text{-}I_i}{population\ median}\right)^{Skewness} - 1}{Skewness * population\ SD}$$ 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.[54]
Change in IGFBP-3 SDS reported for each indication separately.	From baseline (week 0) to visit 7 (week 26).	Score[a]	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:

Title	Time frame	Unit	Details
			$IGFBP\text{-}3\ SDS_i = \frac{\left(\frac{IGFBP\text{-}3_i}{population\ median}\right)^{Skewness} - 1}{Skewness * population\ SD}$ 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.[55]

[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.

9.3.4 Exploratory endpoint(s)/estimand(s) analysis

Not applicable.

9.3.5 Other safety analyses

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 cross-reactivity to hGH antibodies and in vitro neutralising effect will be tabulated by time of assessment for each indication, SGA, TS, NS or ISS.

9.3.6 Other analyses

Other parameters

Table 9-2 Overview of other parameters

Title	Time frame	Unit	Details
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
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
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
Child treatment burden measure:	Visit 5	Score[a]	GH-INJ-CTB-Overall treatment burden score at week 13 (visit 5).

Title	Time frame	Unit	Details
GH-INJ-CTB Overall treatment burden[e]			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.
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).
Near adult height (NAH)	18 months prior to screening to end of treatment	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.
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.
Midparental target height (MPH)	Screening (visit 1)	cm	Derived as: Girls TH: (mother's height + father's height-13)/2[56] Boys TH: (mother's height + 13 + father's height)/2[56]
MPH SDS	Screening (visit 1)	Score[c]	MPH SDS is derived as: $$MPH\ SDS\ = \frac{Fathers\ height\ SDS + mothers\ height\ SDS}{2}$$ Where parental height SDS is derived as: $$MPH\ SDS\ = \frac{Height\ -\ population\ mean}{population\ SD}$$ The population mean and standard deviation comes from reference data.[57]
Index of genetic height potential	From baseline (week 0) to the visit NAH is reached	Score[d]	Derived as NAH SDS – MPH SDS

Title	Time frame	Unit	Details
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: $\text{IVSed SDS}_{\,i} = \frac{ln(IVSed)_i - intercept + ln(Weight_i * slope)}{SD\ residual}$ 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.[58]
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) for Turner syndrome. LVPWed SDS is derived as: $\text{LVPWed SDS}_{\,i} = \frac{ln(LVPWed)_i - intercept + ln(Weight_i * slope)}{SD\ residual}$ 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.[58]
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: $\text{LVIDed SDS}_{\,i} = \frac{ln(LVIDed)_i - intercept + ln(Weight_i * slope)}{SD\ residual}$ 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.[58]
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: $\text{LVIDes SDS}_{\,i} = \frac{ln(LVIDes)_i - intercept + ln(Weight_i * slope)}{SD\ residual}$ 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.[58]

Title	Time frame	Unit	Details
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**.
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: $\text{SH/H } SDS_i = \frac{\left(\frac{SH/H_i}{population\ median}\right)^{Skewness} - 1}{Skewness * population\ SD}$ where i indicates the visit. The population median and standard deviation are the ones corresponding to the age at visit i.
Change in bone 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 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.

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.

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.

9.4 Interim analysis

Not applicable.

9.5 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.

10 Supporting documentation and operational considerations

10.1 Appendix 1: Regulatory, ethical, and study oversight considerations

10.1.1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki[59] and applicable ICH Good Clinical Practice (GCP) Guideline[60] for studies with an IMP
- Applicable laws and regulations

The protocol, informed consent form, investigator's brochure (as applicable) and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC and reviewed and approved by the IRB/IEC before the study is initiated.

Regulatory authorities will receive the clinical trial application, protocol amendments/modifications, reports on SAEs, and the CSR according to national requirements.

Any amendments/modifications to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate safety hazard to study participants.

Before a site is allowed to start screening participants, written notification from Novo Nordisk must be received.

The investigator will be responsible for:

- providing written summaries of the status of the study annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC and/or regulatory authorities
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of the conduct of the study at the site and adherence to requirements of ICH guidelines, the IRB/IEC, and all other applicable local regulations
- ensuring submission of the CSR synopsis to the IRB/IEC
- reporting any potential serious breaches to the sponsor immediately (within 24 hours after discovery). A serious breach is a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of data generated in the clinical study. This includes persistent or systematic non-compliance with ICH GCP E6 and the protocol.

10.1.2 Financial disclosure

Investigators and sub-investigators will provide Novo Nordisk with sufficient, accurate financial information as requested to allow Novo Nordisk to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and one year after completion of the study.

For US sites: Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

10.1.3 Informed consent process

The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant and the participant's parent(s)/participant's LAR and answer all questions regarding the study. This includes the use of an impartial witness where required according to local requirements.

The investigator must ensure the participant ample time to come to a decision whether or not to participate in the study.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/LAR will be required to sign and date a statement of informed consent ('Agreement to take part' form) that meets the requirements of local regulations, ICH GCP[60] guidelines, Declaration of Helsinki,[59] privacy and data protection requirements, where applicable, and the IRB/IEC or site.

The medical record must include a statement that written informed consent was obtained before any study-related activity and the date when the written consent was obtained. The authorised person obtaining the informed consent must also sign and date the informed consent form before any study-related activity.

The responsibility of seeking informed consent must remain with the investigator, but the investigator may delegate the task to a medically qualified person, in accordance with local requirements.

Participants and/or their parent(s)/LAR must be re-consented to the most current version of the informed consent form(s) during their participation in the study.

A copy of the informed consent form(s) must be provided to the participant or the participant's parent(s)/participant´s LAR.

During the study, the investigator should reassess the assent of a child in recognition of their advancing age, evolving maturity and competency.

If the minor reaches legal age while participating in the study and has only signed an age specific informed assent form, the participant has to re-consent to an informed consent form for participants reaching legal age.

10.1.4 Recruitment and information to participants during the study

Children of short stature, in scope for treatment, are usually known in the endocrinology departments, which are the relevant sites in this study. Furthermore, the children are typically already attending regular checks or are in the site's database. Therefore, the main focus is not on identification of potential participants but on educating families about clinical studies. Getting children enrolled in clinical studies takes time and therefore generic clinical study booklets for parents/LARs as well as for children have been developed. These can be used at the sites if

evaluated relevant by the site staff. It has been evaluated, that once the children and parents/LARs understand the concept of a clinical study, they can more easily be enrolled through conversations with the site staff.

The site will be offered a communication package for the participant during the conduct of the study. The package content is issued by Novo Nordisk. The communication package will contain written information intended for distribution to the participants. The written information will be translated and adjusted to local requirements and distributed to the participant at the discretion of the investigator. The participant may receive a "thank you for your participation letter" after completion of the study. Further, the participant may receive other written information during the study.

All written information to participants must be sent to IRB/IEC for approval/favourable opinion and to regulatory authorities for approval or notification according to local regulations.

10.1.5 Data protection

Participants will be assigned a 6-digit unique identifier, a subject ID. Any participant records or datasets that are transferred to Novo Nordisk will contain the identifier only. No direct identifiers from the participant are transferred to Novo Nordisk.

The participant and any biological material obtained from the participant will be identified by subject ID, visit number and study ID. Appropriate measures such as encryption or leaving out certain identifiers will be enforced to protect the identity of participants as required by local, regional and national requirements.

The participant must be informed about his/her privacy rights, including that his/her personal study-related data will be used by Novo Nordisk in accordance with local data protection law. The disclosure of the data must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by auditors or other authorised personnel appointed by Novo Nordisk, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

Personal data may be collected from participants due to process requirements from Novo Nordisk's suppliers. This data is needed to ensure that the relevant data analysis for the study can be performed, but will not be part of the data transferred to Novo Nordisk, the assessment of the study endpoints or the clinical study report. A list of any such data values must be kept as part of the study documentation along with an explanation of why it was required.

The contract between sponsor and study sites specifies responsibilities of the parties related to data protection, including handling of data security breaches and respective communication and cooperation of the parties.

Information technology systems used to collect, process, and store study-related data are secured by technical and organisational security measures designed to protect such data against accidental or unlawful loss, alteration, or unauthorised disclosure or access.

10.1.6 Committees structure

10.1.6.1 Novo Nordisk safety committee

Novo Nordisk will perform ongoing safety surveillance. If new safety signals are identified, these will be evaluated by an internal safety committee. The safety committee may recommend unblinding of any data for further analysis.

10.1.6.2 Data monitoring committee

The Data monitoring committee (DMC) is an independent, external committee composed of members whose expertise covers relevant specialties including statistics. The DMC is established to review and evaluate accumulated data from the study at predefined time points as well as ad hoc. This is done in order to protect the safety of the participants and to evaluate the benefit-risk balance. The DMC will have access to unblinded data, and will provide recommendations on study continuation, modification or termination.

Information regarding responsibilities, procedures and workflow to be used by the DMC are specified in the DMC charter.

10.1.7 Dissemination of clinical study data

This is a multinational study including both EU/EEA and non-EU/EEA sites, and the end of study is defined as the global end of study. The summary of study results and layperson summary of results will be submitted per indication within 6 months after the global end of study, as the planned statistical analyses cannot be performed until data from all sites are available.

Study information will be disclosed at clinicaltrials.gov, novonordisk-trials.com and euclinicaltrials.eu and, if applicable, also on other national or regional study registries. It will be disclosed according to applicable requirements, relevant recommendations or regulations, such as the Declaration of Helsinki,[59] the International Committee of Medical Journal Editors (ICMJE),[61] the Food and Drug Administration Amendment Act (FDAAA),[62] European Commission Requirements[1, 63, 64] and in accordance with Novo Nordisk commitment to clinical transparency. If a participant requests to be included in the study via the Novo Nordisk e-mail contact at these web sites, Novo Nordisk may disclose the investigator's contact details to the participant. As a result of increasing requirements for transparency, some countries require public disclosure of investigator names and their affiliations.

10.1.8 Data quality assurance

10.1.8.1 Case report forms

Novo Nordisk or designee is responsible for the data management of this study including quality checking of the data.

To demonstrate his/her oversight of the collected data, the investigator should sign the CRF on a regular basis during the conduct of the study as well as at the end of the study.

All participant data relating to the study will be recorded in paper diaries and on CRFs unless transmitted electronically to Novo Nordisk or designee (e.g., laboratory data). The investigator is

responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The following will be provided as paper CRFs:
- Pregnancy forms

The following will be provided as paper CRFs to be used when access to the CRF is revoked or the CRF is temporarily unavailable:
- AE forms
- Safety information forms
- Technical complaint forms (to be used to report complaints on study intervention not yet allocated to a participant)

Corrections to the CRF data may be made by the investigator or the investigator's delegated staff. An audit trail will be maintained in the CRF application containing as a minimum: the old and the new data, identification of the person entering the data, date and time of the entry and reason for the correction. If corrections are made by the investigator's delegated staff after the date when the investigator signed the CRF, the CRF must be signed and dated again by the investigator.

The investigator must ensure that data is recorded in the CRF as soon as possible, preferably within 5 working days after the visit. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

10.1.8.2 Monitoring

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents (original documents, data and records). Remote access to the source data documents by Novo Nordisk monitors and auditors can be agreed in countries where this is acceptable according to regulatory requirements and national legislation. Direct access includes permission to examine, analyse, verify and reproduce any record(s) and report(s) that are important to the evaluation of the study. If the electronic source data does not have a visible audit trail, the investigator must provide the monitor with signed and dated printouts. In addition, the relevant site staff should be available for discussions at monitoring visits and between monitoring visits (e.g., by telephone).

Study monitors will perform ongoing source data verification of critical data points to confirm that data entered into the CRF by authorised site personnel are accurate, complete and verifiable from source documents. Study monitors will perform ongoing source data review to ensure that the study is being conducted in accordance with the current approved protocol and any other study agreements, ICH GCP[60], and all applicable regulatory requirements, evaluating the adequacy of critical processes at site for the execution of the protocol, collection of study data, to ensure that the safety and rights of participants are being protected.

Monitoring will be conducted using a risk-based approach including risk assessment, monitoring plans, centralised monitoring (remote assessment of data by Novo Nordisk) and visits to sites.

Quality tolerance limits (QTLs) will be predefined in the relevant monitoring plan to identify systematic issues that can impact participant safety and/or reliability of study results. These

predefined parameters will be monitored during the study, and important deviations from the QTLs and remedial actions taken will be summarised in the clinical study report.

10.1.8.3 Protocol compliance

Deviations from the protocol should be avoided. If deviations do occur, the investigator must inform the monitor without delay and the implications of the deviation must be reviewed and discussed.

Deviations must be documented and explained in a protocol deviation by stating the reason, date, and the action(s) taken. Some deviations, for which corrections are not possible, can be acknowledged and confirmed via edit checks in the CRF or via listings from the study database.

10.1.9 Source documents

All data entered in the CRF must be verifiable in source documentation other than the CRF.

If source data is entered directly in a paper CRF, each data entry or clear series of data entries must be signed and dated separately by the study staff making the entry.

The original of the completed dosing diaries and/or COAs must not be removed from the site, unless they form part of the CRF and a copy is kept at the site.

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the site. Any source data generated by investigator's subcontractors must be archived and accessible by the site.
Data that is transcribed into the CRF from source documents must be consistent with the source documents, or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records. Also, current medical records must be available.

It must be possible to verify participant's medical history related to the relevant diagnosis (SGA, TS, NS, ISS) in source documents, such as participant's medical record.

The investigator must document any attempt to obtain external medical information by noting the date(s) when information was requested, and who was contacted.

Definition of what constitutes source data can be found in a source document agreement at each site. There will only be one source document defined at any time for any data element.

10.1.10 Retention of clinical study documentation

Records and documents, including signed informed consent forms, pertaining to the conduct of this study must be retained by the investigator for 25 years after end of study unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of Novo Nordisk. No records may be transferred to another location or party without written notification to Novo Nordisk. **United States:** Please see local requirement in Appendix 11 (Section 10.11).

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the study. The investigator must be able to

access his/her study documents without involving Novo Nordisk in any way. If applicable, electronic CRF (eCRF) and other participant data will be provided in an electronic readable format to the investigator before access is revoked to the systems and electronic devices supplied by Novo Nordisk. Site-specific CRFs and other participant data (in an electronic readable format or as paper copies or prints) must be retained by the site. A copy of all data will be stored by Novo Nordisk.

Participant's medical records must be kept for the maximum period permitted by the hospital, institution or private practice.

10.1.11 Study and site start and closure

First act of recruitment

The start of study is defined as the date when the clinical study will be open for recruitment of participants, i.e., the 'first act of recruitment'. The first act of recruitment is defined as the first site activation in the study.

Study or site termination

Novo Nordisk reserves the right to close the site or terminate the study at any time for any reason at the sole discretion of Novo Nordisk. If the study is suspended or terminated, the investigator must inform the participants promptly and ensure appropriate therapy and follow-up. The investigator and/or Novo Nordisk must also promptly inform the regulatory authorities and IRBs/IECs and provide a detailed written explanation.

Sites will be closed upon study completion. A site is considered closed when all required documents and study supplies have been collected and a site closure visit has been performed.

The investigator may initiate site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a site by Novo Nordisk or investigator may include but are not limited to:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, Novo Nordisk procedures or GCP guidelines
- inadequate recruitment of participants by the investigator
- discontinuation of further study intervention development.

10.1.12 Responsibilities

The investigator is accountable for the conduct of the study at his/her site and must ensure adequate supervision of the conduct of the study at the site. If any tasks are delegated, the investigator must maintain a log of appropriately qualified persons to whom he/she has delegated specified study-related duties. The investigator must ensure that there is adequate and documented training for all staff participating in the conduct of the study. It is the investigator's responsibility to supervise the conduct of the study and to protect the rights, safety, dignity and well-being of the participants.

A qualified physician, who is an investigator or a sub investigator for the study, must be responsible for all study-related medical decisions.

The investigator is responsible for filing essential documents (i.e., those documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced) in the investigator trial master file. The documents, including the participant identification code list must be kept in a secure locked facility so that no unauthorised persons can get access to the data.

The investigator will take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The investigator will prevent any unauthorised access to data or any other processing of data against applicable law. This also includes ensuring that no indirect sharing of user credentials for IT systems used in this study takes place (e.g., by not sharing IT equipment with others in a way where user credentials have the possibility of being shared). The investigator must be able to provide the necessary information or otherwise demonstrate to Novo Nordisk that such technical and organisational safety measures have been taken.

During any period of unavailability, the investigator must delegate responsibility for medical care of participants to a specific qualified physician who will be readily available to participants during that time.

If the investigator is no longer able to fulfil the role as investigator (e.g., if he/she moves or retires), a new investigator will be appointed in consultation with Novo Nordisk.

The investigator and other site personnel must have sufficient English skills according to their assigned task(s).

10.1.13 Indemnity statement

Novo Nordisk carries product liability for its products, and liability as assumed under the special laws, acts and/or guidelines for conducting clinical studies in any country, unless others have shown negligence.

Novo Nordisk assumes no liability in the event of negligence or any other liability of the sites or investigators conducting the study or by persons for whom the said site or investigator are responsible.

Novo Nordisk accepts liability in accordance with: **Poland:** Please see local requirements in Appendix 11 (Section 10.11).

