Protocol

Study ID: NN8640-4787

REAL 10

A Non-Interventional, Observational, Registry-Based Study to Investigate Long-Term Safety and Clinical Parameters of Somapacitan Treatment in Paediatric Patients with Growth Hormone Deficiency During Routine Clinical Practice.

Non-interventional (NIS) post authorisation safety study (PASS)

Redacted protocol
Includes redaction of personal identifiable information only.

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PASS information

Title	A non-interventional, observational, registry-based study to investigate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with growth hormone deficiency during routine clinical practice.
Protocol author	[redacted], [redacted], Novo Nordisk A/S [redacted]
Protocol version identifier	3.0
Date of last version of protocol	Not applicable
EU PAS Register number	Pending
Active substance	Somapacitan; ATC code: H01AC07
Medicinal product	Sogroya®
Product reference	EU/1/20/1501
Procedure number	EMEA/H/C/005030/MEA/005
Marketing authorisation holder(s)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
Joint Post Authorisation Safety Study (PASS)	No
Research question and objectives	**Primary objective** To investigate long-term safety of somapacitan treatment in paediatric patients with growth hormone deficiency (GHD) in the setting of routine clinical practice with special focus on neoplasms and type 2 diabetes mellitus (T2DM). **Secondary objective** To investigate safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice. To compare the occurrence of adverse drug reactions including neoplasms and T2DM in patients treated with somapacitan with historical data from literature (NordiNet® IOS, ANSWER studies and GeNeSIS registry) of paediatric GHD patients treated with daily somatropin.
Country(-ies) of study	NN8640-4787 is a registry-based study and data for this study will be drawn from the Global Registry for Novel Therapies in Rare Bone and Endocrine Conditions (GloBE-Reg).

Marketing authorisation holder(s)

Marketing authorisation holder (MAH)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
MAH contact person	[redacted] Novo Nordisk A/S Vandtårnsvej 108-114 2860 Søborg, Denmark

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2 List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ATC	anatomical therapeutic chemical (classification system)
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOS	end of study
EU PAS	The EU electronic register of post-authorisation studies maintained by the European Medicines Agency
FPFV	first patient first visit
GH	growth hormone
GHD	growth hormone deficiency
GPP	Good pharmacoepidemiology practice
GloBE-Reg	Global Registry for Novel Therapies in Rare Bone and Endocrine Conditions
GVP	Good pharmacovigilance practice
hGH	human growth hormone
IEC	Independent Ethics Committee
IGF-I	insulin-like growth factor 1
IRB	Institutional Review Board
LAR	legally acceptable representative
LPLV	last patient last visit
MAH	marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	non-interventional Study
PASS	post authorisation safety study
PT	preferred term
RMP	risk management plan
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
SDS	standard deviation score
SIR	standardised incidence ratio
SOC	system organ class
SmPC	summary of product characteristic

T2DM	type 2 diabetes mellitus
UTN	universal trial number

3 Responsible parties

Novo Nordisk A/S will be responsible for the preparation of the protocol.

In this document physician/treating physician refers to the individual overall responsible for entering data from the paediatric patient with growth hormone deficiency (GHD) into the Global registry for novel therapies in rare bone and endocrine conditions (GloBE-Reg).

GloBE-Reg is an international consortium-led registry project owned by the University of Glasgow, with industry partners (including Novo Nordisk A/S), major professional endocrine societies, and patient representatives, collecting real-world data on the safety and clinical parameters of several medicinal products (including somapacitan) in the field of rare bone and endocrine conditions. The data for this study will be drawn from GloBE-Reg.

4 Abstract

4.1 Title

A non-interventional, observational, registry-based study to investigate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with growth hormone deficiency during routine clinical practice.

4.2 Milestones

Milestone	Planned date
Start of data collection – First patient first visit (FPFV)	Q4 2024
Last patient first visit – end of study recruitment	5-year recruitment period from Q4 2024
Interim report	Q4 2030 (6 years from start of data collection)
Last patient last visit (LPLV)	Planned to be conducted until Q3 2034
End of data collection – defined as data base lock	Q4 2034
Final report of study results	Q4 2035
Study progress reports	To follow PSUR timelines[a]

[a]Annual progress reports, submitted with PSUR (when applicable).

4.3 Rationale and background

Sogroya® (somapacitan) (hereafter only referred to as somapacitan) is a long-acting human growth hormone (hGH) derivative, with a single amino acid substitution in the backbone to which a non-covalent albumin binding moiety has been attached. Somapacitan is intended for once weekly subcutaneous administration with the aim of reducing injection frequency and treatment burden and potentially decreasing the barrier to initiating and/or maintaining replacement therapy in GHD.[1, 2] The mechanism of action of somapacitan is via insulin-like growth factor 1 (IGF-I).[1, 2] Daily growth hormone (GH) injections can be burdensome for paediatric patients and their caregivers, disrupting and interfering with daily life. This could lead to non-adherence to prescribed replacement therapy and suboptimal clinical outcomes.[3, 4]

As part of the risk management plan (RMP) for somapacitan, this non-interventional, observational, registry-based study is planned to evaluate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice.

The data for this study will be drawn from GloBE-Reg (see Section 9.4). In line with European Medicines Agency (EMA) guidelines[5] (EMA/426390/2021, current version), the GloBE-Reg is an international consortium-led registry project owned by the University of Glasgow, with industry partners (such as Novo Nordisk A/S), major professional endocrine societies, and patient representatives, collecting real-world data on the safety and clinical parameters of several medicinal products (including somapacitan) in the field of rare bone and endocrine conditions.

This registry-based study will only investigate paediatric GHD patients from GloBE-Reg who have been treated with somapacitan.

4.4 Research question and objectives

4.4.1 Primary objective

To investigate long-term safety of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice with special focus on neoplasms, medication errors and T2DM.

4.4.2 Secondary objective

- To investigate safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice.
- To compare the occurrence of adverse events (AEs), serious adverse events (SAEs), serious adverse drug reactions (serious ADRs) including neoplasms and T2DM in patients treated with somapacitan with historical data from literature (NordiNet® IOS, ANSWER studies and GeNeSIS registry) of paediatric GHD patients treated with daily somatropin.

