Protocol

Study ID: NN8640-4515

A multi-national, multi-centre, prospective, single-arm, observational, non-interventional post-authorisation safety study to investigate long-term safety of Sogroya® (somapacitan) in adults with growth hormone deficiency (AGHD) under routine clinical practice

Redacted report
includes redaction of personal identifiable information only.

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

PASS information

Title	A multi-national, multi-centre, prospective, single-arm, observational, non-interventional post-authorisation safety study to investigate long-term safety of Sogroya® (somapacitan) in adults with growth hormone deficiency (AGHD) under routine clinical practice
Protocol author	[redacted] Trial Manager Biopharm ClinOps 5 Novo Nordisk A/S Vandtårnsvej 108-114 2860 Søborg, Denmark
Protocol version identifier	Version 3.0
Date of last version of protocol	15 February 2022
EU PAS Register number	Study not yet registered
Active substance	ATC code: H01AC07
Medicinal product	Sogroya®
Product reference	EU/1/20/1501
Procedure number	EMEA/H/C/005030/MEA/001
Marketing authorisation holder(s)	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
Joint Post Authorisation Safety Study (PASS)	No
Research question and objective	**Primary objective** To investigate long-term safety of Sogroya® (somapacitan) therapy in patients with Adult Growth Hormone Deficiency (AGHD) in the setting of routine clinical practice with special focus on neoplasms and diabetes mellitus type 2. **Secondary objectives** To investigate safety and clinical parameters in patients treated with Sogroya® (somapacitan) under routine clinical practice. To investigate safety and clinical parameters of Sogroya® (somapacitan) treatment under routine clinical practice in patients with AGHD for the subgroups childhood-onset GHD and females on oral oestrogen therapy, respectively.

	To investigate the number of patients achieving the age-adjusted IGF-I SDS levels up to the upper limit of the normal reference range (0 and +2). To evaluate the impact of Sogroya® (somapacitan) on patient functioning and wellbeing through a patient reported outcome measure (TRIM-AGHD) **Exploratory objective** Change in number of different anti-diabetic medications for patients with diabetes mellitus type 2 at baseline. To evaluate the impact of Sogroya® (somapacitan) on patient sick days and physician visits, work and study productivity and ability to do regular daily activities through a patient reported outcome measure (AGHD WSI)
Country(-ies) of study	Countries have not been finalized; the study will be conducted internationally including in all European countries where the product is launched and where treating physicians and patients can be recruited.

Marketing authorisation holder(s)

Marketing authorisation holder(s) (MAH(s))	Novo Nordisk A/S Novo Allé DK-2880 Bagsvaerd Denmark
MAH contact person	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
AGHD	Adult Growth Hormone Deficiency
ALT	Alanine transaminase
AR	Adverse Reaction
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical (Classification System)
BMI	Body Mass Index
CRA	Clinical Research Associate
CRF	Case Report Form
CV	Curriculum Vitae
DXA	Dual energy x-ray absorptiometry
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU PAS	The EU electronic register of post-authorisation studies maintained by the European Medicines Agency
FPFV	First Patient First Visit
GGT	Gamma-Glytamyltransferase
GH	Growth Hormone
GHD	Growth Hormone Deficiency
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
HDL	High Density Lipoprotein
IEC	Independent Ethics Committee
IGF-I	Insulin-like growth factor I
IGFBP-3	Insulin-like growth factor binding protein -3
IOS	International Outcome Study
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LDL	Low Density Lipoprotein

LPLV	Last Patient Last Visit
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-interventional Study
PAS	Post Authorisation studies
PASS	Post Authorisation Safety Study
PRO	Patient reported outcome
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SAS	Safety Analysis Set
SDS	Standard Deviation Score
s.c	Subcutaneous
SOC	System Organ Class
TMF	Trial Master File
TRIM-AGHD	Treatment Related Impact Measure - Adult Growth Hormone Deficiency
UTN	Universal Trial Number
VV	Veeva Vault
VAT	Visceral adipose Tissue
WHO	World Health Organisation
WMA	World Medical Association
AGHD-WSI	Adult Growth Hormone Deficiency Work Study Impact

3 Responsible parties

In this document physician refers to the individual overall responsible for the conduct of the non-interventional study at a study site.