10.1.14 Publication policy

The information obtained during the conduct of this study is considered confidential and may be used by or on behalf of Novo Nordisk for regulatory purposes as well as for the general development of the study intervention. All information supplied by Novo Nordisk in connection with this study shall remain the sole property of Novo Nordisk and is to be considered confidential information.

No confidential information shall be disclosed to others without prior written consent from Novo Nordisk. Such information shall not be used except in the performance of this study.

The information obtained during this study may be made available to other investigators who are conducting other clinical studies with the study intervention, if deemed necessary by Novo Nordisk. Provided that certain conditions are fulfilled, Novo Nordisk may grant access to information obtained during this study to researchers who require access for research projects studying the same or related diseases and/or study intervention studied in this study.

Novo Nordisk may publish on its clinical studies website a redacted CSR for this study.

One investigator will be appointed by Novo Nordisk to review and sign the indication-specific CSR (signatory investigator) on behalf of all participating investigators.

10.1.14.1 Communication of results

Novo Nordisk commits to communicate and disclose results of studies regardless of outcome. Disclosure includes publication of a manuscript in a peer-reviewed scientific journal, abstract submission with a poster or oral presentation at a scientific meeting or disclosure by other means.

The results of this study will be subject to public disclosure on external web sites according to international and national regulations. Novo Nordisk reserves the right to defer the release of data until specified milestones are reached, for example when the CSR is available. This includes the right not to release the results of interim analyses, because the release of such information may influence the results of the entire study.

At the end of the study, one or more scientific publications may be prepared collaboratively by the investigator(s) and Novo Nordisk. Novo Nordisk reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property.

In all cases, the study results will be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations. In the event of any disagreement on the content of any publication, both the investigators' and Novo Nordisk opinions will be fairly and sufficiently represented in the publication.

10.1.14.2 Authorship

Novo Nordisk will work with one or more investigator(s) and other experts who have contributed to the study concept or design, acquisition, analysis or interpretation of data to report the results in one or more publications.

Authorship of publications should be in accordance with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals by the International Committee of Medical Journal Editors.[65]

All authors will be provided with the relevant statistical tables, figures, and reports needed to evaluate the planned publication.

Where required by the journal, the investigator from each site will be named in an acknowledgement or in the supplementary material, as specified by the journal.

10.1.14.3 Site-specific publication(s) by investigator(s)

For a multicentre clinical study, analyses based on single-site data usually have significant statistical limitations and frequently do not provide meaningful information for healthcare professionals or participants, and therefore may not be supported by Novo Nordisk. Thus, Novo Nordisk may deny a request or ask for deferment of the publication of individual site results until the primary manuscript is accepted for publication. In line with Good Publication Practice, such individual reports should not precede the primary manuscript and should always reference the primary manuscript of the study.

10.1.14.4 Investigator access to data and review of results

As owner of the study database, Novo Nordisk has the discretion to determine who will have access to the database.

Individual investigators will have their own research participants' data.

10.2 Appendix 2: Clinical laboratory tests

The tests detailed in Table 10-1 and Table 10-2 will be performed by the central laboratory or designated special laboratories.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Only laboratory samples specified in the protocol should be sent to the central laboratory for analysis; if additional laboratory sampling is needed, e.g., to follow up on AEs, this must be done at a local laboratory.

The use of topical anaesthetics (e.g., numbing cream) for blood sampling should be according to local practice.

At visits where it is not possible to perform blood sampling on the actual visit day (e.g., if the child does not cooperate during blood sampling) the samples can be taken within a week from the actual visit. The sample conditions (fasting or non-fasting) and timing of sampling in relation to study intervention should always be followed. If the child is not fasting at a visit where a blood sample for analysis of fasting plasma glucose is collected, the child must have a blood sample for glucose metabolism taken within a week from the actual visit.

The investigator should follow local guidelines such as the European guideline for blood sampling and volume of blood[37] at each visit in accordance with the participant's body weight and age. If no local guidelines are available, the European guideline should be followed.

Blood sample volume limits, according to body weight, are described in the laboratory manual.
Blood volumes of samples at each visit are likewise specified in the laboratory manual.
Blood sampling must be prioritised as described in the laboratory manual. This means that some assessments will only be assessed if blood sample volumes allow.

If the investigator justifies that higher blood volumes, than allowed, are needed, the blood sampling can be split into two different occasions with maximum one week apart. The sampling conditions and timing of sampling in relation to study intervention should always be followed.

The central lab will communicate to the investigator abnormal values of parameters not requested in the protocol but identified by the laboratory equipment and/or their processes according to their laboratory SOPs. These data will not be transferred to the study database. The investigator should review such values for AEs and report these according to this protocol.

The investigator must review all laboratory results for concomitant illnesses and AEs.

The investigator must keep an overview, e.g., a log, of laboratory samples not handled according to the laboratory manual. In addition, the investigator must keep an overview, e.g., a log, of laboratory samples stored at site.

Unless otherwise stated, laboratory samples will be destroyed on an ongoing basis and no later than at end of study or no later than at finalisation of the CSR.

Antibody samples may be retained for later analysis for further characterisation of antibody responses towards drug, if required by health authorities or for safety reasons.

Table 10-1 Protocol-required efficacy laboratory assessments

Laboratory assessments	Parameters
Pharmacokinetics	• Somapacitan
Pharmacodynamics	• IGFBP-3 • IGF-I • Bioactive IGF-I[a]

Notes:
[a]Bioactive IGF-I is an exploratory assessment.

Table 10-2 Protocol-required safety laboratory assessments

Laboratory assessments	Parameters
Haematology	• Haematocrit • Leucocytes (white blood cells (WBC)) • Thrombocytes
Biochemistry[a]	• Alanine Aminotransferase (ALT) • Alkaline phosphatase (ALP) • Aspartate Aminotransferase (AST) • Bilirubin (total) • Creatinine kinase • Creatinine • Potassium • Sodium • Phosphorus
Glucose metabolism	• Fasting insulin • Fasting plasma glucose • HbA1c • HOMA will be calculated
Lipids	• Total cholesterol • High density lipoprotein (HDL) cholesterol • Low density lipoprotein (LDL) cholesterol • Triglycerides
Hormones	• Cortisol • Serum Free T3 • Serum Free T4 • Thyroid stimulting hormone
Pregnancy Testing[b]	• Highly sensitive urine human chorionic gonadotropin (hCG) pregnancy test (as needed for women becoming of childbearing potential during the study)[b]
Coagulation parameters[c]	• Prothrombin time (PT) • Partial thromboplastin time (PTT)
Other tests	• Anti somapacitan antibodies

Notes:
[a]Details of required actions and follow-up assessments for increased liver parameters including any discontinuation criteria are given in Appendix 3 (Section 10.3) (Hy's Law) and Section 7.1.

[b]For women of childbearing potential, as needed, local urine testing will be standard unless serum testing is required by local regulation or IRB/IEC, see Appendix 4 (Section 10.4).

[c]Only relevant for NS.

Table 10-3 Other protocol-required laboratory assessments

Laboratory assessment	Parameter
Other tests	• Genetic sampling[a]

Notes:
[a]Relevant for treatment naïve participants with TS or NS without previous test results available. Analyses for TS karyotype determination or TS mosaicism / NS genetic testing to be performed locally, if available. If NS genetic testing is not available at local laboratory, the analysis can be performed by the engaged special laboratory.

Timing of visits and blood sampling

Visits with blood sampling for PK and IGF-I are planned with specific timing in connection with trial product administration. The planned windows were designed based on phase 2 data in SGA to capture PK C_{max} (12–47 hours after dosing), peak IGF-I (48–95 hours after dosing), the IGF-I levels approximating weekly mean (96–143 hours after dosing) and trough (on a planned dosing day).

At the allocation visit (Visit 2) blood samples must be collected prior to first trial product administration. In order to ensure correct timing of PK and antibody sampling in relation to trial product administration, the visits after allocation should be scheduled within the allowed visit window according to the flowchart (Section 1.2). Blood sampling should always be collected prior to trial product administration if the visit is planned on a dosing day. If blood sampling is not planned on a dosing day, it is important to perform the visit and the blood sampling within the allowed number of hours/days after dosing. Guidance for the timing of visits and blood sampling is outlined in Table 10-4.

If the visit window in the flowchart is '±7 exactly', the visit and blood sampling should be on a dosing day either 7 days before the planned visit date, on the visit date, or 7 days after the planned visit date.

Table 10-4 Timing of visits and blood sampling

Visit	Timing of visit
3	12 to 47 hours after dosing (up to 2 days after dosing)
4	Prior to treatment administration on a planned dosing day
5	48 to 95 hours after dosing (2 to 4 days after dosing)
6	Prior to treatment administration on a planned dosing day
7	96 to 143 hours after dosing (4 to 6 days after dosing)
8	Prior to treatment administration on a planned dosing day
9	96 to 143 hours after dosing (4 to 6 days after dosing)
10	No requirements
11	Prior to treatment administration on a planned dosing day
12	No requirements
13	12 to 95 hours after dosing (up to 4 days after dosing)
14	No requirements
15	Prior to treatment administration on a planned dosing day
16	No requirements
17/ Visit 17A	96 to 143 hours after dosing (4 to 6 days after dosing)
18 (Follow-up visit after extension period I)	Preferably at least 7 days after last dose of trial product
19	No requirements
20	Prior to treatment administration on a planned dosing day

21	No requirements
22	12 to 95 hours after dosing (up to 4 days after dosing)
23	No requirements
24	Prior to treatment administration on a planned dosing day
25	No requirements
98	No requirements
99	Preferably at least 7 days after last dose of trial product

10.3 Appendix 3: Adverse Events and Serious Adverse Events: Definitions and procedures for recording, evaluating, follow-up, and reporting

10.3.1 Definition of AE

An AE is any untoward medical occurrence in a clinical study participant that is temporally associated with the use of IMP, whether or not considered related to the IMP. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease (new or exacerbated) temporally associated with the use of an IMP.

Events to be reported as AEs:

- Any abnormal laboratory test results or safety assessments considered clinically significant in the medical and scientific judgment of the investigator, including events that have worsened from prior to the time point from which AEs are collected
- Conditions detected or diagnosed after IMP administration even though it may have been present prior to the time point from which AEs are collected
- Exacerbation/worsening of a chronic or intermittent condition including either an increase in frequency and/or intensity of the condition
- Signs, symptoms or the clinical sequelae of a suspected drug-drug interaction
- Signs, symptoms or the clinical sequelae of a suspected overdose of IMP regardless of intent

Events NOT to be reported as AEs:

- Conditions present prior to the time point from which AEs are collected and anticipated day-to-day fluctuations of these conditions. This includes those conditions identified during screening or identified during other study procedures performed before exposure to IMP.
  Note: Conditions present or occurring prior to the time point from which AEs are collected should be recorded as concomitant illness/medical history.
- Medical or surgical procedures (e.g., endoscopy, appendectomy). The condition that leads to the procedure is the AE.
- Medical or surgical procedures not preceded by an AE or worsening of a known condition.

10.3.2 Definition of an SAE

An SAE is any untoward medical occurrence that fulfils at least one of the following criteria:

- **Results in death**
- **Is life-threatening**
  - The term ‘life-threatening’ refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
- **Requires inpatient hospitalisation or prolongation of existing hospitalisation**
  - Hospitalisation signifies that the participant has been admitted at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other seriousness criteria, the event is serious. When in doubt as to whether ‘hospitalisation’ occurred or was necessary, the AE should be considered serious.

- Hospitalisation for elective treatment (e.g., elective medical or surgical procedures) of a condition that was present prior to the time point from which AEs are collected, and that did not worsen, is not considered an AE.
  Note: Hospitalisations for administrative, study-related, social and convenience reasons do not constitute AEs and should therefore not be reported as AEs or SAEs. Hospital admissions for medical or surgical procedures, planned before study inclusion, are not considered AEs or SAEs

- **Results in persistent or significant disability/incapacity**
  - The term 'disability' means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experience of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g., sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Is a congenital anomaly/birth defect**
- **Important medical event:**
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations. This includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious and reported as SAEs using the important medical event criterion.
  - The following must be reported as an SAE using the important medical event criterion if no other seriousness criteria are applicable:
    - Suspicion of transmission of infectious agents via IMP
    - Risk of liver injury defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x ULN and total bilirubin >2x ULN where no alternative aetiology exists (Hy's law)

10.3.3 Description of AEs requiring additional data collection

Adverse events requiring additional data collection

An AE requiring additional data collection is an AE where Novo Nordisk has evaluated that additional data is needed in the evaluation of safety.

Injection site reactions:
- An injection site reaction is defined as: An injection site reaction considered clinically significant by the investigator.
- An injection site reaction form should be filled in, in addition to the AE form (and safety information form (SIF) for SAE).

Medication error:

A medication error is an unintended failure in the IMP treatment process that leads to, or has the potential to lead to, harm to the participant, such as:

- administration of wrong drug and/or use of wrong device
  Note: Use of wrong Kit ID is not considered a medication error unless it results in administration of wrong drug.
- wrong route of administration, such as intramuscular instead of subcutaneous
- accidental administration of a higher dose than intended. The administered dose must deviate from the intended dose to an extent where clinical consequences for the study participant were likely to happen as judged by the investigator, although they did not necessarily occur.

Misuse and abuse:

- Situations where the IMP is intentionally and inappropriately used not in accordance with the protocol (e.g., overdose to maximise effect)
- Persistent or sporadic, intentional excessive use of an IMP which is accompanied by harmful physical or psychological effects (e.g., overdose with the intention to cause harm)

Note: Medication error, misuse and abuse must always be reported on an AE form and a specific event form must be completed. The AE diagnosis on the AE form must reflect what occurred (e.g., accidental overdose, intentional overdose or other). If the medication error and/or misuse and abuse resulted in a clinical consequence, this must be reported on an additional AE form.

Hepatic events:
In all cases where one or more results from liver lab parameters (ALT, AST or ALP) are increased above the limits defined below an AE must be reported and the specific event form (Hepatic Event form) must be completed. Criteria for discontinuation of study intervention may also apply; see Section 7.1.1.1).

- Alanine aminotransferase (ALT): >3.0 x ULN if baseline was normal; >3.0 x above baseline if baseline was abnormal
- Aspartate aminotransferase (AST): >3.0 x ULN if baseline was normal; >3.0 x above baseline if baseline was abnormal
- Alkaline phosphatase (ALP): >2.5 x ULN if baseline was normal; >2.5 x above baseline if baseline was abnormal

10.3.4 Recording and follow-up of AE and/or SAE

10.3.4.1 AE and SAE recording

The investigator will record all relevant AE/SAE information in the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory and diagnostics reports) related to the event.

There may be instances when copies of source documents (e.g., medical records) for certain cases are requested by Novo Nordisk. In such cases, all participant identifiers, with the exception of the subject ID, must be redacted on the copies of the source documents before submission to Novo Nordisk.

For all non-serious AEs, the applicable forms should be signed when the event is resolved or at the end of the study at the latest. For sign-off of SAE-related forms, refer to "AE and SAE reporting via paper CRF" later in this section.

Novo Nordisk products used as concomitant medication: if an AE is considered to have a causal relationship with a Novo Nordisk marketed product used as concomitant medication in the study, it is important that the suspected relationship is reported to Novo Nordisk, e.g., in the alternative aetiology section on the safety information form. Novo Nordisk may need to report this adverse event to relevant regulatory authorities.

10.3.4.2 Assessment of severity

The investigator will assess severity for each event reported during the study and assign it to one of the following categories:

- **Mild**: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- **Moderate**: An event that causes sufficient discomfort and interferes with normal everyday activities.
- **Severe**: An event that prevents normal everyday activities.
  Note: An AE that is assessed as severe should not be confused with an SAE. Both AEs and SAEs can be assessed as severe.

10.3.4.3 Assessment of causality

The investigator is obligated to assess the relationship between IMP and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

Relationship between an AE/SAE and the relevant IMP should be assessed as:

- **Probable** - Good reason and sufficient documentation to assume a causal relationship.
- **Possible** - A causal relationship is conceivable and cannot be dismissed.
- **Unlikely** - The event is most likely related to aetiology other than the IMP.

Alternative aetiology, such as underlying disease(s), concomitant medication, and other risk factors, as well as the temporal relationship of the event to IMP administration, should be considered and investigated.

The investigator should use the investigator's brochure for the assessment. For each AE/SAE, the investigator must document in the medical records that he/she has reviewed the AE/SAE and has provided an assessment of causality.

There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report. However, **it is important that the investigator always**

makes an assessment of causality for every event before the initial transmission of the SAE data.

The investigator may change his/her opinion of causality, in light of follow-up information, and update the causality assessment in the CRF.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

10.3.4.4 Final outcome

The investigator will select the most appropriate outcome:

- **Recovered/resolved**: The participant has fully recovered, or by medical or surgical treatment the condition has returned to the level observed when first documented.
- **Recovering/resolving**: The condition is improving, and the participant is expected to recover from the event. This term may also be applicable for AEs ongoing at the time of death (where death was due to another AE).
  Note: For SAEs, this term is only applicable if the participant has completed the follow-up period and is expected to recover.
- **Recovered/resolved with sequelae**: The participant has recovered from the condition but with lasting effect due to a disease, injury, treatment or procedure. If a sequela meets an SAE criterion, the AE must be reported as an SAE.
- **Not recovered/not resolved**: The condition of the participant has not improved, and the symptoms are unchanged, or the outcome is not known. This term may be applicable in cases of chronic conditions, cancer or AEs ongoing at time of death (where death is due to another AE).
- **Fatal**: This term is only applicable if the participant died from a condition related to the reported AE. Outcomes of other reported AEs in a participant before he/she died should be assessed as 'recovered/resolved', 'recovering/resolving', 'recovered/resolved with sequelae' or 'not recovered/not resolved'. An AE with a fatal outcome must be reported as an SAE.
- **Unknown**: This term is only applicable if the participant is lost to follow-up.