4.5 Study design

This is a non-interventional, multi-national, single-treatment arm, observational, registry-based study to investigate the long-term safety and clinical parameters of somapacitan in paediatric patients with GHD under routine clinical practice conditions. The study population will consist of at least 400 paediatric GHD patients from the GloBE-Reg registry treated with once-weekly somapacitan who meet the inclusion criteria.

Patients will be treated with commercially available somapacitan according to routine clinical practice at the discretion of the treating physician.

The total duration of the study is planned to be 10 years consisting of a 5-year recruitment period in the GloBE-Reg followed by at least a 5-year follow-up period. The study is planned to be conducted from Q4 of 2024 until Q4 of 2034.

4.6 Population

The study population will consist of at least 400 paediatric GHD patients (both naïve and non-naïve) from the GloBE-Reg registry treated with once weekly somapacitan.

4.6.1 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered ‘yes’.

1. Treated with commercially available somapacitan according to local practice at the discretion of the physician.
2. Primary confirmed diagnosis of GHD as per local practice.
3. Male or female below 18 years of age at the time of signing informed consent in the GloBE-Reg.

4.6.2 Exclusion criterion

For an eligible patient, the following exclusion criterion must be answered 'no'.

1. Patients with active malignancy or in treatment for active pre-existing malignancy.

4.7 Variables

For the primary and secondary endpoints, data on the following variables will be extracted from the GloBE-Reg registry.

The number of ADRs from baseline to the EOS will be recorded as primary endpoint. Safety endpoints such as number of AEs, SAEs, serious ADRs, medication errors, incident neoplasm, incident T2DM from baseline (week 0) to EOS will be recorded as secondary endpoints. Additionally, other clinical parameters will also be recorded as secondary endpoints. Safety data will be collected by GloBE-Reg for the registered paediatric patients with GHD.

Incidence rates for neoplasms will be compared to incidence rates published in the combined NordiNET/ANSWER studies.[6-8] Similarly, incidence rates for T2DM will be compared to published results from the GeNeSIS study.[9, 10] From both studies, the incidence rates for isolated GHD will be used for the comparison.

4.8 Data Sources

The data for this study will be drawn from GloBE-Reg. .

4.9 Study sample size

The study is planned for the sample size of at least 400 patients (inclusive of both naïve and non-naïve).

4.10 Data analysis

Data from at least 400 paediatric patients with GHD (inclusive of both naïve and non-naïve) will be analysed using safety analysis set (SAS). The number of ADRs from baseline to EOS will be analysed. EOS will differ from patient to patient. AEs, SAEs and serious ADRs during the study period will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term (PT). This summary is displayed with number and proportion of patients with at least one event, number of events and event rate (events per 100 patient-years of exposure).

The combined data from NordiNet® IOS and ANSWER studies will be used as external comparator for the occurrence of ADRs including neoplasms[6-8]. Data from the GeNeSIS registry will be used as external comparator for the occurrence of T2DM.[9, 10] The aggregated data from isolated GHD from both publications will be used for the comparison.

The standardised incidence ratio (SIR) with a 95% confidence interval will be used as an additional estimate for neoplasms and new-onset T2DM.

A statistical analysis plan (SAP) will be written, including a detailed elaboration of the statistical analyses. The SAP will be finalised before database lock. Data from the registry will be analysed and reported.

5 Amendments and updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	28 February 2024	General update of the protocol	Update	Following PRAC review
2	17 July 2024	General update of the protocol	Update	Following PRAC review

6 Milestones

Milestone	Planned date
Start of data collection	Q4 2024
End of data collection	Q4 2034
Study progress report	To follow PSUR timelines[a]
Interim report	Q4 2030 (6 years from start of data collection)
Final report of study results	Q4 2035

[a]Annual progress reports, submitted with PSUR (when applicable).

7 Rationale and background

Somapacitan is a long-acting hGH derivative, with a single amino acid substitution in the backbone to which a non-covalent albumin binding moiety has been attached. Somapacitan is intended for once weekly subcutaneous administration with the aim of reducing injection frequency and treatment burden and potentially decreasing the barrier to initiating and/or maintaining replacement therapy in GHD.[1, 2] The mechanism of action of somapacitan is via IGF-I.[1, 2] Daily GH injections can be burdensome for paediatric patients and their caregivers, disrupting and interfering with daily life. This could lead to non-adherence to prescribed replacement therapy and suboptimal clinical outcomes.[3, 4]

As part of the European marketing authorisation for somapacitan for the treatment of paediatric patients with GHD, Novo Nordisk A/S received a requirement from the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMA) to conduct a non-interventional, observational registry-based study to investigate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice.

As per the RMP, the primary aim of this non-interventional, observational registry-based study is to assess the long-term safety profile of somapacitan with special focus on the important potential risks (neoplasm, T2DM, and medication errors). This post authorisation safety study (PASS) will also provide additional long-term safety information (AEs, SAEs and serious ADRs) and will further substantiate the evaluation of potential risks in relation to treatment with somapacitan.

The secondary aim is to investigate the clinical parameters in patients treated with somapacitan with regards to changes in height velocity SDS, height SDS, IGF-I SDS, and bone age.

To draw clinically relevant conclusions on long-term safety of somapacitan, this study will compare safety data with historical data from literature (NordiNet® IOS, ANSWER[6-8] studies and GeNeSIS[9, 10] registry) of paediatric GHD patients treated with daily somatropin.

Brief description of these external comparators has been outlined below:

NordiNet® IOS (study GHLIQUID-3676) and ANSWER (study HGH-2149)

The NordiNet® International Outcome Study (IOS) and the ANSWER (American Norditropin® Studies: Web Enabled Research) programs were post-marketing non-interventional studies that collected data concerning the treatment management and outcomes of patients, both paediatric and adult, who were prescribed Norditropin® in a real-world setting. The two studies were complementary with common design where NordiNet® IOS covered Europe and Middle East (2006-2016) and ANSWER covered the US (2002-2016). The combined studies enrolled a total of 37,702 paediatric patients with short stature due to different aetiologies of which around 22,000 patients had GHD. The studies included both GH treatment naïve and non-naïve patients. These real-world clinical practice studies of paediatric patients with GHD, treated with Norditropin® supported the long-term effectiveness and safety profile of this treatment in the specified populations.[6,11] The NordiNet® and ANSWER studies evaluated the safety of GH treatment as frequency and incidence rates of SAEs and/or treatment-related AEs including incidence rates of neoplasms.