The physician is accountable for the conduct of the study. If any tasks are delegated, the physician should maintain a list of appropriately qualified persons to whom he/she has delegated specified significant study-related duties. During any period of unavailability, the physician should delegate responsibility for study activities of patients to a specific qualified physician who should be readily available to patients during that time. If the physician is no longer able to fulfil the role of physician (e.g. if he/she retires), a new physician must be appointed in consultation with Novo Nordisk. The physician and site personnel must have sufficient English skills according to their assigned task(s). The physician must follow the instructions from Novo Nordisk when processing data. The physician must take all necessary technical and organisational safety measures to prevent accidental or wrongful destruction, loss or deterioration of data. The physician must prevent any unauthorised access to data or any other processing of data against applicable law. Upon request from Novo Nordisk, the physician must provide Novo Nordisk with the necessary information to enable Novo Nordisk to ensure that technical and organisational safety measures have been taken.

Please refer to the Stand-alone documents (Annex 1) for additional information about responsible parties. A list of all collaborating institutions and physicians will be made available to authorities upon request.

4 Abstract

4.1 Title

A multi-national, multi-centre, prospective, single-arm, observational, non-interventional post-authorisation safety study (PASS) to investigate long-term safety of Sogroya® (somapacitan) in adults with growth hormone deficiency (AGHD) under routine clinical practice
(version 3.0, dated 15-Feb-2022)

4.2 Milestones

Milestone	Planned date
Start of data collection – First patient first visit (FPFV)	15 Dec 2022
Interim report 1	Data cut 3 years following FPFV 15 Dec 2025
Last patient first visit – end of study recruitment	15 Dec 2027
Interim report 2	Data cut 6 years following FPFV 15 Dec 2028
Last patient last visit (LPLV)	15 Dec 2032
End of data collection – defined as data base lock	Q1 2033

Milestone	Planned date
Final report of study results	Q1 2034
Study progress reports	To follow PSUR timelines

4.3 Rationale and background

Sogroya® (somapacitan) is a recombinant human GH analog developed by Novo Nordisk, indicated for replacement of endogenous GH in adults with growth hormone deficiency (AGHD).

Replacement therapy with once-weekly somapacitan and once-daily-somatropin differ from endogenous GH release under normal physiological conditions.

In clinical phase 3 trials, IGF-I levels obtained with somapacitan were within the age-adjusted normal reference range with temporary peaks above the upper limit of normal range for a small subset of patients. Importantly, modestly and transiently elevated IGF-I levels in GH replacement therapy have not been linked to adverse effects in published literature nor in the somapacitan phase 3 trials.

Even after over 20 years of adult GH replacement, evidence suggesting that rhGH replacement in adults increases cancer risk or accelerates recurrences of tumours in the hypothalamic-pituitary region remains unclear; With conflicting results in the literature, the overall effect of rhGH replacement on the development of diabetes is also unclear. Somapacitan has been studied in AGHD patients for up to 86 weeks. Thus, the safety information during longer period of treatment is limited.

If patients taking GH replacement report significant QoL benefits and/or there are objective improvements, such as in cardio-vascular risk markers, BMD, body composition, or physical activity tolerance, then GH treatment can be continued indefinitely. Therefore, further investigations, including long-term surveillance studies after regulatory approval are essential to improve our understanding of the safety and effectiveness of prolonged exposure to Sogroya®.

As part of the marketing authorisation of Sogroya®, Novo Nordisk has received a requirement from the Committee for Medicinal Products for Human Use (CHMP) under European Medicines Agency (EMA) to conduct a non-interventional PASS to investigate long-term safety of Sogroya® (somapacitan) in patients with AGHD.