10.3.4.5 Follow-up of AE and SAE

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Novo Nordisk to elucidate the nature and/or causality of the AE or SAE as fully as possible (e.g., severe hypersensitivity reactions, Hy's law). This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognised follow-up period, the investigator should, upon request, provide Novo Nordisk with a copy of the autopsy report including histopathology.

New or updated information should be recorded in the CRF.

10.3.5 Reporting of SAEs

AE and SAE reporting via CRF

Relevant forms must be completed in the CRF.

For SAEs, initial notification via telephone is acceptable, although it does not replace the need for the investigator to complete the AE and safety information forms within the designated reporting timelines (see Figure 10-1):

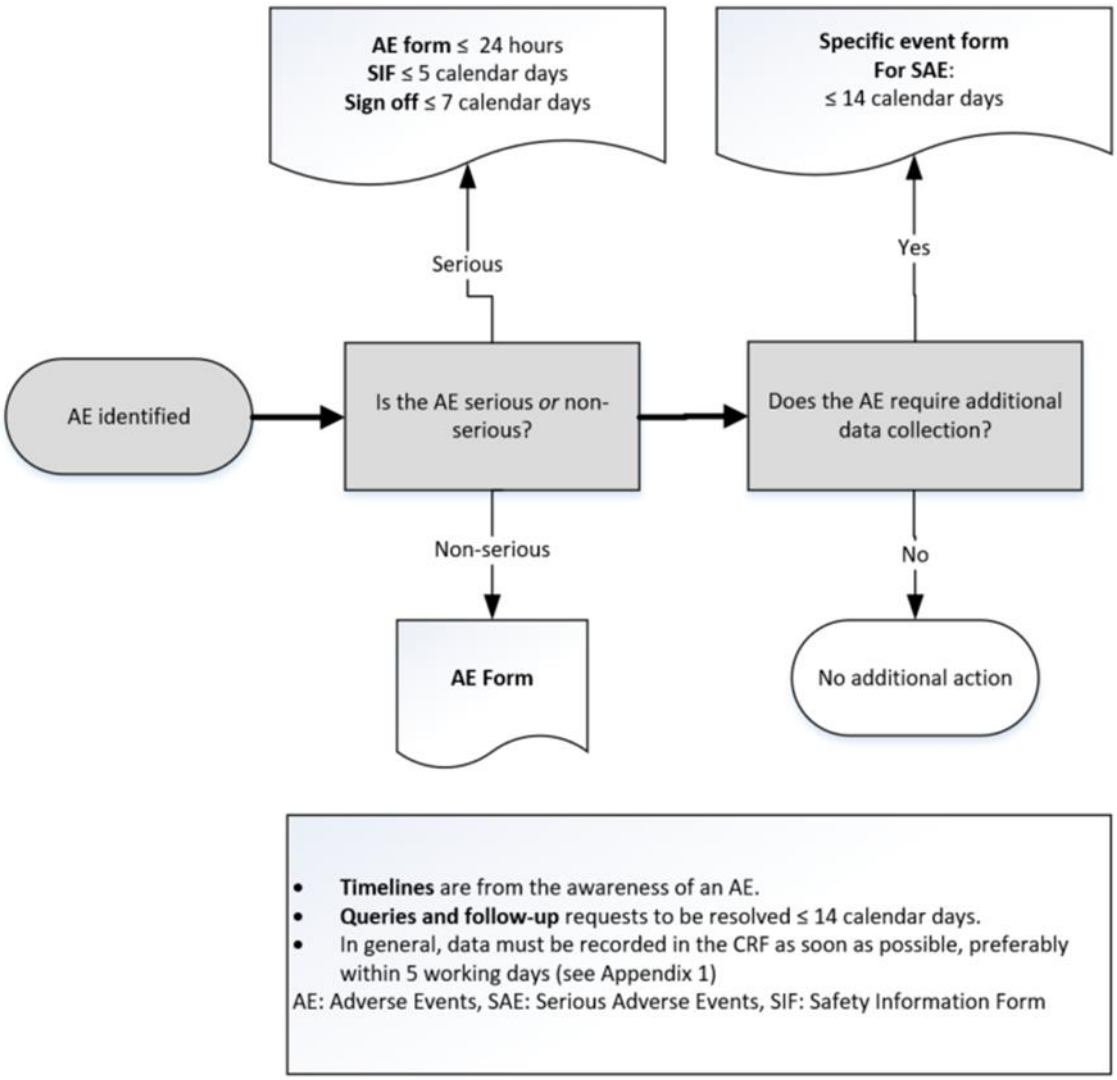
- AE form without undue delay, but not later than within 24 hours.
- Safety information form within 5 calendar days.
- Both forms must be signed within 7 calendar days after first knowledge by the investigator.
- Specific event form within 14 calendar days.

If the eCRF is unavailable for more than 24 hours, then the sites will use the paper AE form, and if the eCRF is unavailable for more than 5 calendar days, then the site will use the paper safety information form. The site should enter the SAE data in the eCRF as soon as it becomes available.

The relevant CRF forms (AE and safety information forms) must be forwarded to Novo Nordisk in accordance with Section 10.1.5.

After the study is completed, the study database will be locked, and the CRF will be decommissioned to prevent the entry of new data or changes to existing data. If a new SAE from a participant or updated information on a previously reported SAE needs to be reported after CRF decommission, a paper AE and safety information form should be used to notify Novo Nordisk.

Figure 10-1 Decision tree for determining the event type and the respective forms to complete with associated timelines



Contact details for SAE reporting can be found in the investigator trial master file.

10.4 Appendix 4: Contraceptive guidance and collection of pregnancy information

10.4.1 Definitions

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile.
If fertility is unclear (e.g., amenorrhea in adolescents or athletes), and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Females in the following categories are not considered WOCBP

1. Premenarcheal
2. Females with one or more of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For females with permanent infertility due to an alternate medical cause other than the above (e.g., Müllerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study enrolment.

Note: Documentation regarding categories 1 and 2 can come from the site staff's review of participant's medical records, medical examination or medical history interview.

10.4.2 Contraceptive guidance

Male participants

Male participants becoming sexually active during the study should receive age-appropriate guidance regarding contraceptives.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use methods of contraception consistently and correctly. Table 10-5 lists the highly effective and acceptable methods of contraception allowed. **Poland and Spain:** Please see local requirements in Appendix 11 (Section 10.11).

Female participants having first menstrual period during the study should receive age-appropriate guidance regarding contraception if sexually active.

Highly effective or acceptable contraception should be utilised until the end of treatment.

Table 10-5 Highly effective and acceptable contraceptive methods allowed[66]

Highly effective methods[a] (Failure rate of <1% per year when used consistently and correctly):
• Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation[b]
  • oral
  • intravaginal
  • transdermal
• Progestogen-only hormone contraception associated with inhibition of ovulation
  • oral
  • injectable
  • implantable
• Intrauterine device (IUD)
• Intrauterine hormone-releasing system (IUS)
• Bilateral tubal occlusion
• Vasectomized partner
Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential, and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Spermatogenesis cycle is approximately 90 days.
• Sexual abstinence
Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

Acceptable methods[c] • Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action • Male or female condom with or without spermicide[d] • Cervical cap, diaphragm, or sponge with spermicide • A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods)
Notes: a. Contraceptive use by men or women should comply with local regulations regarding the use of contraceptive methods for those participating in clinical studies. b. Male condoms must be used in addition to hormonal contraception during the treatment period and until the end of study. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action. c. Considered effective, but not highly effective - failure rate of ≥1% per year. d. Male condom and female condom should not be used together (due to risk of failure from friction).

The following methods are not acceptable methods of contraception: Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM).

10.4.3 Collection of pregnancy information

Female participants who become pregnant

Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study.

Information will be recorded on the appropriate form and submitted to Novo Nordisk within 14 calendar days of learning of a participant's pregnancy (see Figure 10-2).

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on participant and neonate which will be forwarded to Novo Nordisk

within 14 calendar days. Generally, follow-up will not be required for longer than 1 month beyond the delivery date.

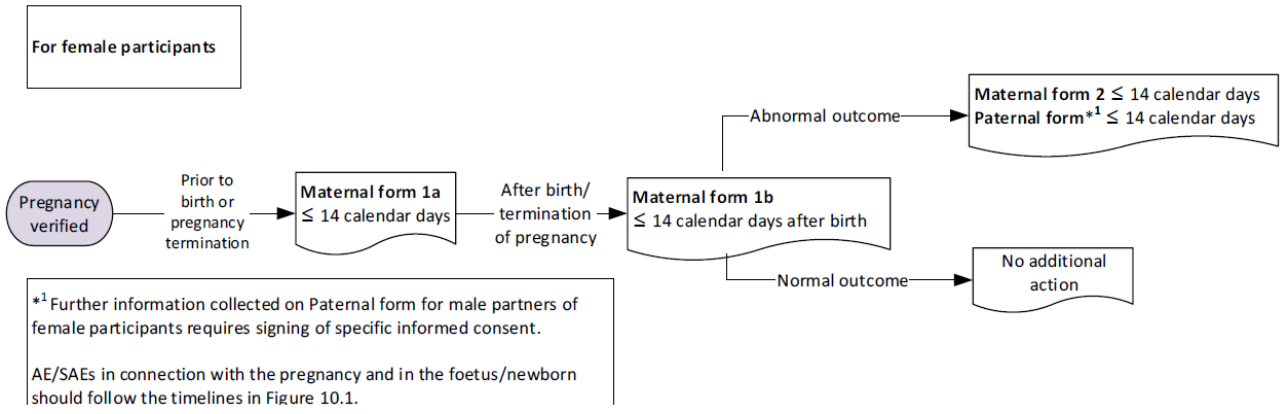
Any termination of pregnancy will be reported, regardless of foetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any adverse event in connection with pregnancy or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. If relevant, consider adding 'gestational', 'pregnancy-related' or a similar term when reporting the AE/SAE.

Pregnancy outcome should be documented in the participant's medical record. Abnormal pregnancy outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) is considered an SAE. In case of abnormal pregnancy outcome, paternal information should be recorded in the appropriate form after obtaining the necessary signed paternal informed consent.

If the investigator learns of an SAE occurring as a result of a post-study pregnancy which is considered related to the IMP by the investigator, the SAE should be reported to Novo Nordisk as described in Appendix 3 (Section 10.3).

Figure 10-2 Decision tree for determining the forms to complete for collection of pregnancy information and timelines for reporting – For female participants



Any female participant who becomes pregnant while participating in the study will discontinue study intervention.

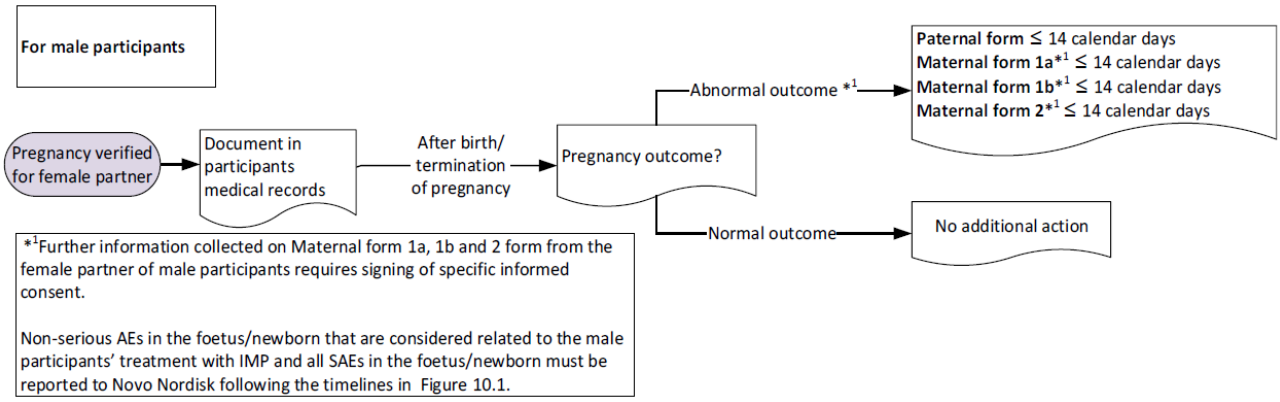
Male participants with partners who become pregnant

Investigator will attempt to collect pregnancy information on any female partner who becomes pregnant while male participant is participating in this study. The pregnancy should be documented in the medical record of the male participant. Only in case of abnormal outcome (e.g., spontaneous abortion, foetal death, stillbirth, congenital anomalies and ectopic pregnancy) of the pregnancy and in case the male participant receives IMP, should the investigator inform Novo Nordisk. Abnormal pregnancy outcome is considered an SAE.

After obtaining the necessary signed informed consent from the pregnant female partner, the investigator will record pregnancy information on the appropriate form and submit it to Novo Nordisk within 14 calendar days of learning of the abnormal outcome of the partner's pregnancy (see Figure 10-3). Information on the status of the mother and child will be included.

Generally, follow-up will be 1 month following the delivery date.

Figure 10-3 Decision tree for determining the forms to complete for collection of pregnancy information with timelines for reporting – For male participants



10.5 Appendix 5: Genetics

For TS:

Blood samples will be collected as part of the screening process for GH treatment naïve participants with TS, unless previous analysis results are available. The samples will be analysed for 30-cell karyotype or TS mosaicism.

For NS:

DNA samples will be collected as part of the screening process for participants with NS, unless previous genetic testing results are available.

Only staff at the relevant engaged special laboratory will have access to the samples and adequate measures to protect confidentiality will be ensured. When the collected samples have been analysed, the samples will be destroyed.

NS: Relevant genes for genetic testing are outlined in Table 10-6. 'Detected'/'Not detected' for each of the genes must be documented in the eCRF.

Table 10-6 List of genes to be tested at local or engaged special laboratory

Gene
PTPN11
SOS1
RAF1
RIT1
KRAS
SHOC2
BRAF
CBL
HRAS
LZTR1
MAP2K1
MAP2K2
NF1
NRAS
RASA2
SOS2
SPRED1

10.6 Appendix 6: Hepatic Safety: Suggested actions and follow-up assessments

The following suggested actions and follow-up assessments should be considered. See also Section 7.1.1.1 for information on temporary discontinuation of study intervention, if relevant.

For all hepatic events, defined as:

- ALT (or AST) ≥ 3 x upper limit of normal (ULN) and total bilirubin ≥ 2 x ULN (> 35% direct bilirubin) or ALT (or AST) ≥ 3 x ULN and international normalised ratio (INR) > 1.5 (if INR measured), which may indicate severe liver injury (potential Hy's law)

- ALT (or AST) ≥ 3 x ULN with the appearance of fatigue, nausea, vomiting, anorexia, abdominal pain or tenderness, fever, rash, and/or eosinophilia (>5%),

where no alternative or competing aetiology exists, repeat testing within 48 to 72 hours, follow-up assessments and work-up for alternative aetiologies must be performed, including:

- Complete liver profile including ALT, AST, ALP, total bilirubin, liver function tests (INR/coagulation factors, albumin, PT), performed at the central laboratory. Repeat testing and frequency of retesting should be determined at the discretion of the investigator.

- Detailed clinical information, such as related symptoms, risk factors, medical history, family history, including contributing conditions (e.g., viral hepatitis, autoimmune hepatitis, alcoholic hepatitis, hypoxic/ischemic hepatopathy, hepatobiliary or pancreatic disorders, exposure to environmental chemical agents) should be gathered to seek a possible alternative aetiology of the observed laboratory test abnormalities.

- Evaluation of the need for imaging and other examinations and procedures such as liver biopsy, ultrasonography, computerised tomography (CT) scan, magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), echocardiography.

- History of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, special diets, recent events of food poisoning or excessive physical activity should also be evaluated.

- Referral to hepatologist/gastroenterologist should be considered.

10.7 Appendix 7: Tool for evaluation of inclusion criterium for height

Tool to assess Inclusion criteria – Impaired height

Below table (Table 10-7) must be used to assess the inclusion criteria for impaired height at screening. The table shows height measurements at both 2.5 and 2.0 SD below the mean for chronological age and sex in cm. Values in inches provided in Table 10-7 have been calculated by Novo Nordisk in alignment with height tables prepared by Centers for Disease Control and Prevention.[67]

Guideline to find the correct age in the table:

Age at screening must be provided in years, months, and days.
For example:
A child's date of birth is 10-Aug-2010
Screening date is 15-Sep-2022
Calculated age is 12 years, 1 month and 5 days at the screening visit.

Eligibility

Reference the specific SD in the inclusion criteria per indication in the study's protocol. To be eligible, the child's height must be equal to or below the height shown in the table below.