GeNeSIS - Genetics and Neuroendocrinology of Short Stature International Study

GeNeSIS was an international, observational, open-label and post-authorisation safety study in children with growth disorders covering Canada, France, Germany, Japan, and the US (1999-2015). Data from 11,686 GH-treated paediatric patients, 7,523 with GHD[9], were analysed for diabetes incidence. Baseline diabetes prevalence was determined from a GH-naïve subgroup. Prevalence and incidence (by SIR) were compared with results from patients aged less than 20 years in the U.S. SEARCH for Diabetes in Youth study.[10]

The data for this registry-based study will be drawn from GloBE-Reg (see Section 9.4). In line with EMA guideline on registry-based studies[5] (EMA/426390/2021, current version), GloBE-Reg is an international consortium-led registry project owned by the University of Glasgow, with industry partners (including Novo Nordisk A/S), major professional endocrine societies, and patient representatives. GloBE-Reg collects real-world data on the safety and clinical parameters of several medicinal products (including somapacitan) in the field of rare bone and endocrine conditions.

This registry-based study will only investigate paediatric patients from the GloBE-Reg who have GHD and have been treated with somapacitan.

Additional information on each of the safety concerns to be addressed by this PASS is provided below.

Long term safety

Novo Nordisk A/S has included ‘long-term safety’ as missing information in the RMP for paediatric GHD.

The paediatric pivotal trial NN8640-4263, included in the submission package, included safety information from subjects with up to one year (52 weeks) of somapacitan exposure (i.e., short term/intermediate term). No safety data for patients with >1 year (52 weeks) of somapacitan exposure were included. Therefore, ‘long term safety’ is classified as missing information in the RMP and is included as the primary objective in this PASS.

Neoplasms

GH is anabolic and mitogenic, and IGF-I is antiapoptotic. Both hormones can cause proliferation of normal and malignant cells. In general, hGH treatment increases the blood IGF-I levels, but data do not generally support a carcinogenic effect of treatment with GH and there is no established relationship between high blood IGF-I levels and the risk of a malignancy.[12-14]

T2DM

Treatment with GH may decrease insulin sensitivity, particularly at higher doses in susceptible patients. Consequently, hyperglycaemia may occur in subjects with inadequate insulin secretory capacity. As a result, previously undiagnosed impaired glucose tolerance and overt T2DM may be unmasked during GH treatment.

Impaired insulin sensitivity is a hallmark of T2DM. This effect of GH has been partly linked to the lipolytic effects of GH resulting in increased plasma levels of free fatty acids, plasma glucose and insulin levels in the hours following injections of hGH.[15, 16]

Medication error

When there are both daily and weekly GH products on the market, there is a risk that the once weekly product might be mistakenly (by the patient/caregiver) administered daily, which could lead to incorrect dose administration rate and overdose.

When patients are used to take their injection daily, there is a risk that this will continue.

No events of medication errors (incorrect dose administration rate) have been reported from completed/ongoing trials for paediatric GHD.

8 Research question and objectives

8.1 Primary objective

To investigate long-term safety of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice with special focus on neoplasms, medication errors and T2DM.

8.2 Secondary objectives

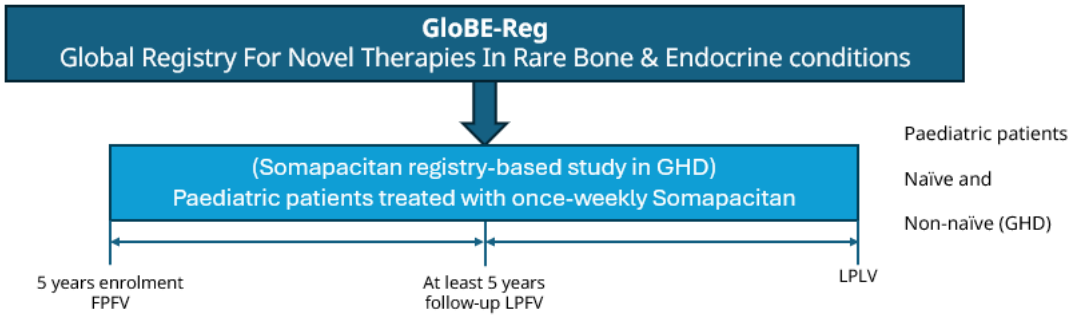
- To investigate safety and clinical parameters of somapacitan treatment in paediatric patients with GHD in the setting of routine clinical practice.
- To compare the occurrence of AEs, SAEs, serious ADRs including neoplasms and T2DM in patients treated with somapacitan with historical data from literature (NordiNet® IOS, ANSWER studies and GeNeSIS registry) paediatric GHD patients treated with daily somatropin.

9 Research methods

9.1 Study design

This is a non-interventional, multi-national, single-treatment arm, observational, registry-based study to investigate the long-term safety and clinical parameters of somapacitan in paediatric patients with GHD under routine clinical practice conditions. The study design is shown schematically in Figure 9-1.

Figure 9-1 Schematic diagram of the study design



Abbreviations: GHD = growth hormone deficiency, FPFV = first patient first visit, LPFV = last patient first visit, and LPLV = last patient last visit.

The study population will consist of at least 400 paediatric GHD patients from the GloBE-Reg registry treated with once-weekly somapacitan and fulfilling the eligibility criteria of the present study (see Sections 9.2.2 and 9.2.3). The total duration of the study is planned for 10 years consisting of a 5-year recruitment period in the registry followed by a follow-up period of at least 5 years. Individual patients will be followed up from inclusion into GloBE-Reg until last routine visit within the full study duration, i.e. individual follow-up time is expected to be above 5 years. Patient data are planned to be collected beyond the age of 18 years and irrespective of discontinuation of somapacitan. The main purpose of this study is to observe patients for long-term safety. The planned study duration is from Q4 2024 until Q4 2034.