Therefore, as part of the risk management plan for Sogroya® (somapacitan) for treatment of AGHD, the primary aim of this non-interventional study (NIS) is to characterise the long-term safety profile of Sogroya® (somapacitan) with special focus on the important potential risks (diabetes mellitus type 2, neoplasms and medication errors) and additional long-term safety information. Therefore, this PASS may allow a further evaluation of these potential risks in relation to treatment with Sogroya®. Medication errors are of specific interest since some patients will switch from daily GH injections to weekly injections with Sogroya®. Therefore, the PASS may provide information on whether this might lead to medication errors in clinical practice

Only data generated as part of routine clinical practice will be collected in this study.

In order to draw clinically relevant conclusions on long-term safety of Sogroya® (somapacitan), the study will compare data from a non-interventional registry (NordiNet® International Outcome Study (IOS)) study which has been monitoring the long-term use of once daily Norditropin® as a historical comparison group consisting of approximately 2300 AGHD patients.[1,2]

4.4 Research question and objectives

4.4.1 Primary objective

To investigate long-term safety of Sogroya® (somapacitan) therapy in patients with AGHD in the setting of routine clinical practice with special focus on neoplasms and diabetes mellitus type 2.

4.4.2 Secondary objectives

To investigate safety and clinical parameters of Sogroya® (somapacitan) treatment under routine clinical practice in patients with AGHD.

To investigate safety and clinical parameters of Sogroya® (somapacitan) treatment under routine clinical practice in patients with AGHD for the subgroups childhood-onset GHD and females on oral oestrogen therapy, respectively.

To investigate the number of patients achieving the age-adjusted IGF-I SDS levels up to the upper limit of the normal reference range (0 and +2)

To evaluate the impact of Sogroya® (somapacitan) on patient functioning and wellbeing through a patient reported outcome measure (TRIM-AGHD)

4.4.3 Exploratory objective(s)

Change in number of different anti-diabetic medication for patients with diabetes mellitus type 2 at baseline.

To evaluate the impact of Sogroya® (somapacitan) on patient sick days and physicians' visits, work and study productivity and the ability to do regular daily activities through a patient reported outcome measure (AGHD WSI).

4.5 Study design

This is a non-interventional, multinational, multi-centre, prospective, single-treatment arm, observational PASS in AGHD patients. The study will, under routine clinical practice conditions, investigate the long-term safety of Sogroya® (somapacitan), including but not limited to the occurrence of neoplasm, development of type 2 diabetes and medication errors.

Moreover, the titration regimen and clinical parameters of Sogroya® (somapacitan) therapy in AGHD patients will be collected and evaluated, when available as part of routine clinical practice.

Patients will be treated with commercially available Sogroya® (somapacitan) according to local practice at the discretion of the physician.

The duration of the study is planned with patient participation for 5 years or longer up to a total study duration of 10 years, if possible. The main purpose of the study is to observe patients for long-term safety.

4.6 Population

Approximately 400 patients with AGHD will be included globally.

4.6.1 Inclusion criteria

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

1. Signed consent obtained before any study-related activities (study-related activities are any procedure related to recording of data according to the protocol).
2. The decision to initiate treatment with commercially available Sogroya® (somapacitan) has been made by the patient and the treating physician before and independently from the decision to include the patient in this study.
3. Male or female, age above or equal to 18 years assigned to Sogroya® (somapacitan) treatment at the time of signing informed consent.
4. Diagnosis of adult growth hormone deficiency (AGHD) as per local practice

4.6.2 Exclusion criteria

For an eligible patient, all exclusion criteria must be answered "no".

1. Previous participation in this study. Participation is defined as signed informed consent
2. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation
3. Patient with hypersensitivity to the active substance or to any of the excipients.
4. Patient with active malignancy or in treatment for active pre-existing malignancy.
5. Patient with acute critical illness, suffering from complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions per investigator judgement.

4.7 Variables

Data within safety (AEs), clinical parameters and PRO questionnaires will be collected. Data and results from assessments and laboratory analyses will be recorded if performed according to routine clinical practice or physician discretion at the participating sites.