Table 10-7 Tool to assess Inclusion criteria – Impaired height

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
9	11	22	-	10	0	6	.	.	.	.	125.0	49.2	121.9	48.0
10	0	7	-	10	0	21	.	.	.	.	125.2	49.3	122.1	48.1
10	0	22	-	10	1	6	.	.	.	.	125.4	49.4	122.3	48.1
10	1	7	-	10	1	21	.	.	.	.	125.6	49.4	122.4	48.2
10	1	22	-	10	2	6	.	.	.	.	125.7	49.5	122.6	48.3
10	2	7	-	10	2	21	.	.	.	.	125.9	49.6	122.7	48.3
10	2	22	-	10	3	6	.	.	.	.	126.1	49.6	122.9	48.4
10	3	7	-	10	3	21	.	.	.	.	126.3	49.7	123.1	48.4
10	3	22	-	10	4	6	.	.	.	.	126.4	49.8	123.2	48.5
10	4	7	-	10	4	21	.	.	.	.	126.6	49.8	123.4	48.6
10	4	22	-	10	5	6	.	.	.	.	126.8	49.9	123.5	48.6
10	5	7	-	10	5	21	.	.	.	.	127.0	50.0	123.7	48.7
10	5	22	-	10	6	6	.	.	.	.	127.2	50.1	123.9	48.8
10	6	7	-	10	6	21	.	.	.	.	127.4	50.1	124.1	48.8
10	6	22	-	10	7	6	.	.	.	.	127.6	50.2	124.2	48.9
10	7	7	-	10	7	21	.	.	.	.	127.7	50.3	124.4	49.0
10	7	22	-	10	8	6	.	.	.	.	127.9	50.4	124.6	49.0
10	8	7	-	10	8	21	.	.	.	.	128.1	50.5	124.8	49.1
10	8	22	-	10	9	6	.	.	.	.	128.3	50.5	125.0	49.2
10	9	7	-	10	9	21	.	.	.	.	128.6	50.6	125.1	49.3
10	9	22	-	10	10	6	.	.	.	.	128.8	50.7	125.3	49.3
10	10	7	-	10	10	21	.	.	.	.	129.0	50.8	125.5	49.4

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
10	10	22	-	10	11	6	.	.	.	.	129.2	50.9	125.7	49.5
10	11	7	-	10	11	21	.	.	.	.	129.4	51.0	125.9	49.6
10	11	22	-	11	0	6	129.8	51.1	126.5	49.8	129.6	51.0	126.1	49.7
11	0	7	-	11	0	21	130.0	51.2	126.7	49.9	129.9	51.1	126.3	49.7
11	0	22	-	11	1	6	130.2	51.3	126.9	49.9	130.1	51.2	126.6	49.8
11	1	7	-	11	1	21	130.4	51.3	127.0	50.0	130.3	51.3	126.8	49.9
11	1	22	-	11	2	6	130.6	51.4	127.2	50.1	130.6	51.4	127.0	50.0
11	2	7	-	11	2	21	130.7	51.5	127.4	50.2	130.8	51.5	127.2	50.1
11	2	22	-	11	3	6	130.9	51.5	127.6	50.2	131.1	51.6	127.5	50.2
11	3	7	-	11	3	21	131.1	51.6	127.8	50.3	131.3	51.7	127.7	50.3
11	3	22	-	11	4	6	131.3	51.7	127.9	50.4	131.6	51.8	127.9	50.4
11	4	7	-	11	4	21	131.5	51.8	128.1	50.4	131.9	51.9	128.2	50.5
11	4	22	-	11	5	6	131.7	51.8	128.3	50.5	132.1	52.0	128.4	50.6
11	5	7	-	11	5	21	131.9	51.9	128.5	50.6	132.4	52.1	128.7	50.7
11	5	22	-	11	6	6	132.1	52.0	128.7	50.7	132.7	52.2	128.9	50.8
11	6	7	-	11	6	21	132.3	52.1	128.9	50.7	132.9	52.3	129.2	50.9
11	6	22	-	11	7	6	132.5	52.2	129.1	50.8	133.2	52.5	129.5	51.0
11	7	7	-	11	7	21	132.7	52.2	129.3	50.9	133.5	52.6	129.8	51.1
11	7	22	-	11	8	6	132.9	52.3	129.5	51.0	133.8	52.7	130.0	51.2
11	8	7	-	11	8	21	133.1	52.4	129.7	51.1	134.1	52.8	130.3	51.3
11	8	22	-	11	9	6	133.3	52.5	129.9	51.1	134.4	52.9	130.6	51.4
11	9	7	-	11	9	21	133.5	52.6	130.1	51.2	134.7	53.0	130.9	51.5
11	9	22	-	11	10	6	133.7	52.6	130.3	51.3	135.0	53.1	131.2	51.7

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
11	10	7	-	11	10	21	133.9	52.7	130.5	51.4	135.3	53.3	131.5	51.8
11	10	22	-	11	11	6	134.2	52.8	130.7	51.5	135.6	53.4	131.8	51.9
11	11	7	-	11	11	21	134.4	52.9	130.9	51.5	135.9	53.5	132.1	52.0
11	11	22	-	12	0	6	134.6	53.0	131.1	51.6	136.2	53.6	132.4	52.1
12	0	7	-	12	0	21	134.8	53.1	131.3	51.7	136.5	53.8	132.7	52.3
12	0	22	-	12	1	6	135.0	53.2	131.6	51.8	136.8	53.9	133.0	52.4
12	1	7	-	12	1	21	135.3	53.3	131.8	51.9	137.2	54.0	133.3	52.5
12	1	22	-	12	2	6	135.5	53.3	132.0	52.0	137.5	54.1	133.7	52.6
12	2	7	-	12	2	21	135.7	53.4	132.2	52.1	137.8	54.2	134.0	52.7
12	2	22	-	12	3	6	136.0	53.5	132.4	52.1	138.1	54.4	134.3	52.9
12	3	7	-	12	3	21	136.2	53.6	132.7	52.2	138.4	54.5	134.6	53.0
12	3	22	-	12	4	6	136.4	53.7	132.9	52.3	138.7	54.6	134.9	53.1
12	4	7	-	12	4	21	136.7	53.8	133.1	52.4	139.0	54.7	135.2	53.2
12	4	22	-	12	5	6	136.9	53.9	133.3	52.5	139.3	54.8	135.6	53.4
12	5	7	-	12	5	21	137.2	54.0	133.6	52.6	139.6	55.0	135.9	53.5
12	5	22	-	12	6	6	137.4	54.1	133.8	52.7	139.9	55.1	136.2	53.6
12	6	7	-	12	6	21	137.7	54.2	134.0	52.8	140.2	55.2	136.5	53.7
12	6	22	-	12	7	6	137.9	54.3	134.3	52.9	140.5	55.3	136.8	53.9
12	7	7	-	12	7	21	138.2	54.4	134.5	53.0	140.8	55.4	137.1	54.0
12	7	22	-	12	8	6	138.4	54.5	134.8	53.1	141.1	55.5	137.4	54.1
12	8	7	-	12	8	21	138.7	54.6	135.0	53.1	141.3	55.6	137.7	54.2
12	8	22	-	12	9	6	139.0	54.7	135.2	53.2	141.6	55.8	138.0	54.3
12	9	7	-	12	9	21	139.2	54.8	135.5	53.3	141.9	55.9	138.3	54.4

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
12	9	22	-	12	10	6	139.5	54.9	135.7	53.4	142.2	56.0	138.5	54.5
12	10	7	-	12	10	21	139.7	55.0	136.0	53.5	142.4	56.1	138.8	54.6
12	10	22	-	12	11	6	140.0	55.1	136.2	53.6	142.7	56.2	139.1	54.8
12	11	7	-	12	11	21	140.3	55.2	136.5	53.7	142.9	56.3	139.3	54.9
12	11	22	-	13	0	6	140.5	55.3	136.7	53.8	143.2	56.4	139.6	55.0
13	0	7	-	13	0	21	140.8	55.4	137.0	53.9	143.4	56.5	139.8	55.1
13	0	22	-	13	1	6	141.1	55.5	137.2	54.0	143.6	56.5	140.1	55.2
13	1	7	-	13	1	21	141.4	55.7	137.5	54.1	143.8	56.6	140.3	55.2
13	1	22	-	13	2	6	141.6	55.8	137.7	54.2	144.1	56.7	140.6	55.3
13	2	7	-	13	2	21	141.9	55.9	138.0	54.3	144.3	56.8	140.8	55.4
13	2	22	-	13	3	6	142.2	56.0	138.2	54.4	144.5	56.9	141.0	55.5
13	3	7	-	13	3	21	142.5	56.1	138.5	54.5	144.7	57.0	141.2	55.6
13	3	22	-	13	4	6	142.7	56.2	138.7	54.6	144.9	57.0	141.4	55.7
13	4	7	-	13	4	21	143.0	56.3	139.0	54.7	145.1	57.1	141.6	55.8
13	4	22	-	13	5	6	143.3	56.4	139.3	54.8	145.2	57.2	141.8	55.8
13	5	7	-	13	5	21	143.6	56.5	139.5	54.9	145.4	57.3	142.0	55.9
13	5	22	-	13	6	6	143.9	56.6	139.8	55.0	145.6	57.3	142.2	56.0
13	6	7	-	13	6	21	144.1	56.7	140.0	55.1	145.8	57.4	142.4	56.1
13	6	22	-	13	7	6	144.4	56.9	140.3	55.2	145.9	57.4	142.5	56.1
13	7	7	-	13	7	21	144.7	57.0	140.5	55.3	146.1	57.5	142.7	56.2
13	7	22	-	13	8	6	145.0	57.1	140.8	55.4	146.2	57.6	142.9	56.2
13	8	7	-	13	8	21	145.3	57.2	141.1	55.5	146.4	57.6	143.0	56.3
13	8	22	-	13	9	6	145.5	57.3	141.3	55.6	146.5	57.7	143.2	56.4

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
13	9	7	-	13	9	21	145.8	57.4	141.6	55.7	146.6	57.7	143.3	56.4
13	9	22	-	13	10	6	146.1	57.5	141.8	55.8	146.8	57.8	143.4	56.5
13	10	7	-	13	10	21	146.4	57.6	142.1	55.9	146.9	57.8	143.6	56.5
13	10	22	-	13	11	6	146.7	57.7	142.4	56.0	147.0	57.9	143.7	56.6
13	11	7	-	13	11	21	146.9	57.9	142.6	56.2	147.1	57.9	143.8	56.6
13	11	22	-	14	0	6	147.2	58.0	142.9	56.3	147.2	58.0	143.9	56.7
14	0	7	-	14	0	21	147.5	58.1	143.1	56.4	147.3	58.0	144.1	56.7
14	0	22	-	14	1	6	147.8	58.2	143.4	56.5	147.4	58.0	144.2	56.8
14	1	7	-	14	1	21	148.1	58.3	143.7	56.6	147.5	58.1	144.3	56.8
14	1	22	-	14	2	6	148.3	58.4	143.9	56.7	147.6	58.1	144.4	56.8
14	2	7	-	14	2	21	148.6	58.5	144.2	56.8	147.7	58.2	144.5	56.9
14	2	22	-	14	3	6	148.9	58.6	144.4	56.9	147.8	58.2	144.6	56.9
14	3	7	-	14	3	21	149.1	58.7	144.7	57.0	147.9	58.2	144.6	56.9
14	3	22	-	14	4	6	149.4	58.8	144.9	57.1	148.0	58.3	144.7	57.0
14	4	7	-	14	4	21	149.7	58.9	145.2	57.2	148.1	58.3	144.8	57.0
14	4	22	-	14	5	6	149.9	59.0	145.5	57.3	148.1	58.3	144.9	57.0
14	5	7	-	14	5	21	150.2	59.1	145.7	57.4	148.2	58.3	145.0	57.1
14	5	22	-	14	6	6	150.4	59.2	146.0	57.5	148.3	58.4	145.0	57.1
14	6	7	-	14	6	21	150.7	59.3	146.2	57.6	148.3	58.4	145.1	57.1
14	6	22	-	14	7	6	151.0	59.4	146.5	57.7	148.4	58.4	145.2	57.2
14	7	7	-	14	7	21	151.2	59.5	146.7	57.8	148.5	58.5	145.2	57.2
14	7	22	-	14	8	6	151.5	59.6	146.9	57.9	148.5	58.5	145.3	57.2
14	8	7	-	14	8	21	151.7	59.7	147.2	57.9	148.6	58.5	145.4	57.2

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
14	8	22	-	14	9	6	151.9	59.8	147.4	58.0	148.6	58.5	145.4	57.3
14	9	7	-	14	9	21	152.2	59.9	147.7	58.1	148.7	58.5	145.5	57.3
14	9	22	-	14	10	6	152.4	60.0	147.9	58.2	148.7	58.6	145.5	57.3
14	10	7	-	14	10	21	152.7	60.1	148.1	58.3	148.8	58.6	145.6	57.3
14	10	22	-	14	11	6	152.9	60.2	148.4	58.4	148.8	58.6	145.6	57.3
14	11	7	-	14	11	21	153.1	60.3	148.6	58.5	148.9	58.6	145.7	57.4
14	11	22	-	15	0	6	153.3	60.4	148.8	58.6	148.9	58.6	145.7	57.4
15	0	7	-	15	0	21	153.6	60.5	149.1	58.7	149.0	58.7	145.8	57.4
15	0	22	-	15	1	6	153.8	60.5	149.3	58.8	149.0	58.7	145.8	57.4
15	1	7	-	15	1	21	154.0	60.6	149.5	58.9	149.1	58.7	145.8	57.4
15	1	22	-	15	2	6	154.2	60.7	149.7	58.9	149.1	58.7	145.9	57.4
15	2	7	-	15	2	21	154.4	60.8	149.9	59.0	149.1	58.7	145.9	57.4
15	2	22	-	15	3	6	154.6	60.9	150.2	59.1	149.2	58.7	146.0	57.5
15	3	7	-	15	3	21	154.8	61.0	150.4	59.2	149.2	58.7	146.0	57.5
15	3	22	-	15	4	6	155.0	61.0	150.6	59.3	149.2	58.8	146.0	57.5
15	4	7	-	15	4	21	155.2	61.1	150.8	59.4	149.3	58.8	146.1	57.5
15	4	22	-	15	5	6	155.4	61.2	151.0	59.4	149.3	58.8	146.1	57.5
15	5	7	-	15	5	21	155.6	61.3	151.2	59.5	149.3	58.8	146.1	57.5
15	5	22	-	15	6	6	155.8	61.3	151.4	59.6	149.4	58.8	146.1	57.5
15	6	7	-	15	6	21	156.0	61.4	151.6	59.7	149.4	58.8	146.2	57.5
15	6	22	-	15	7	6	156.1	61.5	151.8	59.7	149.4	58.8	146.2	57.6
15	7	7	-	15	7	21	156.3	61.5	151.9	59.8	149.4	58.8	146.2	57.6
15	7	22	-	15	8	6	156.5	61.6	152.1	59.9	149.5	58.8	146.2	57.6

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
15	8	7	-	15	8	21	156.6	61.7	152.3	60.0	149.5	58.9	146.3	57.6
15	8	22	-	15	9	6	156.8	61.7	152.5	60.0	149.5	58.9	146.3	57.6
15	9	7	-	15	9	21	157.0	61.8	152.7	60.1	149.5	58.9	146.3	57.6
15	9	22	-	15	10	6	157.1	61.9	152.8	60.2	149.6	58.9	146.3	57.6
15	10	7	-	15	10	21	157.3	61.9	153.0	60.2	149.6	58.9	146.4	57.6
15	10	22	-	15	11	6	157.4	62.0	153.2	60.3	149.6	58.9	146.4	57.6
15	11	7	-	15	11	21	157.6	62.0	153.3	60.4	149.6	58.9	146.4	57.6
15	11	22	-	16	0	6	157.7	62.1	153.5	60.4	149.6	58.9	146.4	57.6
16	0	7	-	16	0	21	157.9	62.1	153.6	60.5	149.7	58.9	146.4	57.7
16	0	22	-	16	1	6	158.0	62.2	153.8	60.5	149.7	58.9	146.5	57.7
16	1	7	-	16	1	21	158.1	62.3	153.9	60.6	149.7	58.9	146.5	57.7
16	1	22	-	16	2	6	158.3	62.3	154.1	60.7	149.7	58.9	146.5	57.7
16	2	7	-	16	2	21	158.4	62.4	154.2	60.7	149.7	58.9	146.5	57.7
16	2	22	-	16	3	6	158.5	62.4	154.4	60.8	149.7	59.0	146.5	57.7
16	3	7	-	16	3	21	158.6	62.5	154.5	60.8	149.8	59.0	146.5	57.7
16	3	22	-	16	4	6	158.8	62.5	154.6	60.9	149.8	59.0	146.5	57.7
16	4	7	-	16	4	21	158.9	62.5	154.8	60.9	149.8	59.0	146.6	57.7
16	4	22	-	16	5	6	159.0	62.6	154.9	61.0	149.8	59.0	146.6	57.7
16	5	7	-	16	5	21	159.1	62.6	155.0	61.0	149.8	59.0	146.6	57.7
16	5	22	-	16	6	6	159.2	62.7	155.1	61.1	149.8	59.0	146.6	57.7
16	6	7	-	16	6	21	159.3	62.7	155.2	61.1	149.8	59.0	146.6	57.7
16	6	22	-	16	7	6	159.4	62.8	155.4	61.2	149.9	59.0	146.6	57.7
16	7	7	-	16	7	21	159.5	62.8	155.5	61.2	149.9	59.0	146.6	57.7