9.1.1 Endpoint(s)

The primary endpoint of this study is to report all ADRs from baseline (week 0) to EOS (up to 10 years) to investigate the long-term safety in paediatric patients with GHD under routine clinical practice conditions.

The secondary endpoints and clinical parameters are described in Section 9.3.

External comparators:

The combined data from NordiNet® IOS and ANSWER will be used as an external comparator for the occurrence of ADRs and neoplasms, and data from the GeNeSIS study will be the external comparator for incident T2DM.

- The NordiNet® and ANSWER studies evaluated the safety of GH treatment as frequency and incidence rates of SAEs and/or treatment-related AEs including incidence rates of neoplasms. Both studies evaluated the safety of real-world treatment with Norditropin® for

the indications requiring GH therapy according to normal clinical practice and treating physicians' discretion, including several paediatric indications including GHD.[6-8]

- The GeNeSIS diabetes study included 11,686 GH-treated patients of which, baseline diabetes prevalence was evaluated from a cohort of 8,568 patients (3,368 in the US) who were GH-naïve at study entry. Prevalence and incidence (by SIR) were compared with results from patients aged less than 20 years in the US SEARCH for Diabetes in Youth study.[9, 10]

9.1.2 Treatment of patients

Patients will be treated with commercially available somapacitan according to routine clinical practice at the discretion of the treating physician. The decision to treat a patient with somapacitan will be made at the treating physician's discretion prior to, and independently from, the decision to include the patient in the GloBE-Reg registry. Novo Nordisk A/S will not provide any products for included subjects during the conduct of the study.

Data collection for the GloBE-Reg registry will happen in conjunction with the patient's usual visits in the clinic. Additionally, optional visits are allowed per local standard of care.

9.2 Setting

9.2.1 Study population

The planned number of patients to be included is at least 400 (both naïve and non-naïve).

9.2.2 Inclusion criteria

For an eligible patient, all inclusion criteria must be answered 'yes'.

1. Treated with commercially available somapacitan according to local practice at the discretion of the physician.
2. Primary confirmed diagnosis of GHD as per local practice.
3. Male or female below 18 years of age at the time of signing informed consent in the GloBE-Reg.

9.2.3 Exclusion criterion

For an eligible patient, the following exclusion criterion must be answered 'no'.

1. Patients with active malignancy or in treatment for active pre-existing malignancy.

9.2.4 Rationale for selection criteria

The study population comprises all patients eligible according to the inclusion and exclusion criteria for this registry-based study as well as the inclusion and exclusion criteria defined for inclusion in the GloBE-Reg. The eligibility criteria have been kept to a minimum to ensure that the study population will represent the broader real-world population of paediatric patients with GHD treated with somapacitan.

9.2.5 Withdrawal criteria

The patient or/and the legally acceptable representative (LAR) may withdraw the consent at will at any time.

GloBE-Reg is responsible for the data collected from the registered paediatric patients. As per the registry on which this protocol is based, there are no specific withdrawal criteria outlined for the patients.

The patient/LAR may choose to withdraw from the registry at any point during the study at the discretion of the local treating physician. Any data that has been processed by GloBE-Reg and has already been shared with the treating physician will be marked as 'deleted case from Registry' so that it is not shared with anybody else or re-used. However, these data will still be retained in case they are required in the future for regulatory purposes.

If the participant withdraws consent, Novo Nordisk A/S may retain and continue to use any data collected before such a withdrawal of consent for the purpose of the study or scientific research. Withdrawals from GloBE-Reg would therefore only affect subsequent data extractions for the study. Therefore, the patient will be regarded as lost to follow-up from the date of last data entry in the latest extract of study data from GloBE-Reg before the date of withdrawal.

9.2.6 Visit procedures

No study-related activities (study-related activities are any procedure related to recording of data according to the protocol) may take place before signed informed consent is obtained.

Data collection for the GloBE-Reg registry will happen in conjunction with usual visits in the clinic. As the data for this study will be drawn directly from GloBE-Reg, the visit procedures are not in the scope of this protocol.

9.2.6.1 Study flow chart

Not included.

9.2.6.2 Study visits

Long-term safety and clinical parameters of somapacitan in paediatric patients with GHD will be investigated under routine clinical practice conditions.

9.2.7 Assessments for safety and clinical parameters

Safety Assessment

- **Primary endpoint:** Number of ADRs (from baseline [week 0] to EOS)
- **Secondary endpoints:** AEs, SAEs, serious ADRs, medication errors, incident neoplasm and incident T2DM from baseline (week 0) to EOS will be assessed.

Note: The EOS will differ from patient to patient.

Clinical parameters

For the list of clinical parameters, see Section 9.3.2.2.

9.2.8 Other assessments

Not applicable.

9.3 Variables

9.3.1 Exposure

- Start date of somapacitan treatment
- Initial dose of somapacitan treatment
- Change of dose (date and new dose)

9.3.2 Endpoints and outcomes

9.3.2.1 Primary endpoint

Table 9-1 Safety parameters (primary endpoints)

Endpoint title	Time frame	Unit
Number of ADRs	From baseline (week 0) to EOS[a] (up to 10 years)	Count

[a]EOS will differ from patient to patient

Abbreviations: ADR = adverse drug reaction, EOS = End of study

9.3.2.2 Secondary endpoint(s)

Safety

Table 9-2 Safety parameters (secondary endpoints)

Endpoint title	Time frame	Unit
Adverse events (AEs)	From baseline (week 0) to EOS[a] (up to 10 years)	Count
Serious adverse events (SAEs)	From baseline (week 0) to EOS[a] (up to 10 years)	Count
Serious adverse drug reactions	From baseline (week 0) to EOS[a] (up to 10 years)	Count
Number of medication errors	From baseline (week 0) to EOS[a] (up to 10 years)	Count
Incident neoplasm	From baseline (week 0) to EOS[a] (up to 10 years)	Yes/no
Incident T2DM	From baseline (week 0) to EOS[a] (up to 10 years)	Yes/no

[a]EOS will differ from patient to patient.

Abbreviations: EOS = end of study, T2DM = type 2 diabetes mellitus.