4.8 Data sources

Relevant data and results available in the patient's medical record and from assessments and laboratory analyses performed according to routine clinical practice at the participating sites will be recorded in the eCRF.

4.9 Study size

The study is planned for the sample size of 400 patients.

4.10 Data analysis

Adverse drug reactions will be analysed using descriptive statistics based on the 'on–treatment' observation period (primary evaluation) and 'in-study' observation period (secondary evaluation) within the study period. The Adverse drug reactions (ADRs) will be summarised by treatment, MedDRA (Medical Dictionary for Regulatory Activities) system organ class (SOC) and MedDRA preferred term (PT).

Incidence rates will be calculated for the endpoints Neoplasm and Diabetes Mellitus type 2.

5 Amendments and updates

Amendment or update no	Date	Section of study protocol	Amendment or update	Reason
1	21-Oct-2021	General update of the protocol	update	following PRAC review
2	15-Feb-2022	Minor updates to sections: "PASS information", 9.1 and 9.7	update	following 2nd-round PRAC review

6 Milestones

Milestone	**Planned date**
Registration in the EU PAS Register	Prior to start of data collection, i.e., before FPFV
Start of data collection – first patient first visit (FPFV)	15 Dec 2022
Interim report 1	Data cut 3 years following FPFV 15 Dec 2025
Last patient first visit – end of study recruitment	15 Dec 2027
Interim report 2	Data cut 6 years following FPFV 15 Dec 2028
Last patient last visit (LPLV)	15 Dec 2032
End of data collection (defined as database lock)	Q1 2033
Final report of study results	Q1 2034
Study progress reports	To follow PSUR timelines

7 Rationale and background

Sogroya® (somapacitan) is a recombinant human GH analog developed by Novo Nordisk, indicated for replacement of endogenous GH in AGHD. Replacement therapy with recombinant GH is the standard of care for patients with AGHD. Sogroya® (somapacitan) is a long-acting GH product developed for once weekly subcutaneous (s.c.) administration.

Replacement therapy with once-weekly somapacitan and once-daily somatropin differ from endogenous GH release under normal physiological conditions.

In clinical phase 3 trials, IGF-I levels obtained with somapacitan were within the age-adjusted normal reference range with temporary peaks above the upper limit of normal range for a small subset of patients. Importantly, modestly and transiently elevated IGF-I levels in GH replacement therapy have not been linked to adverse effects in published literature nor in the somapacitan phase 3 trials.

Even after over 20 years of adult GH replacement, evidence suggesting that rhGH replacement in adults increases cancer risk or accelerates recurrences of tumours in the hypothalamic-pituitary region remains unclear; With conflicting results in the literature, the overall effect of rhGH replacement on the development of diabetes is also unclear. Somapacitan has been studied in AGHD patients for up to 86 weeks. Thus, the safety information during longer period of treatment is limited.

If patients taking GH replacement report significant QoL benefits and/or there are objective improvements, such as in cardio-vascular risk markers, BMD, body composition, or physical activity tolerance, then GH treatment can be continued indefinitely. Therefore, further investigations, including long-term surveillance studies after regulatory approval are essential to improve our understanding of the safety and effectiveness of prolonged exposure to Sogroya®.

As part of the marketing authorisation of Sogroya®, Novo Nordisk has received a requirement from the Committee for Medicinal Products for Human Use (CHMP) under European Medicines Agency (EMA) to conduct a non-interventional PASS to investigate long-term safety of Sogroya® in patients with AGHD.

Therefore, as part of the risk management plan for Sogroya®(somapacitan) as treatment of AGHD, the primary aim of this NIS is to characterise the long-term safety profile of Sogroya® (somapacitan) with special focus on the important potential risks (diabetes mellitus type 2, neoplasms and medication errors) and additional long-term safety information. Therefore, this PASS may allow a further evaluation of these potential risks in relation to treatment with Sogroya®. Medication errors are of specific interest since some patients will switch from daily GH injections to weekly injections with Sogroya®. Therefore, the PASS may provide information on whether this might lead to medication errors in clinical practice.