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
16	7	22	-	16	8	6	159.6	62.8	155.6	61.3	149.9	59.0	146.6	57.7
16	8	7	-	16	8	21	159.7	62.9	155.7	61.3	149.9	59.0	146.7	57.7
16	8	22	-	16	9	6	159.8	62.9	155.8	61.3	149.9	59.0	146.7	57.7
16	9	7	-	16	9	21	159.9	62.9	155.9	61.4	149.9	59.0	146.7	57.7
16	9	22	-	16	10	6	160.0	63.0	156.0	61.4	149.9	59.0	146.7	57.8
16	10	7	-	16	10	21	160.0	63.0	156.1	61.5	149.9	59.0	146.7	57.8
16	10	22	-	16	11	6	160.1	63.0	156.2	61.5	149.9	59.0	146.7	57.8
16	11	7	-	16	11	21	160.2	63.1	156.3	61.5	150.0	59.0	146.7	57.8
16	11	22	-	17	0	6	160.3	63.1	156.4	61.6	150.0	59.0	146.7	57.8
17	0	7	-	17	0	21	160.4	63.1	156.4	61.6	150.0	59.0	146.7	57.8
17	0	22	-	17	1	6	160.4	63.2	156.5	61.6	150.0	59.1	146.7	57.8
17	1	7	-	17	1	21	160.5	63.2	156.6	61.7	150.0	59.1	146.8	57.8
17	1	22	-	17	2	6	160.6	63.2	156.7	61.7	150.0	59.1	146.8	57.8
17	2	7	-	17	2	21	160.6	63.2	156.8	61.7	150.0	59.1	146.8	57.8
17	2	22	-	17	3	6	160.7	63.3	156.8	61.7	150.0	59.1	146.8	57.8
17	3	7	-	17	3	21	160.8	63.3	156.9	61.8	150.0	59.1	146.8	57.8
17	3	22	-	17	4	6	160.8	63.3	157.0	61.8	150.0	59.1	146.8	57.8
17	4	7	-	17	4	21	160.9	63.3	157.0	61.8	150.0	59.1	146.8	57.8
17	4	22	-	17	5	6	160.9	63.4	157.1	61.9	150.1	59.1	146.8	57.8
17	5	7	-	17	5	21	161.0	63.4	157.2	61.9	150.1	59.1	146.8	57.8
17	5	22	-	17	6	6	161.0	63.4	157.2	61.9	150.1	59.1	146.8	57.8
17	6	7	-	17	6	21	161.1	63.4	157.3	61.9	150.1	59.1	146.8	57.8
17	6	22	-	17	7	6	161.2	63.4	157.4	62.0	150.1	59.1	146.8	57.8

Age from				Age to			Boys				Girls			
Years	Month	Days		Years	Month	Days	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)	SDS -2 (cm)	SDS -2 (inches)	SDS -2.5 (cm)	SDS -2.5 (inches)
17	7	7	-	17	7	21	161.2	63.5	157.4	62.0	150.1	59.1	146.8	57.8
17	7	22	-	17	8	6	161.2	63.5	157.5	62.0	150.1	59.1	146.9	57.8
17	8	7	-	17	8	21	161.3	63.5	157.5	62.0	150.1	59.1	146.9	57.8
17	8	22	-	17	9	6	161.3	63.5	157.6	62.0	150.1	59.1	146.9	57.8
17	9	7	-	17	9	21	161.4	63.5	157.6	62.1	150.1	59.1	146.9	57.8
17	9	22	-	17	10	6	161.4	63.6	157.7	62.1	150.1	59.1	146.9	57.8
17	10	7	-	17	10	21	161.5	63.6	157.7	62.1	150.1	59.1	146.9	57.8
17	10	22	-	17	11	6	161.5	63.6	157.8	62.1	150.1	59.1	146.9	57.8
17	11	7	-	17	11	21	161.5	63.6	157.8	62.1	150.1	59.1	146.9	57.8
17	11	22	-	18	0	6	161.6	63.6	157.9	62.1	150.2	59.1	146.9	57.8

10.8 Appendix 8: Dosing tables

Procedure to find the correct dose

A pen strength of 15 mg/1.5 mL will be used in this study. The dose table covers a body weight range from 9 to 125 kg. Use the dose table (Table 10-8) to find the precise dose using the participant's current weight. In case of dose reduction, dosing tables will be provided by Novo Nordisk.

Information to participant's parents/LAR regarding dose

Participant's parents/LAR must be informed about the prescribed dose to be administered. Instruct the participant's parents/LAR on how to select the prescribed dose on the pen injector.

Splitting the dose

A dose may be split into equal administrations in case the dose is higher than the pen can dispense for one administration. If a dose is split, it should be injected into the same body location.

Table 10-8 Dose table for 0.24 mg/kg somapacitan – 15 mg/1.5 mL strength

Somapacitan 15mg/1.5ml - Dose Level 0.24mg/kg								
Weight (kg)		Weight (lb)		Dosing				
Start	End	Start	End	Total Dose	Dose 1	Dose 2	Dose 3	Dose 4
9.0	9.3	19.8	20.6	2.2	2.2	0.0	0.0	0.0
9.4	9.7	20.7	21.5	2.3	2.3	0.0	0.0	0.0
9.8	10.1	21.6	22.4	2.4	2.4	0.0	0.0	0.0
10.2	10.6	22.5	23.5	2.5	2.5	0.0	0.0	0.0
10.7	11.0	23.6	24.4	2.6	2.6	0.0	0.0	0.0
11.1	11.4	24.5	25.3	2.7	2.7	0.0	0.0	0.0
11.5	11.8	25.4	26.1	2.8	2.8	0.0	0.0	0.0
11.9	12.2	26.2	27.0	2.9	2.9	0.0	0.0	0.0
12.3	12.6	27.1	27.9	3.0	3.0	0.0	0.0	0.0
12.7	13.1	28.0	29.0	3.1	3.1	0.0	0.0	0.0
13.2	13.5	29.1	29.9	3.2	3.2	0.0	0.0	0.0
13.6	13.9	30.0	30.8	3.3	3.3	0.0	0.0	0.0
14.0	14.3	30.9	31.6	3.4	3.4	0.0	0.0	0.0
14.4	14.7	31.7	32.5	3.5	3.5	0.0	0.0	0.0
14.8	15.1	32.6	33.4	3.6	3.6	0.0	0.0	0.0
15.2	15.6	33.5	34.5	3.7	3.7	0.0	0.0	0.0
15.7	16.0	34.6	35.4	3.8	3.8	0.0	0.0	0.0
16.1	16.4	35.5	36.3	3.9	3.9	0.0	0.0	0.0
16.5	16.8	36.4	37.2	4.0	4.0	0.0	0.0	0.0
16.9	17.2	37.3	38.0	4.1	4.1	0.0	0.0	0.0
17.3	17.6	38.1	38.9	4.2	4.2	0.0	0.0	0.0
17.7	18.1	39.0	40.0	4.3	4.3	0.0	0.0	0.0
18.2	18.5	40.1	40.9	4.4	4.4	0.0	0.0	0.0
18.6	18.9	41.0	41.8	4.5	4.5	0.0	0.0	0.0
19.0	19.3	41.9	42.7	4.6	4.6	0.0	0.0	0.0
19.4	19.7	42.8	43.6	4.7	4.7	0.0	0.0	0.0
19.8	20.1	43.7	44.4	4.8	4.8	0.0	0.0	0.0
20.2	20.6	44.5	45.5	4.9	4.9	0.0	0.0	0.0
20.7	21.0	45.6	46.4	5.0	5.0	0.0	0.0	0.0

Somapacitan 15mg/1.5ml - Dose Level 0.24mg/kg								
Weight (kg)		Weight (lb)		Dosing				
Start	End	Start	End	Total Dose	Dose 1	Dose 2	Dose 3	Dose 4
21.1	21.4	46.5	47.3	5.1	5.1	0.0	0.0	0.0
21.5	21.8	47.4	48.2	5.2	5.2	0.0	0.0	0.0
21.9	22.2	48.3	49.1	5.3	5.3	0.0	0.0	0.0
22.3	22.6	49.2	49.9	5.4	5.4	0.0	0.0	0.0
22.7	23.1	50.0	51.0	5.5	5.5	0.0	0.0	0.0
23.2	23.5	51.1	51.9	5.6	5.6	0.0	0.0	0.0
23.6	23.9	52.0	52.8	5.7	5.7	0.0	0.0	0.0
24.0	24.3	52.9	53.7	5.8	5.8	0.0	0.0	0.0
24.4	24.7	53.8	54.6	5.9	5.9	0.0	0.0	0.0
24.8	25.1	54.7	55.5	6.0	6.0	0.0	0.0	0.0
25.2	25.6	55.6	56.6	6.1	6.1	0.0	0.0	0.0
25.7	26.0	56.7	57.4	6.2	6.2	0.0	0.0	0.0
26.1	26.4	57.5	58.3	6.3	6.3	0.0	0.0	0.0
26.5	26.8	58.4	59.2	6.4	6.4	0.0	0.0	0.0
26.9	27.2	59.3	60.1	6.5	6.5	0.0	0.0	0.0
27.3	27.6	60.2	61.0	6.6	6.6	0.0	0.0	0.0
27.7	28.1	61.1	62.1	6.7	6.7	0.0	0.0	0.0
28.2	28.5	62.2	63.0	6.8	6.8	0.0	0.0	0.0
28.6	28.9	63.1	63.8	6.9	6.9	0.0	0.0	0.0
29.0	29.3	63.9	64.7	7.0	7.0	0.0	0.0	0.0
29.4	29.7	64.8	65.6	7.1	7.1	0.0	0.0	0.0
29.8	30.1	65.7	66.5	7.2	7.2	0.0	0.0	0.0
30.2	30.6	66.6	67.6	7.3	7.3	0.0	0.0	0.0
30.7	31.0	67.7	68.5	7.4	7.4	0.0	0.0	0.0
31.1	31.4	68.6	69.3	7.5	7.5	0.0	0.0	0.0
31.5	31.8	69.4	70.2	7.6	7.6	0.0	0.0	0.0
31.9	32.2	70.3	71.1	7.7	7.7	0.0	0.0	0.0
32.3	32.6	71.2	72.0	7.8	7.8	0.0	0.0	0.0
32.7	33.1	72.1	73.1	7.9	7.9	0.0	0.0	0.0
33.2	33.5	73.2	74.0	8.0	8.0	0.0	0.0	0.0
33.6	33.9	74.1	74.9	8.1	4.1	4.0	0.0	0.0
34.0	34.3	75.0	75.7	8.2	4.1	4.1	0.0	0.0
34.4	34.7	75.8	76.6	8.3	4.2	4.1	0.0	0.0
34.8	35.1	76.7	77.5	8.4	4.2	4.2	0.0	0.0
35.2	35.6	77.6	78.6	8.5	4.3	4.2	0.0	0.0
35.7	36.0	78.7	79.5	8.6	4.3	4.3	0.0	0.0
36.1	36.4	79.6	80.4	8.7	4.4	4.3	0.0	0.0
36.5	36.8	80.5	81.2	8.8	4.4	4.4	0.0	0.0
36.9	37.2	81.3	82.1	8.9	4.5	4.4	0.0	0.0
37.3	37.6	82.2	83.0	9.0	4.5	4.5	0.0	0.0
37.7	38.1	83.1	84.1	9.1	4.6	4.5	0.0	0.0
38.2	38.5	84.2	85.0	9.2	4.6	4.6	0.0	0.0
38.6	38.9	85.1	85.9	9.3	4.7	4.6	0.0	0.0
39.0	39.3	86.0	86.8	9.4	4.7	4.7	0.0	0.0
39.4	39.7	86.9	87.6	9.5	4.8	4.7	0.0	0.0
39.8	40.1	87.7	88.5	9.6	4.8	4.8	0.0	0.0
40.2	40.6	88.6	89.6	9.7	4.9	4.8	0.0	0.0
40.7	41.0	89.7	90.5	9.8	4.9	4.9	0.0	0.0
41.1	41.4	90.6	91.4	9.9	5.0	4.9	0.0	0.0

Somapacitan 15mg/1.5ml - Dose Level 0.24mg/kg								
Weight (kg)		Weight (lb)		Dosing				
Start	End	Start	End	Total Dose	Dose 1	Dose 2	Dose 3	Dose 4
41.5	41.8	91.5	92.3	10.0	5.0	5.0	0.0	0.0
41.9	42.2	92.4	93.2	10.1	5.1	5.0	0.0	0.0
42.3	42.6	93.3	94.0	10.2	5.1	5.1	0.0	0.0
42.7	43.1	94.1	95.1	10.3	5.2	5.1	0.0	0.0
43.2	43.5	95.2	96.0	10.4	5.2	5.2	0.0	0.0
43.6	43.9	96.1	96.9	10.5	5.3	5.2	0.0	0.0
44.0	44.3	97.0	97.8	10.6	5.3	5.3	0.0	0.0
44.4	44.7	97.9	98.7	10.7	5.4	5.3	0.0	0.0
44.8	45.1	98.8	99.5	10.8	5.4	5.4	0.0	0.0
45.2	45.6	99.6	100.7	10.9	5.5	5.4	0.0	0.0
45.7	46.0	100.8	101.5	11.0	5.5	5.5	0.0	0.0
46.1	46.4	101.6	102.4	11.1	5.6	5.5	0.0	0.0
46.5	46.8	102.5	103.3	11.2	5.6	5.6	0.0	0.0
46.9	47.2	103.4	104.2	11.3	5.7	5.6	0.0	0.0
47.3	47.6	104.3	105.1	11.4	5.7	5.7	0.0	0.0
47.7	48.1	105.2	106.2	11.5	5.8	5.7	0.0	0.0
48.2	48.5	106.3	107.0	11.6	5.8	5.8	0.0	0.0
48.6	48.9	107.1	107.9	11.7	5.9	5.8	0.0	0.0
49.0	49.3	108.0	108.8	11.8	5.9	5.9	0.0	0.0
49.4	49.7	108.9	109.7	11.9	6.0	5.9	0.0	0.0
49.8	50.1	109.8	110.6	12.0	6.0	6.0	0.0	0.0
50.2	50.6	110.7	111.7	12.1	6.1	6.0	0.0	0.0
50.7	51.0	111.8	112.6	12.2	6.1	6.1	0.0	0.0
51.1	51.4	112.7	113.4	12.3	6.2	6.1	0.0	0.0
51.5	51.8	113.5	114.3	12.4	6.2	6.2	0.0	0.0
51.9	52.2	114.4	115.2	12.5	6.3	6.2	0.0	0.0
52.3	52.6	115.3	116.1	12.6	6.3	6.3	0.0	0.0
52.7	53.1	116.2	117.2	12.7	6.4	6.3	0.0	0.0
53.2	53.5	117.3	118.1	12.8	6.4	6.4	0.0	0.0
53.6	53.9	118.2	118.9	12.9	6.5	6.4	0.0	0.0
54.0	54.3	119.0	119.8	13.0	6.5	6.5	0.0	0.0
54.4	54.7	119.9	120.7	13.1	6.6	6.5	0.0	0.0
54.8	55.1	120.8	121.6	13.2	6.6	6.6	0.0	0.0
55.2	55.6	121.7	122.7	13.3	6.7	6.6	0.0	0.0
55.7	56.0	122.8	123.6	13.4	6.7	6.7	0.0	0.0
56.1	56.4	123.7	124.5	13.5	6.8	6.7	0.0	0.0
56.5	56.8	124.6	125.3	13.6	6.8	6.8	0.0	0.0
56.9	57.2	125.4	126.2	13.7	6.9	6.8	0.0	0.0
57.3	57.6	126.3	127.1	13.8	6.9	6.9	0.0	0.0
57.7	58.1	127.2	128.2	13.9	7.0	6.9	0.0	0.0
58.2	58.5	128.3	129.1	14.0	7.0	7.0	0.0	0.0
58.6	58.9	129.2	130.0	14.1	7.1	7.0	0.0	0.0
59.0	59.3	130.1	130.9	14.2	7.1	7.1	0.0	0.0
59.4	59.7	131.0	131.7	14.3	7.2	7.1	0.0	0.0
59.8	60.1	131.8	132.6	14.4	7.2	7.2	0.0	0.0
60.2	60.6	132.7	133.7	14.5	7.3	7.2	0.0	0.0
60.7	61.0	133.8	134.6	14.6	7.3	7.3	0.0	0.0
61.1	61.4	134.7	135.5	14.7	7.4	7.3	0.0	0.0
61.5	61.8	135.6	136.4	14.8	7.4	7.4	0.0	0.0