Clinical parameters

Table 9-3 Clinical parameters (secondary endpoints)

Endpoint title	Time frame	Unit
Height velocity	Yearly	Cm/year
Change in Height Velocity SDS	Yearly	-10 to +10
Change in Height SDS	Yearly	-10 to +10
Change in IGF-I SDS	Yearly[a]	-10 to +10

Endpoint title	Time frame	Unit
Change in bone age	Yearly	Years and months
Reaching near adult height[b]	EOS[b]	Yes/no
Change in height SDS in subjects reaching near adult height[b]	From baseline (week 0) to EOS[c] (up to 10 years)	-10 to +10

Note: Near adult height can be defined as: height velocity <2 cm/year over the last 9 months and chronological age >16 years (males) or >15 years (females) or bone age >16 years (males) and > 15 years (females).

[a]This will be reported at shorter intervals if data allows

[b]EOS will differ from patient to patient.

[c]Only for those who are expected to reach near adult height during the study.

Abbreviations: EOS = end of study, IGF-I = insulin-like growth factor 1, SDS = standard deviation score

AEs will be split into all AEs, SAEs and serious ADRs through the evaluation of seriousness and causality entered in GloBE-Reg by the contributing clinics. Seriousness will be categorized into death, life-threatening experience, in-patient or prolongation of existing hospitalization, persistent or significant disability/incapacity or congenital anomaly/birth defect, and important medical event. Causality assessment will be categorized into probable, possible, and unlikely.

9.3.3 Covariates

The following baseline characteristics will be available from the GloBE-Reg data and overlap with the baseline characteristics from NordiNET/ANSWER and GeNeSIS:

- Sex
- Country
- Age at initiation of GH treatment (any GH treatment)
- Duration of GH Treatment at study inclusion (GH naïve or non-naïve patients)
- Height
- Weight
- BMI
- IGF-I
- Bone age
- Medical history of neoplasms
- Medical history of T2DM
- Diabetes risk factors: obesity

9.4 Data sources

The data for this study will be drawn from GloBE-Reg. In line with EMA guidelines[5] (EMA/426390/2021, current version), the GloBE-Reg is an international consortium-led registry project owned by the University of Glasgow, with industry partners (including Novo Nordisk A/S), major professional endocrine societies, and patient representatives, collecting real-world data on the safety and clinical parameters of several medicinal products (including somapacitan) in the field of rare bone and endocrine conditions.

The GloBE-Reg platform was initiated on 1st October 2022.[17] The registry is designed to collect information on any child or adult who is about to start a certain treatment or where treatment is being/has been considered for a bone or endocrine condition. At the time of finalising this protocol,

GloBE-Reg is active in several countries in Europe, US, Asia and South America. Ethics committee approvals have been obtained in these countries.

The present study will investigate the subset of the paediatric patients with GHD from GloBE-Reg treated with somapactitan. As per the protocol, the planned number of patients to be included in the study is at least 400 (both naïve and non-naïve) male or female patients (below 18 years at the time of enrolment) with confirmed diagnosis of GHD. A minimum set of parameters can be extracted from GloBE-Reg e.g., every 6 months.

Details for neoplasms, T2DM and medication errors should be recorded in GloBE-Reg and will be included in the study data for eligible patients.

9.5 Study sample size

The sample size calculations are performed for the primary endpoint (number of ADRs) and based on previous experience from the NordiNet® IOS[6] where 2% of the paediatric patients with GHD experienced an ADR.

Table 9-4 shows the 95% confidence interval for an incidence of 2%, derived using the Wilson-score method.

Table 9-4 Sample size table (Wilson-score method)

Sample size	95% CI
100	(0.55, 7.00)
200	(0.78, 5.02)
300	(0.92, 4.29)
400	(1.02, 3.89)
500	(1.09, 3.64)

Based on the table above, a sample size of at least 400 patients (inclusive of both naïve and non-naïve paediatric patients) would be required to rule out the doubling of the incidence for ADRs. Therefore, the study is planned for the sample size of 400 patients.

9.6 Data management

All data for this study will be drawn from GloBE-Reg (see Section 9.4). GloBE-Reg is responsible for the collection of the data from paediatric patients with GHD treated with somapacitan (see Section 9.3). Data are collected by the collaborating centres during visits as part of the routine clinical practice and are subsequently included in GloBE-Reg. An overview of the data can be found in the GloBE-Reg website.[17,18]

The variables included in this study are listed in Section 9.3.

Extracts from GloBE-Reg will be submitted electronically to Novo Nordisk A/S for inclusion in the interim and final study reports.

Analysis of all study data is the responsibility of Novo Nordisk A/S.

Appropriate measures such as encryption or deletion must be enforced to protect the identity of patients when transmitting data, in all presentations and publications as required by local/regional/national requirements.

9.7 Data analysis

9.7.1 Definition of analysis sets

The safety analysis will be based on the SAS. The SAS will consist of all patients exposed to somapacitan during study period.

9.7.2 Statistical methods

Data of at least 400 paediatric patients will be drawn from the registry (GloBE-Reg) and investigated for long-term safety of somapacitan.

9.7.2.1 Analysis of primary endpoint

The primary endpoint is the number of ADRs from baseline to EOS. EOS will differ from patient to patient.

ADRs during the study period will be summarised by MedDRA SOC and PT. This summary is displayed with number and proportion of patients with at least one event, number of events, and event rate (events per 100 patient-years of exposure).

The combined data from NordiNet® IOS and ANSWER will be used as an external comparator for the occurrence of ADRs.[6] The aggregated data from isolated GHD patients from the NordiNET/ANSWER study will be used for comparison of both baseline characteristics and ADR incidence rates. No statistical comparison is planned due to limitations in the observational nature of the data collection.

The correlation between ADR incidence and duration of somapacitan treatment will be analysed with Spearman rank-order correlation.

9.7.2.2 Analysis of secondary endpoints

Binary secondary endpoints:

The binary secondary endpoints include:

- Incident neoplasm
- Incident T2DM

Incidence rates will be calculated for both endpoints and compared to aggregated data of incident neoplasms from the combined NordiNET/ANSWER study[6] and incident T2DM from the GeNeSIS study.[9] From both studies, the incidence rates for isolated GHD will be used for comparison. The SIR with a 95% confidence interval will be used as an additional estimate for neoplasms and new-onset T2DM.