The secondary aim is to investigate the clinical parameters in patients treated with Sogroya® (somapacitan) on body composition, metabolic parameters, skeletal integrity, and quality of life. Clinical parameters will be analysed in specific sub-populations of AGHD patients, defined in protocol section 9.7.2.2 as these sub-populations have different starting doses of Sogroya® (somapacitan).

Only data generated as part of routine clinical practice will be collected in this study.

In order to draw clinically relevant conclusions on long-term safety of Sogroya® (somapacitan), the study will compare data from a non-interventional registry (NordiNet® International Outcome Study (IOS)) study which has been monitoring the long-term use of once daily Norditropin® as a historical comparison group consisting of approximately 2300 AGHD patients.[1, 2]

8 Research question and objectives

8.1 Primary objective

To investigate long-term safety of Sogroya® (somapacitan) therapy in patients with AGHD in the setting of routine clinical practice with special focus on neoplasms and diabetes mellitus type 2.

8.2 Secondary objectives

To investigate safety and clinical parameters of Sogroya® (somapacitan) treatment under routine clinical practice in patients with AGHD.

To investigate safety and clinical parameters of Sogroya® (somapacitan) treatment under routine clinical practice in patients with AGHD for the subgroups childhood-onset GHD and females on oral oestrogen therapy, respectively.

To investigate the number of patients achieving the age-adjusted IGF-I SDS levels up to the upper limit of the normal reference range (0 and +2).

To evaluate the impact of Sogroya® (somapacitan) on patient functioning and wellbeing through a patient reported outcome measures (TRIM-AGHD).

8.3 Exploratory objective(s)

Change in number of different anti-diabetic medications for patients with diabetes mellitus type 2 at baseline.

To evaluate the impact of Sogroya® (somapacitan) on patient sick days and physician visits, work and study productivity and ability to do regular daily activities through a patient reported outcome measures (AGHD WSI).

9 Research methods

9.1 Study design

This is a non-interventional, multinational multi-centre, prospective, single-treatment arm, observational PASS in AGHD patients. The study will, under routine clinical practice conditions, investigate the long-term safety of Sogroya® (somapacitan), including but not limited to the occurrence of neoplasm, development of type 2 diabetes and medication errors.

Moreover, the titration regimen and clinical parameters of Sogroya® (somapacitan) therapy in AGHD patients will be collected and evaluated, when available as part of routine clinical practice.

Figure 1 Study Design

Note: symbol ( ) Represents interim reporting

The study is planned to collect a broad variety of safety and other clinical parameters data generated during routine clinical care visits and other relevant clinical contacts (e.g. phone calls between patient and clinical site) in AGHD patients treated with commercially available Sogroya® (somapacitan). The duration of the study is planned with patient participation for 5 years or longer up to a total study duration of 10 years, if possible. The main purpose of the study is to observe patients for long-term safety. It is however well known that adult patients on GH therapy, often interrupt or discontinue treatment.[4] Due to this expected dropout from treatment[4], and in the context of the duration of the study, patients switching from or discontinuing treatment with Sogroya® (somapacitan) will be offered continuation in the study in order to collect post treatment data.

The current study will compare data from a non-interventional registry study (NordiNet® IOS) which was monitoring the long-term use of once daily Norditropin® as a historical comparison group consisting of approximately 2300 AGHD patients enrolled in Europe between 2006 and 2016.[1, 2]

The sample size estimation for this study is based on the incidences for neoplasms reported in Nordinet® IOS. It is estimated that a sample size of 400 patients will be required to rule out the doubling of incidence for neoplasms in patients treated with Sogroya® (somapacitan).

Data on concomitant medication, medical history (adult/ childhood onset of GHD), laboratory parameters including but not limited to hepatic, renal, heart and diabetes status as well as data on neoplasms and medication errors will be collected as part of this study if available per routine clinical practice in order to evaluate safety. Other data which are already available in the medical records or being obtained as part of routine clinical practice, such as IGF- I /IGFBP-3 values, measures of body composition and bone health and PROs, will be collected to support the evaluation of clinical parameters.