Somapacitan 15mg/1.5ml - Dose Level 0.24mg/kg								
Weight (kg)		Weight (lb)		Dosing				
Start	End	Start	End	Total Dose	Dose 1	Dose 2	Dose 3	Dose 4
61.9	62.2	136.5	137.2	14.9	7.5	7.4	0.0	0.0
62.3	62.6	137.3	138.1	15.0	7.5	7.5	0.0	0.0
62.7	63.1	138.2	139.2	15.1	7.6	7.5	0.0	0.0
63.2	63.5	139.3	140.1	15.2	7.6	7.6	0.0	0.0
63.6	63.9	140.2	141.0	15.3	7.7	7.6	0.0	0.0
64.0	64.3	141.1	141.9	15.4	7.7	7.7	0.0	0.0
64.4	64.7	142.0	142.8	15.5	7.8	7.7	0.0	0.0
64.8	65.1	142.9	143.6	15.6	7.8	7.8	0.0	0.0
65.2	65.6	143.7	144.7	15.7	7.9	7.8	0.0	0.0
65.7	66.0	144.8	145.6	15.8	7.9	7.9	0.0	0.0
66.1	66.4	145.7	146.5	15.9	8.0	7.9	0.0	0.0
66.5	66.8	146.6	147.4	16.0	8.0	8.0	0.0	0.0
66.9	67.2	147.5	148.3	16.1	5.4	5.4	5.3	0.0
67.3	67.6	148.4	149.2	16.2	5.4	5.4	5.4	0.0
67.7	68.1	149.3	150.3	16.3	5.4	5.4	5.5	0.0
68.2	68.5	150.4	151.1	16.4	5.5	5.5	5.4	0.0
68.6	68.9	151.2	152.0	16.5	5.5	5.5	5.5	0.0
69.0	69.3	152.1	152.9	16.6	5.5	5.5	5.6	0.0
69.4	69.7	153.0	153.8	16.7	5.6	5.6	5.5	0.0
69.8	70.1	153.9	154.7	16.8	5.6	5.6	5.6	0.0
70.2	70.6	154.8	155.8	16.9	5.6	5.6	5.7	0.0
70.7	71.0	155.9	156.6	17.0	5.7	5.7	5.6	0.0
71.1	71.4	156.7	157.5	17.1	5.7	5.7	5.7	0.0
71.5	71.8	157.6	158.4	17.2	5.7	5.7	5.8	0.0
71.9	72.2	158.5	159.3	17.3	5.8	5.8	5.7	0.0
72.3	72.6	159.4	160.2	17.4	5.8	5.8	5.8	0.0
72.7	73.1	160.3	161.3	17.5	5.8	5.8	5.9	0.0
73.2	73.5	161.4	162.2	17.6	5.9	5.9	5.8	0.0
73.6	73.9	162.3	163.0	17.7	5.9	5.9	5.9	0.0
74.0	74.3	163.1	163.9	17.8	5.9	5.9	6.0	0.0
74.4	74.7	164.0	164.8	17.9	6.0	6.0	5.9	0.0
74.8	75.1	164.9	165.7	18.0	6.0	6.0	6.0	0.0
75.2	75.6	165.8	166.8	18.1	6.0	6.0	6.1	0.0
75.7	76.0	166.9	167.7	18.2	6.1	6.1	6.0	0.0
76.1	76.4	167.8	168.6	18.3	6.1	6.1	6.1	0.0
76.5	76.8	168.7	169.4	18.4	6.1	6.1	6.2	0.0
76.9	77.2	169.5	170.3	18.5	6.2	6.2	6.1	0.0
77.3	77.6	170.4	171.2	18.6	6.2	6.2	6.2	0.0
77.7	78.1	171.3	172.3	18.7	6.2	6.2	6.3	0.0
78.2	78.5	172.4	173.2	18.8	6.3	6.3	6.2	0.0
78.6	78.9	173.3	174.1	18.9	6.3	6.3	6.3	0.0
79.0	79.3	174.2	174.9	19.0	6.3	6.3	6.4	0.0
79.4	79.7	175.0	175.8	19.1	6.4	6.4	6.3	0.0
79.8	80.1	175.9	176.7	19.2	6.4	6.4	6.4	0.0
80.2	80.6	176.8	177.8	19.3	6.4	6.4	6.5	0.0
80.7	81.0	177.9	178.7	19.4	6.5	6.5	6.4	0.0
81.1	81.4	178.8	179.6	19.5	6.5	6.5	6.5	0.0
81.5	81.8	179.7	180.5	19.6	6.5	6.5	6.6	0.0
81.9	82.2	180.6	181.3	19.7	6.6	6.6	6.5	0.0

Somapacitan 15mg/1.5ml - Dose Level 0.24mg/kg								
Weight (kg)		Weight (lb)		Dosing				
Start	End	Start	End	Total Dose	Dose 1	Dose 2	Dose 3	Dose 4
82.3	82.6	181.4	182.2	19.8	6.6	6.6	6.6	0.0
82.7	83.1	182.3	183.3	19.9	6.6	6.6	6.7	0.0
83.2	83.5	183.4	184.2	20.0	6.7	6.7	6.6	0.0
83.6	83.9	184.3	185.1	20.1	6.7	6.7	6.7	0.0
84.0	84.3	185.2	186.0	20.2	6.7	6.7	6.8	0.0
84.4	84.7	186.1	186.9	20.3	6.8	6.8	6.7	0.0
84.8	85.1	187.0	187.7	20.4	6.8	6.8	6.8	0.0
85.2	85.6	187.8	188.8	20.5	6.8	6.8	6.9	0.0
85.7	86.0	188.9	189.7	20.6	6.9	6.9	6.8	0.0
86.1	86.4	189.8	190.6	20.7	6.9	6.9	6.9	0.0
86.5	86.8	190.7	191.5	20.8	6.9	6.9	7.0	0.0
86.9	87.2	191.6	192.4	20.9	7.0	7.0	6.9	0.0
87.3	87.6	192.5	193.2	21.0	7.0	7.0	7.0	0.0
87.7	88.1	193.3	194.3	21.1	7.0	7.0	7.1	0.0
88.2	88.5	194.4	195.2	21.2	7.1	7.1	7.0	0.0
88.6	88.9	195.3	196.1	21.3	7.1	7.1	7.1	0.0
89.0	89.3	196.2	197.0	21.4	7.1	7.1	7.2	0.0
89.4	89.7	197.1	197.9	21.5	7.2	7.2	7.1	0.0
89.8	90.1	198.0	198.8	21.6	7.2	7.2	7.2	0.0
90.2	90.6	198.9	199.9	21.7	7.2	7.2	7.3	0.0
90.7	91.0	200.0	200.7	21.8	7.3	7.3	7.2	0.0
91.1	91.4	200.8	201.6	21.9	7.3	7.3	7.3	0.0
91.5	91.8	201.7	202.5	22.0	7.3	7.3	7.4	0.0
91.9	92.2	202.6	203.4	22.1	7.4	7.4	7.3	0.0
92.3	92.6	203.5	204.3	22.2	7.4	7.4	7.4	0.0
92.7	93.1	204.4	205.4	22.3	7.4	7.4	7.5	0.0
93.2	93.5	205.5	206.3	22.4	7.5	7.5	7.4	0.0
93.6	93.9	206.4	207.1	22.5	7.5	7.5	7.5	0.0
94.0	94.3	207.2	208.0	22.6	7.5	7.5	7.6	0.0
94.4	94.7	208.1	208.9	22.7	7.6	7.6	7.5	0.0
94.8	95.1	209.0	209.8	22.8	7.6	7.6	7.6	0.0
95.2	95.6	209.9	210.9	22.9	7.6	7.6	7.7	0.0
95.7	96.0	211.0	211.8	23.0	7.7	7.7	7.6	0.0
96.1	96.4	211.9	212.6	23.1	7.7	7.7	7.7	0.0
96.5	96.8	212.7	213.5	23.2	7.7	7.7	7.8	0.0
96.9	97.2	213.6	214.4	23.3	7.8	7.8	7.7	0.0
97.3	97.6	214.5	215.3	23.4	7.8	7.8	7.8	0.0
97.7	98.1	215.4	216.4	23.5	7.8	7.8	7.9	0.0
98.2	98.5	216.5	217.3	23.6	7.9	7.9	7.8	0.0
98.6	98.9	217.4	218.2	23.7	7.9	7.9	7.9	0.0
99.0	99.3	218.3	219.0	23.8	7.9	7.9	8.0	0.0
99.4	99.7	219.1	219.9	23.9	8.0	8.0	7.9	0.0
99.8	100.1	220.0	220.8	24.0	8.0	8.0	8.0	0.0
100.2	100.6	220.9	221.9	24.1	6.0	6.0	6.0	6.1
100.7	101.0	222.0	222.8	24.2	6.1	6.1	6.1	5.9
101.1	101.4	222.9	223.7	24.3	6.1	6.1	6.1	6.0
101.5	101.8	223.8	224.5	24.4	6.1	6.1	6.1	6.1
101.9	102.2	224.6	225.4	24.5	6.1	6.1	6.1	6.2
102.3	102.6	225.5	226.3	24.6	6.2	6.2	6.2	6.0

Somapacitan 15mg/1.5ml - Dose Level 0.24mg/kg								
Weight (kg)		Weight (lb)		Dosing				
Start	End	Start	End	Total Dose	Dose 1	Dose 2	Dose 3	Dose 4
102.7	103.1	226.4	227.4	24.7	6.2	6.2	6.2	6.1
103.2	103.5	227.5	228.3	24.8	6.2	6.2	6.2	6.2
103.6	103.9	228.4	229.2	24.9	6.2	6.2	6.2	6.3
104.0	104.3	229.3	230.1	25.0	6.3	6.3	6.3	6.1
104.4	104.7	230.2	230.9	25.1	6.3	6.3	6.3	6.2
104.8	105.1	231.0	231.8	25.2	6.3	6.3	6.3	6.3
105.2	105.6	231.9	232.9	25.3	6.3	6.3	6.3	6.4
105.7	106.0	233.0	233.8	25.4	6.4	6.4	6.4	6.2
106.1	106.4	233.9	234.7	25.5	6.4	6.4	6.4	6.3
106.5	106.8	234.8	235.6	25.6	6.4	6.4	6.4	6.4
106.9	107.2	235.7	236.5	25.7	6.4	6.4	6.4	6.5
107.3	107.6	236.6	237.3	25.8	6.5	6.5	6.5	6.3
107.7	108.1	237.4	238.4	25.9	6.5	6.5	6.5	6.4
108.2	108.5	238.5	239.3	26.0	6.5	6.5	6.5	6.5
108.6	108.9	239.4	240.2	26.1	6.5	6.5	6.5	6.6
109.0	109.3	240.3	241.1	26.2	6.6	6.6	6.6	6.4
109.4	109.7	241.2	242.0	26.3	6.6	6.6	6.6	6.5
109.8	110.1	242.1	242.8	26.4	6.6	6.6	6.6	6.6
110.2	110.6	242.9	243.9	26.5	6.6	6.6	6.6	6.7
110.7	111.0	244.0	244.8	26.6	6.7	6.7	6.7	6.5
111.1	111.4	244.9	245.7	26.7	6.7	6.7	6.7	6.6
111.5	111.8	245.8	246.6	26.8	6.7	6.7	6.7	6.7
111.9	112.2	246.7	247.5	26.9	6.7	6.7	6.7	6.8
112.3	112.6	247.6	248.4	27.0	6.8	6.8	6.8	6.6
112.7	113.1	248.5	249.5	27.1	6.8	6.8	6.8	6.7
113.2	113.5	249.6	250.3	27.2	6.8	6.8	6.8	6.8
113.6	113.9	250.4	251.2	27.3	6.8	6.8	6.8	6.9
114.0	114.3	251.3	252.1	27.4	6.9	6.9	6.9	6.7
114.4	114.7	252.2	253.0	27.5	6.9	6.9	6.9	6.8
114.8	115.1	253.1	253.9	27.6	6.9	6.9	6.9	6.9
115.2	115.6	254.0	255.0	27.7	6.9	6.9	6.9	7.0
115.7	116.0	255.1	255.9	27.8	7.0	7.0	7.0	6.8
116.1	116.4	256.0	256.7	27.9	7.0	7.0	7.0	6.9
116.5	116.8	256.8	257.6	28.0	7.0	7.0	7.0	7.0
116.9	117.2	257.7	258.5	28.1	7.0	7.0	7.0	7.1
117.3	117.6	258.6	259.4	28.2	7.1	7.1	7.1	6.9
117.7	118.1	259.5	260.5	28.3	7.1	7.1	7.1	7.0
118.2	118.5	260.6	261.4	28.4	7.1	7.1	7.1	7.1
118.6	118.9	261.5	262.2	28.5	7.1	7.1	7.1	7.2
119.0	119.3	262.3	263.1	28.6	7.2	7.2	7.2	7.0
119.4	119.7	263.2	264.0	28.7	7.2	7.2	7.2	7.1
119.8	120.1	264.1	264.9	28.8	7.2	7.2	7.2	7.2
120.2	120.6	265.0	266.0	28.9	7.2	7.2	7.2	7.3
120.7	121.0	266.1	266.9	29.0	7.3	7.3	7.3	7.1
121.1	121.4	267.0	267.8	29.1	7.3	7.3	7.3	7.2
121.5	121.8	267.9	268.6	29.2	7.3	7.3	7.3	7.3
121.9	122.2	268.7	269.5	29.3	7.3	7.3	7.3	7.4
122.3	122.6	269.6	270.4	29.4	7.4	7.4	7.4	7.2
122.7	123.1	270.5	271.5	29.5	7.4	7.4	7.4	7.3

Somapacitan 15mg/1.5ml - Dose Level 0.24mg/kg								
Weight (kg)		Weight (lb)		Dosing				
Start	End	Start	End	Total Dose	Dose 1	Dose 2	Dose 3	Dose 4
123.2	123.5	271.6	272.4	29.6	7.4	7.4	7.4	7.4
123.6	123.9	272.5	273.3	29.7	7.4	7.4	7.4	7.5
124.0	124.3	273.4	274.2	29.8	7.5	7.5	7.5	7.3
124.4	124.7	274.3	275.0	29.9	7.5	7.5	7.5	7.4
124.8	125.0	275.1	275.7	30.0	7.5	7.5	7.5	7.5

Dose calculation (somapacitan)

This information is only to be used for dose reduction of somapacitan.

Use the tables below (Table 10-9, 0.21 mg/kg/week or Table 10-10, 0.18 mg/kg/week) to find the required dose level and the participant's current weight.

Information to participant's parents/LARs regarding dose

Participant's parents/LARs must be informed about the prescribed dose and instructed in how to select the prescribed dose on the pen injector to be able to inject at home.

Splitting the dose

A dose may be split into two equal administrations in case the dose is higher than the pen can dispense for the administration. If a dose is split, it should be injected into the same body location.

Table 10-9 Selection of somapacitan dose in mg in case of dose reduction to a dose level of 0.21mg/kg

Somapacitan 15mg/1.5ml - Dose Level 0.21mg/kg				
Weight (kg)		Weight (lb)		
Start	End	Start	End	Dose
11.0	11.1	24.3	24.6	2.30
11.2	11.6	24.7	25.7	2.40
11.7	12.1	25.8	26.8	2.50
12.2	12.5	26.9	27.7	2.60
12.6	13.0	27.8	28.8	2.70
13.1	13.5	28.9	29.9	2.80
13.6	14.0	30.0	31.0	2.90
14.1	14.4	31.1	31.9	3.00
14.5	14.9	32.0	33.0	3.10
15.0	15.4	33.1	34.1	3.20
15.5	15.9	34.2	35.2	3.30
16.0	16.4	35.3	36.3	3.40
16.5	16.8	36.4	37.2	3.50
16.9	17.3	37.3	38.3	3.60

Somapacitan 15mg/1.5ml - Dose Level 0.21mg/kg				
17.4	17.8	38.4	39.4	3.70
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
17.9	18.3	39.5	40.5	3.80
18.4	18.7	40.6	41.3	3.90
18.8	19.2	41.4	42.4	4.00
19.3	19.7	42.5	43.6	4.10
19.8	20.2	43.7	44.7	4.20
20.3	20.6	44.8	45.5	4.30
20.7	21.1	45.6	46.6	4.40
21.2	21.6	46.7	47.7	4.50
21.7	22.1	47.8	48.8	4.60
22.2	22.5	48.9	49.7	4.70
22.6	23.0	49.8	50.8	4.80
23.1	23.5	50.9	51.9	4.90
23.6	24.0	52.0	53.0	5.00
24.1	24.4	53.1	53.9	5.10
24.5	24.9	54.0	55.0	5.20
25.0	25.4	55.1	56.1	5.30
25.5	25.9	56.2	57.2	5.40
26.0	26.4	57.3	58.3	5.50
26.5	26.8	58.4	59.2	5.60
26.9	27.3	59.3	60.3	5.70
27.4	27.8	60.4	61.4	5.80
27.9	28.3	61.5	62.5	5.90
28.4	28.7	62.6	63.4	6.00
28.8	29.2	63.5	64.5	6.10
29.3	29.7	64.6	65.6	6.20
29.8	30.2	65.7	66.7	6.30
30.3	30.6	66.8	67.6	6.40
30.7	31.1	67.7	68.7	6.50
31.2	31.6	68.8	69.8	6.60
31.7	32.1	69.9	70.9	6.70
32.2	32.5	71.0	71.8	6.80
32.6	33.0	71.9	72.9	6.90
33.1	33.5	73.0	74.0	7.00
33.6	34.0	74.1	75.1	7.10
34.1	34.4	75.2	76.0	7.20