Count-data secondary endpoints:

The analyses of the following secondary endpoints (counted from the baseline (week 0) to the EOS[a]) will be done in the same way as the analysis of the primary endpoint:

- Number of AEs
- Number of SAEs
- Number of serious ADRs
- Number of medication errors

[a]EOS will differ from patient to patient.

Continuous secondary endpoints

For the following secondary endpoints (clinical parameters), the change will be estimated by length of follow up and treatment duration.

- Height velocity
- Change in height velocity SDS
- Change in height SDS
- Change in IGF-I SDS
- Change in bone age

Patients reaching near adult height will be evaluated at EOS only for those who are expected to reach near adult height during the study. Change in height SDS in subjects reaching near adult height will be calculated from baseline (week 0) to EOS.

Note: Near adult height can be defined as height velocity <2 cm/year over the last 9 months and chronological age >16 years (males) or >15 years (females) or bone age >16 years (males) and >15 years (females).

IGF-I SDS will be used to evaluate treatment adherence assuming an increase in IGF-I SDS represents a response to GH treatment.

To deal with patients switching medication in-study and on-treatment analyses will be performed as defined below. The analyses will be repeated separately for GH treatment naïve and non-naïve patients previously receiving other GH treatment as data allows.

In-study

The observation period represents the time frame during which patients are considered to be part of the study, regardless of their adherence to somapacitan treatment. The in-study period starts at the time of informed consent and ends at the date of whichever comes first:

- EOS visit (last visit within the study duration)
- Withdrawal of informed consent date
- Other (e.g. patient is deceased, or physician is no longer providing data to GloBE-Reg)

On-treatment

This observation period represents the period in which patients are treated with somapacitan. This observation period is a part of the in-study observation period. The on-treatment period starts at the date of treatment start and ends at the first date of any of the following:

- Date of treatment stop of somapacitan

- EOS visit (last visit within the study duration)
- Withdrawal of informed consent date
- Other (e.g. patient deceased or physician no longer providing data to GloBE-Reg)

The following subgroup analyses will be performed if data allows:

- Sex
- Age groups:
  - Females: 0-3, 4-8, 9-14, 15-18, >18 years
  - Males: 0-3, 4-9, 10-15, 16-18, >18 years
- GH treatment dose (GH naive or non-naïve):
  - 0.04≤mg/kg/week≤0.08
  - 0.08<mg/kg/week≤0.16
  - 0.16<mg/kg/week≤0.24
  - 0.24<mg/kg/week≤0.34
- By country/regions
- By Tanner stage 1 and >=2

Age groups are different for females and males due to the different timing in puberty and in growth velocity.[19]

9.8 Quality control

9.8.1 Monitoring procedures

As this is a post marketing, non-interventional study, Novo Nordisk A/S does not have the right to conduct monitoring on a case-to-case basis.

9.8.2 Critical documents

Before starting the study (which is when informed consent is obtained from the first patient), the following documents must be available to Novo Nordisk A/S:

- Regulatory approval and/or notification as required
- Approval/favourable opinion from Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for GloBE-Reg.
- Agreement with GloBE-Reg.

9.8.3 Retention of study documentation

Novo Nordisk A/S will comply with Good Pharmacoepidemiology Practice[20] (GPP) and relevant national legislation related to archiving of study documentation.

Novo Nordisk A/S will retain the documentation pertaining to the study according to company procedure and in accordance with national regulations if they require a longer retention period.

The data collected by GloBE-Reg into the registry will be subject to data retention in accordance with GloBE-Reg's retention procedures.

9.9 Limitations of the research methods

Data collection for this study will reflect routine clinical practice rather than mandatory assessments at pre-specified time points. The study captures data in GloBE-Reg from many different regions and settings. As data collection will reflect national, regional, and local differences in routine clinical practice regarding diagnostics, laboratory analyses, and reporting of events, potential issues may arise due to the study design. These issues may result in heterogeneous reporting of specific outcomes and time points for collection. Therefore, it is important to take these differences into account during the interpretation of data.

AEs are collected into GloBE-Reg based on the answer to the below question:

"Since the last recorded clinical encounter in the GloBE-Reg registry, has the patient experienced any untoward medical occurrence (sign, symptom or disease)"

In addition, the physician is responsible for evaluating the seriousness and causality of the AEs.

The safety endpoints are therefore limited to the physician's evaluation of these questions, and due to the secondary collection of data this evaluation cannot be further investigated.

The data source for the study, GloBE-Reg, captures data from many different regions and settings. This leads to a potentially heterogeneous patient population and different local standard of care and data capture, e.g., local differences in diagnostics, laboratory analyses, and reporting of events. This could result in a risk of information bias.

There is a risk of selection bias in the study, affected by the willingness and/or ability of physicians and patients to participate in GloBE-Reg. In addition, any undiagnosed patients will not be able to participate, and the rate of underdiagnosis may vary between regions. This may lead to a selected patient population, which does not accurately reflect the underlying patient population and may result in limited data on certain subgroups.

The long-term follow-up is a strength of this non-interventional study, but also leads to a risk of loss to follow up.

As with any observational study, there is potential for bias resulting from variable quality and completeness in the information on potential confounders. Age, gender, previous GH treatment and medical history are among the potential confounders, and information on these will be collected to the extent possible. However, potential unmeasured confounding factors cannot be ruled out.

The extent of missing information on IGF-I and other endpoints at EOS visit will be reported in the final report by descriptive summaries and graphical presentations of extent, and pattern of missing data. Missing data will not be imputed.

The proposed external comparators are finalised non-interventional studies and therefore have the same potential limitations as mentioned above. The comparability between the results of the studies and any limitations in the conclusions will therefore be thoroughly discussed in the final study report.

9.10 Other aspects

Not applicable.

10 Protection of human subjects

The study will be conducted in accordance with GPP[20] and in accordance with relevant data privacy laws and internal requirements.

10.1 Informed consent form for study patients

A voluntary, signed and personally dated informed consent form will be obtained from the patient or/and the patient's LAR by GloBE-Reg prior to any study-related activity.

The treating physician must give the patient and the patient's LAR information in a form that the patient and the patient's LAR can read and understand. This includes the use of impartial witness where required.

In obtaining and documenting informed consent, the physician must comply with the applicable local regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki.[21]

If a patient is not of legal age, then the patient's assent must also be obtained according to local requirements.

The task of seeking informed consent can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must sign and date the patient information/informed consent form.

10.2 Data handling

If the patient (or the patient's LAR) withdraws the previously given informed consent, the patient's data will be handled as follows:

- Data already extracted for the study will be used as part of the statistical analysis.
- Data will be deleted/removed from GloBE-Reg if the patient or patient's LAR no longer want to participate in the study. However, the data will still be retained in case they are required in the future for regulatory purposes.

Data will be collected and handled in accordance with local privacy laws and IRB/IEC procedures.

10.3 Institutional Review Boards/Independent Ethics Committee, health authorities and other relevant national institutions/bodies

Study specific documentation (for example study protocol, Patient Information/Informed Consent Form, patient materials) must be submitted to the relevant national bodies as required by national regulation and procedures in the participating countries.

The study must be approved by the IEC/IRB for each participating country and/or other appropriate bodies as required locally.

10.4 Premature termination of the study

Novo Nordisk A/S may decide to stop the study or part of the study at any time. The study may only be terminated prematurely after consultation and in agreement with the relevant regulatory

authorities. This study is being conducted as a RMP requirement to evaluate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with GHD.

If a study is prematurely terminated or suspended, information must be provided to the relevant national bodies as required by national regulation and procedures.

10.5 Responsibilities

For details on responsibilities, see Section 3.

11 Management and reporting of adverse events/adverse drug reactions

11.1 Safety definitions

Adverse Event (AE)

Any untoward medical occurrence in a patient administered/using a product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a product, whether or not it is considered to be related to the product. An AE may be associated with the use of a drug, a medical device or both.

Adverse drug reaction (ADR)

An ADR is a response to a medicinal product which is noxious and unintended. This includes ADR which arises from:

- The use of a product within the terms of the marketing authorisation
- The use of a product outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors
- Occupational exposure.

An ADR may be associated with the use of a drug, a medical device or both.
An ADR is an AE for which the causal relationship between the product and the AE is suspected; that is judged to be possible or probable by either Novo Nordisk A/S or the reporter.

Causality assessment

- 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 an aetiology other than somapacitan

Serious Adverse Event (SAE)

An SAE is an experience that at any dose results in any of the following:

- Death
- Life-threatening experience (actual risk not hypothetically)
- Inpatient hospitalisation or prolongation of existing hospitalisation
- A persistent or significant disability/incapacity or is a congenital anomaly/birth defect
- Important medical events that may not result in death, be life-threatening or require hospitalisation may be considered an SAE, when based upon appropriate medical judgement - they may jeopardise the patient or require medical or surgical intervention to prevent one of the outcomes listed in this definition. Suspicion of transmission of infectious agents must always be considered an SAE.

Note: Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

Serious Adverse Drug Reaction (Serious ADR)

Is an AE that fulfils the criteria for both a SAE and an ADR.

Non-serious

An AE or ADR that does not fulfil the requirement for being an SAE or serious ADR.

Medication error

A medication error is an unintended failure in the drug treatment process that leads to, or has the potential to lead to, harm to the patient. A failure in the drug treatment process does not refer to lack of efficacy of the drug, rather to human or process mediated failure.

Medication errors can therefore be:

- Associated with an ADR
- Not associated with an ADR
- An intercepted medication error ('near miss') is when an intervention caused a break in the chain of events in the treatment process before reaching the patient which would have resulted in a 'potential' adverse drug reaction. This intervention has prevented actual harm being caused to the patient; for example, a wrongly prepared medicine was actually not administered to the patient because the error was noticed by the nurse.
- A potential medication error which is recognition of circumstances that could lead to a medication error and may or may not involve a patient. The term potential medication error refers to all possible mistakes in the prescribing, storing, dispensing, preparation for administration or administration of a medicinal product by all persons who are involved in the medication process. An example is a pharmacist who noticed that the names of two medicines are similar and could clearly lead to product name confusion, but no patient was actually involved or has taken the medicine.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used in a manner not in accordance with the authorised product information.

Off-label use

Situations where a medicinal product is intentionally used for a medical purpose not in accordance with the terms of the marketing authorisation. Examples include the intentional use of a product in situations other than the ones described in the authorised product information, such as a different indication in terms of medical condition, a different group of patients (for example, a different age group), a different route or method of administration or a different posology. The reference terms for off-label use are the terms of marketing authorisation in the country where the product is used.

Overdose

This refers to the administration of a quantity of a medicinal product given per administration or cumulatively, which is above the maximum recommended dose according to the authorised product information. Clinical judgement should always be applied.

11.2 Collection of adverse events and other safety information

The data for the study is based on secondary use of data (collected from GloBE-Reg) and for that Individual Case Safety Reporting (ICSR) will not be performed, in accordance with Good Pharmacovigilance Practice (GVP) module VI.[22] Safety information that will be collected through secondary use of data during the study period includes: ADRs, AEs, SAEs, serious ADRs, incident neoplasm, medication errors and incident T2DM (baseline [week 0] to EOS).

Voluntary reporting of any safety information by the treating physician should follow the spontaneous reporting process, and the resulting safety data are not a part of the data for this study.

11.3 Reporting of adverse events

The data for the study is based on secondary use of data (collected from GloBE-Reg). As the safety data will be drawn from GloBE-Reg, this section is not applicable (see Section 11.2).

11.4 Follow-up on safety information

The risk of incomplete provision of information on AEs will be mitigated by GloBE-Reg using the following measures:

- If a field is not completed, there will be an alert within the GloBE-Reg platform on the clinician's dashboard to ensure completion of applicable fields.
- GloBE-Reg will perform a QA exercise on 10% of cases on an annual basis, with focus on the adverse events.
- GloBE-Reg has regular meetings with the physicians contributing to the data source and will, at those meetings, raise awareness of the need to fill in the details for AEs.
- GloBE-Reg will inspect the data for missing fields and liaise with the reporting centres to ensure that the AE field is completed prior to supplying the data to Novo Nordisk A/S.