Somapacitan 15mg/1.5ml - Dose Level 0.21mg/kg				
34.5	34.9	76.1	77.1	7.30
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
35.0	35.4	77.2	78.2	7.40
35.5	35.9	78.3	79.3	7.50
36.0	36.4	79.4	80.4	7.60
36.5	36.8	80.5	81.2	7.70
36.9	37.3	81.3	82.4	7.80
37.4	37.8	82.5	83.5	7.90
37.9	38.3	83.6	84.6	8.00
38.4	38.7	84.7	85.4	8.10
38.8	39.2	85.5	86.5	8.20
39.3	39.7	86.6	87.6	8.30
39.8	40.2	87.7	88.7	8.40
40.3	40.6	88.8	89.6	8.50
40.7	41.1	89.7	90.7	8.60
41.2	41.6	90.8	91.8	8.70
41.7	42.1	91.9	92.9	8.80
42.2	42.5	93.0	93.8	8.90
42.6	43.0	93.9	94.9	9.00
43.1	43.5	95.0	96.0	9.10
43.6	44.0	96.1	97.1	9.20
44.1	44.4	97.2	98.0	9.30
44.5	44.9	98.1	99.1	9.40
45.0	45.4	99.2	100.2	9.50
45.5	45.9	100.3	101.3	9.60
46.0	46.4	101.4	102.4	9.70
46.5	46.8	102.5	103.3	9.80
46.9	47.3	103.4	104.4	9.90
47.4	47.8	104.5	105.5	10.00
47.9	48.3	105.6	106.6	10.10
48.4	48.7	106.7	107.5	10.20
48.8	49.2	107.6	108.6	10.30
49.3	49.7	108.7	109.7	10.40
49.8	50.2	109.8	110.8	10.50
50.3	50.6	110.9	111.7	10.60
50.7	51.1	111.8	112.8	10.70
51.2	51.6	112.9	113.9	10.80

Somapacitan 15mg/1.5ml - Dose Level 0.21mg/kg				
51.7	52.1	114.0	115.0	10.90
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
52.2	52.5	115.1	115.9	11.00
52.6	53.0	116.0	117.0	11.10
53.1	53.5	117.1	118.1	11.20
53.6	54.0	118.2	119.2	11.30
54.1	54.4	119.3	120.1	11.40
54.5	54.9	120.2	121.2	11.50
55.0	55.4	121.3	122.3	11.60
55.5	55.9	122.4	123.4	11.70
56.0	56.4	123.5	124.5	11.80
56.5	56.8	124.6	125.3	11.90
56.9	57.3	125.4	126.4	12.00
57.4	57.8	126.5	127.5	12.10
57.9	58.3	127.6	128.6	12.20
58.4	58.7	128.7	129.5	12.30
58.8	59.2	129.6	130.6	12.40
59.3	59.7	130.7	131.7	12.50
59.8	60.2	131.8	132.8	12.60
60.3	60.6	132.9	133.7	12.70
60.7	61.1	133.8	134.8	12.80
61.2	61.6	134.9	135.9	12.90
61.7	62.1	136.0	137.0	13.00
62.2	62.5	137.1	137.9	13.10
62.6	63.0	138.0	139.0	13.20
63.1	63.5	139.1	140.1	13.30
63.6	64.0	140.2	141.2	13.40
64.1	64.4	141.3	142.1	13.50
64.5	64.9	142.2	143.2	13.60
65.0	65.4	143.3	144.3	13.70
65.5	65.9	144.4	145.4	13.80
66.0	66.4	145.5	146.5	13.90
66.5	66.8	146.6	147.4	14.00
66.9	67.3	147.5	148.5	14.10
67.4	67.8	148.6	149.6	14.20
67.9	68.3	149.7	150.7	14.30
68.4	68.7	150.8	151.6	14.40

Somapacitan 15mg/1.5ml - Dose Level 0.21mg/kg				
68.8	69.2	151.7	152.7	14.50
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
69.3	69.7	152.8	153.8	14.60
69.8	70.2	153.9	154.9	14.70
70.3	70.6	155.0	155.8	14.80
70.7	71.1	155.9	156.9	14.90
71.2	71.6	157.0	158.0	15.00
71.7	72.1	158.1	159.1	15.10
72.2	72.5	159.2	160.0	15.20
72.6	73.0	160.1	161.1	15.30
73.1	73.5	161.2	162.2	15.40
73.6	74.0	162.3	163.3	15.50
74.1	74.4	163.4	164.1	15.60
74.5	74.9	164.2	165.2	15.70
75.0	75.4	165.3	166.3	15.80
75.5	75.9	166.4	167.4	15.90
76.0	76.4	167.5	168.6	16.00
76.5	76.8	168.7	169.4	16.10
76.9	77.3	169.5	170.5	16.20
77.4	77.8	170.6	171.6	16.30
77.9	78.3	171.7	172.7	16.40
78.4	78.7	172.8	173.6	16.50
78.8	79.2	173.7	174.7	16.60
79.3	79.7	174.8	175.8	16.70
79.8	80.2	175.9	176.9	16.80
80.3	80.6	177.0	177.8	16.90
80.7	81.1	177.9	178.9	17.00
81.2	81.6	179.0	180.0	17.10
81.7	82.1	180.1	181.1	17.20
82.2	82.5	181.2	182.0	17.30
82.6	83.0	182.1	183.1	17.40
83.1	83.5	183.2	184.2	17.50
83.6	84.0	184.3	185.3	17.60
84.1	84.4	185.4	186.2	17.70
84.5	84.9	186.3	187.3	17.80
85.0	85.4	187.4	188.4	17.90
85.5	85.9	188.5	189.5	18.00

Somapacitan 15mg/1.5ml - Dose Level 0.21mg/kg				
86.0	86.4	189.6	190.6	18.10
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
86.5	86.8	190.7	191.5	18.20
86.9	87.3	191.6	192.6	18.30
87.4	87.8	192.7	193.7	18.40
87.9	88.3	193.8	194.8	18.50
88.4	88.7	194.9	195.7	18.60
88.8	89.2	195.8	196.8	18.70
89.3	89.7	196.9	197.9	18.80
89.8	90.2	198.0	199.0	18.90
90.3	90.6	199.1	199.9	19.00
90.7	91.1	200.0	201.0	19.10
91.2	91.6	201.1	202.1	19.20
91.7	92.1	202.2	203.2	19.30
92.2	92.5	203.3	204.0	19.40
92.6	93.0	204.1	205.1	19.50
93.1	93.5	205.2	206.3	19.60
93.6	94.0	206.4	207.4	19.70
94.1	94.4	207.5	208.2	19.80
94.5	94.9	208.3	209.3	19.90
95.0	95.4	209.4	210.4	20.00
95.5	95.9	210.5	211.5	20.10
96.0	96.4	211.6	212.6	20.20
96.5	96.8	212.7	213.5	20.30
96.9	97.3	213.6	214.6	20.40
97.4	97.8	214.7	215.7	20.50
97.9	98.3	215.8	216.8	20.60
98.4	98.7	216.9	217.7	20.70
98.8	99.2	217.8	218.8	20.80
99.3	99.7	218.9	219.9	20.90
99.8	100.0	220.0	220.6	21.00

Table 10-10 Selection of somapacitan dose in mg in case of dose reduction to a dose level of 0.18mg/kg

Somapacitan 15mg/1.5ml - Dose Level 0.18mg/kg				
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**

Somapacitan 15mg/1.5ml - Dose Level 0.18mg/kg				
12.0	12.4	26.5	27.5	2.20
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
12.5	13.0	27.6	28.8	2.30
13.1	13.5	28.9	29.9	2.40
13.6	14.1	30.0	31.2	2.50
14.2	14.6	31.3	32.3	2.60
14.7	15.2	32.4	33.6	2.70
15.3	15.8	33.7	35.0	2.80
15.9	16.3	35.1	36.1	2.90
16.4	16.9	36.2	37.4	3.00
17.0	17.4	37.5	38.5	3.10
17.5	18.0	38.6	39.8	3.20
18.1	18.5	39.9	40.9	3.30
18.6	19.1	41.0	42.2	3.40
19.2	19.6	42.3	43.3	3.50
19.7	20.2	43.4	44.7	3.60
20.3	20.8	44.8	46.0	3.70
20.9	21.3	46.1	47.1	3.80
21.4	21.9	47.2	48.4	3.90
22.0	22.4	48.5	49.5	4.00
22.5	23.0	49.6	50.8	4.10
23.1	23.5	50.9	51.9	4.20
23.6	24.1	52.0	53.3	4.30
24.2	24.6	53.4	54.4	4.40
24.7	25.2	54.5	55.7	4.50
25.3	25.8	55.8	57.0	4.60
25.9	26.3	57.1	58.1	4.70
26.4	26.9	58.2	59.4	4.80
27.0	27.4	59.5	60.5	4.90
27.5	28.0	60.6	61.8	5.00
28.1	28.5	61.9	63.0	5.10
28.6	29.1	63.1	64.3	5.20
29.2	29.6	64.4	65.4	5.30
29.7	30.2	65.5	66.7	5.40
30.3	30.8	66.8	68.0	5.50
30.9	31.3	68.1	69.1	5.60
31.4	31.9	69.2	70.4	5.70

Somapacitan 15mg/1.5ml - Dose Level 0.18mg/kg				
32.0	32.4	70.5	71.5	5.80
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
32.5	33.0	71.6	72.9	5.90
33.1	33.5	73.0	74.0	6.00
33.6	34.1	74.1	75.3	6.10
34.2	34.6	75.4	76.4	6.20
34.7	35.2	76.5	77.7	6.30
35.3	35.8	77.8	79.0	6.40
35.9	36.3	79.1	80.1	6.50
36.4	36.9	80.2	81.5	6.60
37.0	37.4	81.6	82.6	6.70
37.5	38.0	82.7	83.9	6.80
38.1	38.5	84.0	85.0	6.90
38.6	39.1	85.1	86.3	7.00
39.2	39.6	86.4	87.4	7.10
39.7	40.2	87.5	88.7	7.20
40.3	40.8	88.8	90.1	7.30
40.9	41.3	90.2	91.2	7.40
41.4	41.9	91.3	92.5	7.50
42.0	42.4	92.6	93.6	7.60
42.5	43.0	93.7	94.9	7.70
43.1	43.5	95.0	96.0	7.80
43.6	44.1	96.1	97.3	7.90
44.2	44.6	97.4	98.4	8.00
44.7	45.2	98.5	99.8	8.10
45.3	45.8	99.9	101.1	8.20
45.9	46.3	101.2	102.2	8.30
46.4	46.9	102.3	103.5	8.40
47.0	47.4	103.6	104.6	8.50
47.5	48.0	104.7	105.9	8.60
48.1	48.5	106.0	107.0	8.70
48.6	49.1	107.1	108.4	8.80
49.2	49.6	108.5	109.5	8.90
49.7	50.2	109.6	110.8	9.00
50.3	50.8	110.9	112.1	9.10
50.9	51.3	112.2	113.2	9.20
51.4	51.9	113.3	114.5	9.30

Somapacitan 15mg/1.5ml - Dose Level 0.18mg/kg				
52.0	52.4	114.6	115.6	9.40
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
52.5	53.0	115.7	117.0	9.50
53.1	53.5	117.1	118.1	9.60
53.6	54.1	118.2	119.4	9.70
54.2	54.6	119.5	120.5	9.80
54.7	55.2	120.6	121.8	9.90
55.3	55.8	121.9	123.1	10.00
55.9	56.3	123.2	124.2	10.10
56.4	56.9	124.3	125.6	10.20
57.0	57.4	125.7	126.7	10.30
57.5	58.0	126.8	128.0	10.40
58.1	58.5	128.1	129.1	10.50
58.6	59.1	129.2	130.4	10.60
59.2	59.6	130.5	131.5	10.70
59.7	60.2	131.6	132.8	10.80
60.3	60.8	132.9	134.2	10.90
60.9	61.3	134.3	135.3	11.00
61.4	61.9	135.4	136.6	11.10
62.0	62.4	136.7	137.7	11.20
62.5	63.0	137.8	139.0	11.30
63.1	63.5	139.1	140.1	11.40
63.6	64.1	140.2	141.4	11.50
64.2	64.6	141.5	142.5	11.60
64.7	65.2	142.6	143.9	11.70
65.3	65.8	144.0	145.2	11.80
65.9	66.3	145.3	146.3	11.90
66.4	66.9	146.4	147.6	12.00
67.0	67.4	147.7	148.7	12.10
67.5	68.0	148.8	150.0	12.20
68.1	68.5	150.1	151.1	12.30
68.6	69.1	151.2	152.5	12.40
69.2	69.6	152.6	153.6	12.50
69.7	70.2	153.7	154.9	12.60
70.3	70.8	155.0	156.2	12.70
70.9	71.3	156.3	157.3	12.80
71.4	71.9	157.4	158.6	12.90

Somapacitan 15mg/1.5ml - Dose Level 0.18mg/kg				
72.0	72.4	158.7	159.7	13.00
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
72.5	73.0	159.8	161.1	13.10
73.1	73.5	161.2	162.2	13.20
73.6	74.1	162.3	163.5	13.30
74.2	74.6	163.6	164.6	13.40
74.7	75.2	164.7	165.9	13.50
75.3	75.8	166.0	167.2	13.60
75.9	76.3	167.3	168.3	13.70
76.4	76.9	168.4	169.7	13.80
77.0	77.4	169.8	170.8	13.90
77.5	78.0	170.9	172.1	14.00
78.1	78.5	172.2	173.2	14.10
78.6	79.1	173.3	174.5	14.20
79.2	79.6	174.6	175.6	14.30
79.7	80.2	175.7	176.9	14.40
80.3	80.8	177.0	178.3	14.50
80.9	81.3	178.4	179.4	14.60
81.4	81.9	179.5	180.7	14.70
82.0	82.4	180.8	181.8	14.80
82.5	83.0	181.9	183.1	14.90
83.1	83.5	183.2	184.2	15.00
83.6	84.1	184.3	185.5	15.10
84.2	84.6	185.6	186.6	15.20
84.7	85.2	186.7	188.0	15.30
85.3	85.8	188.1	189.3	15.40
85.9	86.3	189.4	190.4	15.50
86.4	86.9	190.5	191.7	15.60
87.0	87.4	191.8	192.8	15.70
87.5	88.0	192.9	194.1	15.80
88.1	88.5	194.2	195.2	15.90
88.6	89.1	195.3	196.6	16.00
89.2	89.6	196.7	197.7	16.10
89.7	90.2	197.8	199.0	16.20
90.3	90.8	199.1	200.3	16.30
90.9	91.3	200.4	201.4	16.40
91.4	91.9	201.5	202.7	16.50

Somapacitan 15mg/1.5ml - Dose Level 0.18mg/kg				
92.0	92.4	202.8	203.8	16.60
Weight (kg)		**Weight (lb)**		
Start	**End**	**Start**	**End**	**Dose**
92.5	93.0	203.9	205.1	16.70
93.1	93.5	205.2	206.3	16.80
93.6	94.1	206.4	207.6	16.90
94.2	94.6	207.7	208.7	17.00
94.7	95.2	208.8	210.0	17.10
95.3	95.8	210.1	211.3	17.20
95.9	96.3	211.4	212.4	17.30
96.4	96.9	212.5	213.7	17.40
97.0	97.4	213.8	214.8	17.50
97.5	98.0	214.9	216.2	17.60
98.1	98.5	216.3	217.3	17.70
98.6	99.1	217.4	218.6	17.80
99.2	99.6	218.7	219.7	17.90
99.7	100.0	219.8	220.6	18.00

10.9 Appendix 9 Technical complaints: Definition and procedures for recording, evaluation, follow-up and reporting

10.9.1 Definition of technical complaint

A technical complaint is any written, electronic or oral communication that alleges product (medicine or device) defects. The technical complaint may be associated with an AE but does not concern the AE itself.

Examples of technical complaints:

- Problems with the physical or chemical appearance of study interventions (e.g., discoloration, particles or contamination)
- Problems with packaging material including labelling
- Problems related to devices (e.g., to the injection mechanism, dose setting mechanism, push button or interface between the pen-injector and the needle)

Time period for detecting technical complaints

All technical complaints which occur from the time of receipt of the product at site until the time of the last usage of the product must be collected for products predefined on the technical complaint form.

10.9.2 Recording and follow-up of technical complaints

Reporting of technical complaints to Novo Nordisk

For contact details for Customer Complaint Center, please refer to Attachment I.

Technical complaints on products allocated to a participant must be reported on a separate technical complaint form:

1. For products with Kit ID: One technical complaint form must be completed for each affected Kit ID.
2. For products without Kit ID: One technical complaint form must be completed for each batch, code or lot number.

Timelines for reporting technical complaints to Novo Nordisk

The investigator must complete the technical complaint form in the CRF within:

- 24 hours if related to an SAE
- 5 days calendar for all other technical complaints

If the CRF is unavailable, or when reporting a technical complaint on a product that is not yet allocated to a participant, the information must be provided on a paper form to Customer Complaint Center, Novo Nordisk, within the same timelines as stated above. When the CRF becomes available again, the investigator must enter the information on the technical complaint form in the CRF.

Follow-up of technical complaints

The investigator is responsible for ensuring that new or updated information will be recorded on the originally completed form.

Collection, storage and shipment of technical complaint samples

The investigator must collect the technical complaint sample and all associated parts and notify the monitor within 5 calendar days of obtaining the sample at site. The sample and all associated parts must be sent as soon as possible to Customer Complaint Center, Novo Nordisk, together with a copy of the completed technical complaint form. The technical complaint sample should contain the batch, code or lot number and, if available, the Kit ID. If the technical complaint sample is unobtainable, the reason must be stated on the technical complaint form. If several samples are shipped in one shipment, the sample and the corresponding technical complaint form should be kept together.

Storage of the technical complaint sample must be done in accordance with the conditions prescribed for the study intervention.

10.9.3 Reporting of technical complaints for products not included in the technical complaint form

Technical complaints on products not included in the technical complaint form should be reported to manufacturing holder.

10.10 Appendix 10: Mitigations to ensure participant safety and data integrity during an emergency situation

10.10.1 Definition and scope of appendix

A major emergency is defined as a situation that causes substantial restrictions to study site access for participants and/or sponsor representatives.

In case local restrictions due to a major emergency (e.g., COVID-19 outbreak, hurricanes, floods) lead to lock-down of a site, the site must contact Novo Nordisk to allow for implementation of mitigations mentioned in this appendix based on mutual agreement.

According to local regulation, health authorities and independent ethics committees should be notified in case elements of the emergency appendix are activated.

This appendix indicates the minimum requirements for assessments that should be performed during a lock-down, but sites should always try to follow the assessments outlined in the original flowchart (Section 1.2) to the extent possible. Implementation of specific mitigations should be based on assessment of feasibility at the individual site.

Sites should comply with local regulations, requirements and/or guidelines if they are issued.

10.10.2 Visits

Screening (Visit 1) and baseline (Visit 2) should always be performed as on-site visits. If a site is unable to perform these visits on-site, screening of new participants at that site should be on hold until on-site visits are possible.

Visit 7 should be performed as an on-site visit, if in any way possible. If visit 7 cannot be performed within the visit window, then the visit should be performed as soon as possible when an on-site visit is possible again, even if the visit will be performed outside the visit window. The visit window for visit 7 can be extended for up to 1 month. A phone or video contact between the investigator/clinical qualified site staff and the participant and the participant's parent(s)/participant's LAR should be performed at the planned time of the visit to ensure safety of the participant. During this phone or video contact, AEs should be collected, and subsequently assessed and reported timely in the eCRF. If another on-site visit is planned around the same time as the postponed visit 7, visit 7 should always be given the highest priority. After the postponed visit 7, the participants should return to the planned visit schedule based on baseline (e.g., if visit 7 is postponed to the date originally planned for visit 8, the participant's next visit should be visit 9 in accordance with original visit schedule. The investigator should provide a reason for why visit 8 is not performed in the eCRF.

Other on-site visits (Visits 3–6 and 8–18) can be converted to remote visits (video, phone or similar) or home or off-site visits.

If the end of treatment visit cannot be performed on-site, using remote (video, phone or similar) or home or off-site visits within the given visit window, the visit window for the assessment can be extended for up to 3 months.

At each visit, the investigator must indicate in the CRF how the visit was performed and specify the reason for the preferred assessment method.

10.10.3 Assessments

Assessments used for safety or the confirmatory endpoints (i.e., height measurements, x-ray, IGF-I) should be prioritised. The preferred order for the method of assessment is: on-site, video, phone, home visit.

Height measurements, TTE and x-ray measurements are only to be performed during on-site visits.

Specifications regarding how to perform these assessments using remote visits or as home visits will be provided by Novo Nordisk or the vendor engaged by Novo Nordisk. Specifications will include training for raters performing remote assessments and adoption of modifications for equivalent administration of assessments using remote visits (video, phone or similar).

Local laboratories or diagnostic facilities can be used for blood sampling and ECG at the investigator's discretion if on-site visits are not possible or in case of temporary lockdown of the central laboratory. Only findings meeting the definition for an AE (refer to Appendix 3 (Section 10.3)) should be reported in the CRF.

Home measurements of weight for dosing calculations can be performed if on-site visits are not possible and if deemed feasible for the participant. Only findings meeting the definition for an AE (refer to Appendix 3 (Section 10.3)) should be reported in the CRF.

If the assessments cannot be performed as outlined above, they should be performed at the first possible timepoint following the originally scheduled visit in agreement with Novo Nordisk.

10.10.4 Study intervention

Alternative dispensing methods of study intervention may be implemented, and details will be communicated and documented. The dispensing options will be provided by Novo Nordisk A/S and will be based on options and requirements at country level and if permitted by local regulations.

10.11 Appendix 11 Country-specific requirements

Korea: Section 5.1, ISS specific inclusion criteria:

Normal GH secretion (GH peak above or equal to 10 ng/ml) during GH stimulation test.

Korea: Section 6.2, Preparation, handling, storage and accountability

If required by site policy, used and partially used trial products can be discarded immediately after drug accountability and only unused trial products and empty packaging will be stored until reconciliation by monitor.

Empty packaging will be used for the monitor to perform reconciliation of used trial product.

Netherlands: Section 1.2, Flowchart:

Full day of birth can only be used if there is a strong need related to the hypothesis of the trial. Generally only Year of Birth is to be used.

Netherlands: Section 8.2.6, Pregnancy testing:

The current EU CTFG guideline ‘Recommendations related to contraception and pregnancy testing in clinical trials' must be followed.

Poland: Section 8.2.6, Pregnancy testing:

The current EU CTFG guideline ‘Recommendations related to contraception and pregnancy testing in clinical trials' must be followed.

Poland: Section 10.1.13, Indemnity statement:

Novo Nordisk carries liability for the study exclusively in the scope defined by the applicable laws and in particular by the Civil Code and the Pharmaceutical Law dated 6 September 2001. In order to support potential claims for liability attributable to the study, Novo Nordisk and Investigator are covered by the Insurance Policy issued according to applicable Polish law.

Poland: Section 10.4.2, Contraceptive guidance:

The current EU CTFG guideline ‘Recommendations related to contraception and pregnancy testing in clinical trials' must be followed.

Spain: Section 8.2.6, Pregnancy testing:

The current EU CTFG guideline ‘Recommendations related to contraception and pregnancy testing in clinical trials' must be followed.

Spain: Section 10.4.2, Contraceptive guidance:

The current EU CTFG guideline ‘Recommendations related to contraception and pregnancy testing in clinical trials' must be followed.

United States: Section 1.2: Flowchart:

A fundoscopic examination should be performed at baseline and according to local practice.

United States: Section 2.3.1: Risk assessment

A fundoscopic examination should be performed at baseline and according to local practice.

United States: Section 8.2.1, Physical examinations:

A fundoscopic examination should be performed at baseline and according to local practice.

United States: Section 10.1.1, Regulatory and ethical considerations:

FDA form 1572:

For US sites:

• Intended for US sites

• Conducted under the IND

• All US investigators, as described above, will sign FDA Form 1572

For sites outside the US:

• Intended for participating sites outside of the US

• Not conducted under the IND

• All investigators outside of the US will not sign FDA form 1572

Novo Nordisk will analyse and report data from all sites together if more than one site is involved in the study.

United States: Section 10.1.2, Financial disclosure

Verification under disclosures per Code of Federal Regulations (CFR) of Financial Conflict of Interest.

United States: Section 10.1.10, Retention of clinical study documentation

Although 21 CFR 312.62(c) and 21 CFR 812.140(d) require 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified, we will be following the global retention requirements specified in the protocol of 25 years.

10.12 Appendix 12: Abbreviations

ADA	anti-drug antibodies
ADHD	attention deficit hyperactivity disorder
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical classification system
CFR	Code of Federal Regulations
CGH	comparative genomic hybridization
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CRF	case report form
CSR	clinical study report
CTFG	clinical trials facilitation and coordination group
DFU	directions for use
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DPS	data points set
ECG	electrocardiogram
eCRF	electronic case report form
ED	end diastolic
EEA	European economic area
EMA	European medicines agency
EU	European Union
FAS	full analysis set
FDA	U.S. Food and Drug Administration
FDAAA	FDA Amendments Act
FPFV	first patient first visit
GCP	Good Clinical Practice
GH	growth hormone
GHD	growth hormone deficiency
GH-INJ-CTB-Child	Growth Hormone Injection - Child Treatment Burden - Child
GH-PPQ-Child	Growth Hormone Patient Preference Questionnaire - Child
GLP-1	glucagon-like peptide-1

H	height
HbA_{1c}	glycated haemoglobin
HDL	high-density lipoprotein
HV	height velocity
IB	investigator's brochure
ICH	International Council for Harmonisation
IEC	independent ethics committee
IgE	immunoglobulin E
IGF-1	insulin-like growth factor 1
IGFBP-3	insulin-like growth factor binding protein-3
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalised ratio
IRB	institutional review board
ISS	idiopathic short stature
IVSed	end-diastolic interventricular septum thickness
LAR	legally acceptable representative
LDL	low-density lipoprotein
LVIDed	end-diastolic left ventricular internal diameter
LVIDes	end-systolic left ventricular internal diameter
LVOT	left ventricular outflow tract
LVPWed	end-diastolic left ventricular posterior wall thickness
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed model for repeated measurements
MPH	midparental target height
NAH	near adult height
NS	Noonan syndrome
NYHA	New York Heart Association
PAS	participant analysis set
PCD	primary completion date
PD	pharmacodynamic
PK	pharmacokinetic
PPQ	patient preference questionnaire
PRO	patient reported outcome
PT	prothrombin time
PTB	patient treatment burden
PTT	partial thromboplastin time

QTL	quality tolerance limits
RAS-MAPK	rat sarcoma-mitogen activated protein kinase
rhGH	recombinant human growth hormone
RTSM	Randomisation and Trial Supply Management
RVIDed	end-diastolic right ventricular internal diameter
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	safety analysis set
SD	standard deviation
SDS	standard deviation score
SGA	small for gestational age
SH	sitting height
SHOX	short stature homeobox
SIF	safety information form
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
TH	target height
TMM	Trial Materials Manual
TS	Turner syndrome
TTE	transthoracic echocardiogram
UK	United Kingdom
ULN	upper limit of normal
US/USA	United States of America
WOCBP	woman of childbearing potential

10.13 Appendix 13: Protocol amendment history

The protocol amendment summary of changes table for the current protocol version is located directly before the table of contents.

Protocol version 4.0 (30 March 2023)

This modification is considered to be non-substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.[1]

Overall rationale for preparing protocol, version 4.0:

The overall rationale for updating the protocol is to clarify the phrasing of Exclusion criteria 10. In addition, the benefit/risk section 2.3 has been updated as requested by Health Authorities. Detailed information about the changes is outlined in the below table.

Section # and name	Description of change	Brief rationale
Section 1.1 Synopsis	Exclusion criteria 8 updated to also include intracranial cysts: History or known presence of any malignancy, intracranial tumour, or intracranial cyst.	To clarify that intracranial cysts are covered by this exclusion criteria.
Section 2.3.1 Risk assessments	Table 2-1 on procedural risks updated: Adrenocortical insufficiency, hypothyroidism and medication errors added.	To comply with request from Health Authorities.
Section 5.2 Exclusion criteria	Exclusion criteria 10 updated to also include intracranial cysts: History or known presence of any malignancy, intracranial tumour, or intracranial cyst.	To clarify that intracranial cysts are covered by this exclusion criteria.
Section 8 Blood sampling	Blood volume has been updated for additional NS tests.	Request from central laboratory to have sufficient blood for genetic analysis.
Section 8.2.4 Transthoracic echocardiogram	Editorial changes	For clarification.
Section 10.5 Appendix 5 Genetics	The following paragraph deleted from the Turner Syndrome (TS) part: 'Only staff at the relevant engaged special laboratory will have access to the samples and adequate measures to protect confidentiality will be ensured. When the collected samples have been analysed, the samples will be destroyed.'	Information deleted as no special laboratory has been engaged to conduct lymphocyte chromosomal analysis for TS participants.
Section 10.8 Appendix 8 Dosing table	The dosing table (Table 10-8) was extended to cover a weight up to 125 kg. A dose may be split into equal administrations.	To provide guidance for dosing of participants with a weight above 100 kg.
Section 10.13, Appendix 13 Protocol amendment history	Appendix updated with summary of changes table from previous protocol version.	To contain amendment history in accordance with sponsor process.

Protocol version 3.0 (21 December 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.[1]

Overall rationale for preparing protocol, version 3.0:

The overall rationale for updating the protocol is to follow a request by the U.S. Food and Drug Administration (FDA) to the pivotal phase 3 study NN8640-4467 regarding dose reduction due to elevated IGF-I levels prior to 6 months after treatment initiation.

Section # and name	Description of change	Brief rationale
Throughout the document	'Molecular genetic testing' is changed to 'genetic testing'.	To use more correct wording.
Section 1.2 Flowchart	'if applicable' added to flowchart footnote c to align with information in section 8.2.6.	To correct an error in previous protocol versions.
Section 6.5.1 Dose reduction criteria	The following sentence is deleted: 'The first dose reduction should take place no earlier than 6 months after treatment initiation (Visit 2).' to allow for dose reduction prior to 6 months treatment.	To align with process in study NN8640-4467 where this update was requested by the FDA.
Section 6.8 Concomitant therapy	The following has been deleted: '(primary endpoint)'.	To correct an error in previous protocol version.
Section 8.2.3 Electrocardiograms	Added that a qualified specialist can evaluate the electrocardiogram recordings.	To ensure flexibility and quality in the evaluations.
Section 8.2.4 Transthoracic echocardiograms	Added that a qualified specialist can evaluate the findings from the transthoracic echocardiogram examinations.	To ensure flexibility and quality in the evaluations.
Section 8.6 Genetics Section 10.5, Appendix 5 Genetics	Paragraph related to Noonan syndrome genetic testing has been updated.	To clarify the Noonan syndrome genetic testing process for the site staff and to clarify that if a relevant mutation is identified no further testing is needed.
Section 9.3.6 Other analyses	Table 9-2 updated to reflect that the time frame for evaluation of 'Change in bone age' is 'From screening (visit 1) to visit 9 (week 52).' instead of 'From screening (visit 1) to visit 7 (week 26).'	To align X-ray assessment timepoints throughout the protocol.
Section 10.13, Appendix 13 Protocol amendment history	Section 10.13, Appendix 13 is included.	To summarise content of previous amendment in accordance with sponsor process.

Protocol version 2.0 (21 October 2022)

This amendment is considered to be substantial based on the criteria set forth in Article 2(13) of Regulation (EU) No 536/2014 of the European Parliament and the Council of 16 April 2014.[1]

Overall rationale for preparing protocol, version 2.0:

The overall rationale for updating the protocol is to update the inclusion criteria, so that the study will include female participants equal to or above 10.0 years and below 18.0 years at screening and male participants equal to or above 11.0 years and below 18.0 years at screening.

Section # and name	Description of change	Brief rationale
Throughout the document	'younger and older children' has been updated to 'children' to reflect the included participants: females equal to or above 10.0 years and below 18.0 years at screening and male participants equal to or above 11.0 years and below 18.0 years at screening.	Based on Health Authority advice, children below the age of 2.5 years are not to be enrolled in this study.
Throughout the document	Information related to children below the age of 2.5 years has been deleted.	Based on Health Authority advice, children below the age of 2.5 years are not to be enrolled in this study.
Throughout the document	Differentiation between 'the two age groups' is no longer applicable as the protocol now only includes participants equal to or above 10.0 years (females) or 11.0 years (males) and below 18.0 years at screening.	Based on Health Authority advice, children below the age of 2.5 years are not to be enrolled in this study.
Throughout the document	Reference to requirements specific for either the younger or the older age group have been deleted.	As the younger age group is no longer included, there is only one age group.
Section 1.1 Synopsis Section 3 Objectives, endpoints and estimands	The following wording '…and if no ancillary therapy were available.' has been deleted from the primary estimand.	To correct an error in previous protocol version.
Section 1.1 Synopsis Section 4.1 Overall design Section 9.5 Sample size determination	Number of participants is updated to up to 50 participants enrolled and at least 40 participants are planned to complete the study.	The planned number of participants has been lowered to reflect that children below the age of 2.5 years are no longer part of the study.
Section 1.2 Flowchart Section 8.1.5 Clinical Outcome Assessments Section 9.3.6 Other analyses	The clinical outcome assessment questionnaire 'Growth Hormone Injection - Parent Treatment Burden (GH-INJ-PTB)' has been deleted. Table 8-1 has been updated.	The questionnaire is no longer applicable as children below the age of 2.5 years are no longer part of the study.
Section 2.3.1 Risk assessment Section 6.1 Study interventions administered Section 10.8, Appendix 8 Dosing table	The description of pen-injectors containing trial product strength 5 mg/1.5 mL and 10 mg/1.5 mL has been deleted. Table 6-1 has been updated. Dosing tables for the pen-injectors containing trial product strength 5 mg/1.5 mL and 10 mg/1.5 mL have been deleted.	The pen-injectors containing trial product strength 15 mg/1.5 mL will cover the treatment of the entire revised study population.

Section # and name	**Description of change**	**Brief rationale**
Section 8.1.1 Body measurements Section 8.2 Safety assessments Section 9.3.3 Secondary endpoints/estimands analysis Section 9.3.6 Other analyses Section 10.7, Appendix 7 Tool for evaluation of inclusion criteria for height Section 10.10.3 Assessments	Information about length measurements and crown-to-rump measurements has been deleted. Table showing 'Overview of supportive secondary Efficacy endpoints' (Table 9-1), table showing 'Overview of other parameters' (Table 9-2) and 'Tool to assess Inclusion criteria – Impaired height' (Table 10-7) have been updated. Table showing 'Tool to assess Inclusion criteria – Impaired length' (previous Table 10-8) has been deleted.	The included participants are able to sit and stand and therefore height and sitting height are applicable.
Section 10.8, Appendix 8 Dosing tables	Unit (mg) added to the right column of 'Dose table for 0.24 mg/kg somapacitan – 15 mg/1.5 mL strength' (current Table 10-8).	To correct omission in previous version of the protocol.

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