11.5 Regulatory reporting requirements for adverse events

For this study, this section is not applicable (see Section 11.2).

11.6 Precautions/Over-dosage

For this study, this section is not applicable (see Section 11.2)

11.7 Novo Nordisk safety committee(s)

Novo Nordisk A/S has an internal somapacitan safety committee that performs ongoing safety surveillance of somapacitan.

The safety committee is a multi-disciplinary team with representatives from relevant functional areas that are necessary to provide integrated assessments of safety data from multiple sources for

somapacitan. The members of the safety committee are highly qualified representatives of the respective departments and include e.g. medical specialists, non-clinical project manager, safety surveillance advisers and regulatory project manager/director. If relevant, internal and/or external ad-hoc members with specific area of expertise (e.g. neoplasms) may be invited to a safety committee meeting.

The somapacitan safety committee is responsible for reviewing the results of ongoing safety surveillance, for ensuring endorsements, and for validating signals and ensuring appropriate actions in case of new safety signals for somapacitan as well as for closing safety signals.

Signal management is an iterative process designed to detect, evaluate, manage, and communicate new risks associated with an active substance or whether known risks have changed.

12 Plans for disseminating and communicating study results

The information obtained during the conduct of this study is considered confidential and can be used by Novo Nordisk A/S for regulatory purposes and for the safety surveillance of somapacitan. All information supplied by Novo Nordisk A/S in connection with this study must remain the sole property of Novo Nordisk A/S and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk A/S. Such information must not be used except in the performance of this study. The information obtained during this study may be made available to other physicians who are conducting other studies with the study product, if deemed necessary by Novo Nordisk A/S.

12.1 Registration of study information

In accordance with Novo Nordisk A/S commitment to transparency in clinical activities, this study will be registered on `ClinicalTrials.gov´ no later than at enrolment of the first study patient.

For studies that include data collected also retrospectively, the study is to be registered prior to the first capture of data.

This non-interventional PASS must be registered in the EU Electronic Register of Post-Authorisation Studies (EU PAS Register) maintained by the EMA and accessible through the EMA's web portal.

12.2 Communication and publication

Novo Nordisk A/S commits to communicating or otherwise making available for public disclosure results of studies regardless of outcome. Public disclosure includes publication of a paper in a scientific journal, abstract submission with a poster or oral presentation at a scientific meeting, or by other means.

The final report will be published in the EU PAS registry and submitted to the respective regulatory authorities within 12 months after the end of data collection.

At the end of the study, one or more publication(s) may be prepared by physician(s) in collaboration with Novo Nordisk A/S. Novo Nordisk A/S reserves the right to postpone publication and/or communication for up to 60 days to protect intellectual property and reserves the right not to release interim results or data until a study report is available. The results of this study will be subject to public disclosure on external websites according to international regulations, as reflected in the Novo Nordisk A/S Commitment to share information about clinical studies.

In a multi-centre study based on the collaboration of all study sites, any publication of results in a journal article must acknowledge all study sites. Where required by the journal, the physician from each site will be named in the acknowledgement.

The results of the study (either abstracts or full study report) must be submitted to IEC/IRB (or other appropriate bodies as required locally) if the protocol or protocol abstract was submitted to any of these.

In all cases, the study results must be reported in an objective, accurate, balanced and complete manner, with a discussion of the strengths and limitations of the study. All authors will be given the relevant statistical tables, figures, and reports needed to support the planned publication. In the event of any disagreement about the content of any publication, both the physicians' and Novo Nordisk's opinions must be fairly and sufficiently represented in the publication.

Novo Nordisk A/S maintains the right to be informed of any physician plans for publication and to review any scientific paper, presentation, communication or other information concerning the investigation described in this protocol. Any such communication must be submitted in writing to the Novo Nordisk A/S study manager prior to submission for comments. Comments will be given within four weeks from receipt of the planned communication. For PASS studies in Europe, an advance agreement on publication policy between Novo Nordisk A/S and physician allows the latter to independently prepare publications based on the study results. Also PASS studies in Europe require Novo Nordisk A/S to communicate to the EMA[5] and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication. This is to allow national competent authorities to review in advance the results and interpretations to be published.

12.3 Physician access to data and review of results

As owners of the study database, Novo Nordisk A/S has discretion to determine who will have access to the database. The data will be received from the registry (GloBE-Reg).

Provided that certain conditions are fulfilled, Novo Nordisk A/S may grant access to information obtained during this study to researchers who require access for research projects studying the same disease and/or product studied in this study.

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ANNEX 1 ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

Study title:

A non-interventional, observational, registry-based study to investigate long-term safety and clinical parameters of somapacitan treatment in paediatric patients with growth hormone deficiency during routine clinical practice.

EU PAS Register® number: pending

Study reference number (if applicable): NN8640-4787

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	12.1
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Study will be registered in the EU PAS Register® prior to start of data collection Progress reports will be submitted in line with PSUR. Annual progress reports, submitted with PSUR (when applicable)

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1-8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	11.2
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.2
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

The safety data will be drawn from GloBE-Reg.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	6, 9.1
4.2.2 Age and sex	☒	☐	☐	9.2.2
4.2.3 Country of origin	☐	☒	☐	
4.2.4 Disease/indication	☒	☐	☐	7
4.2.5 Duration of follow-up	☒	☐	☐	9.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2 9.2.3

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☐	☒	☐	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.7.2

Comments:

As described in Section 9.9, data collection for this study will reflect routine clinical practice rather than mandatory assessments at pre-specified time points, which may have an impact on the completeness of data and its interpretation.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.1.1 9.2.7, 9.3

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.3.3, 9.9
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9

Comments:

As this is a non-interventional study, data collection will reflect routine clinical practice rather than mandatory assessments at pre-specified time points, which may have an impact on the amount of data and its interpretation.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☒	☐	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3, 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3, 9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3, 9.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3, 9.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3, 9.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3, 9.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	4.10 9.7.2.1
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☒	☐	

Comments:

Not relevant for this study

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	11.4
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	9.9
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☐	☒	☐	

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.3
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

[redacted]

Name of the main author of the protocol: [redacted], Novo Nordisk A/S

Date: 17/July/2024

Signature: Signed electronically together as part of protocol signature in sponsor trial master file system

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