To enable intra-personal comparison on dose of previous GH treatment, IGF-I/IGFBP-3 SDS values, measures of body composition and bone health and oral oestrogen treatment status, 12-months retrospective data (i.e., from medical charts, where available.) will be collected at study enrolment.

Additionally, the severity of GH deficiency expressed as IGF-I SDS level prior to any initiation of GH treatment should be collected at baseline, if available.

Data on the number of patients with a minimum of 1-year of follow-up achieving the age-adjusted IGF-I SDS levels up to the upper limit of the normal reference range (0 and +2) will be reported (i) as part of the progress reports in connection with the PSURs - as soon as first data are available and (ii) as part of the interim reporting (data cut 3 and 6 years after FPFV).

Monitoring of safety in this study will be performed from time of enrolment, defined by signing of the informed consent, until the patient's last visit in the study (defined as end of study or withdrawal of informed consent). Adverse events are expected to be captured and reported by the participating sites during routine clinical evaluations (expected every 6-12 months) and any other intermediate contacts with the patient (e.g. phone call etc).

9.1.1 Endpoints

9.1.1.1 Primary endpoints

Endpoint title	Time frame	Unit
Number of Adverse drug reaction (ADRs)	From baseline (week 0) to end of study*	Count
Incident Neoplasm	From baseline (week 0) to end of study*	Yes/No
Incident Diabetes Mellitus type 2	From baseline (week 0) to end of study*	Yes/No

*End of study will differ from patient to patient, but can be between 1 week and a maximum of 10 years

9.1.1.2 Secondary endpoints

9.1.1.2.1 Safety

Endpoint title	Time frame	Unit
Number of Adverse Events (AEs)	From baseline (week 0) to end of study*	Count
Number of Serious Adverse Events (SAEs)	From baseline (week 0) to end of study*	Count
Number of Medication Errors (incorrect dose administration rate)	From baseline (week 0) to end of study*	Count

*End of study will differ from patient to patient, but can be between 1 week and a maximum of 10 years

9.1.1.2.2 Clinical parameters

Endpoint title	Time frame	Unit
Change in IGF-I SDS	From baseline (week 0) to end of study*	-10 to +10
Patient achieving IGF-I SDS target (0-+2)	Approximately**12 months after enrolment in study	Yes/No

Change in Weight	From baseline (week 0) to end of study*	kilogram (kg)
Change in Body Mass Index (BMI)	From baseline (week 0) to end of study*	kg/m^2
Change in waist circumference	From baseline (week 0) to end of study*	cm
Change in waist-hip ratio	From baseline (week 0) to end of study*	ratio
Change in lipid profile (cholesterol, HDL, LDL, triglycerides)	From baseline (week 0) to end of study*	mg/dL
Change in HbA1C	From baseline (week 0) to end of study*	%
Change in bone density	From baseline (week 0) to end of study*	g/cm^2
Change in bone mineral content	From baseline (week 0) to end of study*	g
Change in total body fat-mass	From baseline (week 0) to end of study*	kg
Change in truncal fat-mass	From baseline (week 0) to end of study*	kg
Change in lean body mass	From baseline (week 0) to end of study*	kg
Change in body fat percentage	From baseline (week 0) to end of study*	%
Change in visceral adipose tissue (VAT)	From baseline (week 0) to end of study*	cm^2
Change in Liver function (AST, ALT, GGT, bilirubin)	From baseline (week 0) to end of study*	U/L
Change in PRO score, TRIM-AGHD	From baseline (week 0) to end of study*	-100 to +100
Patient reaching satisfactory clinical response	Approximately** 12 months after enrolment in study	Yes/No

*End of study will differ from patient to patient, but can be between 1 week and a maximum of 10 years

** i.e., the closest routine clinical after 12 months post enrolment

9.1.1.3 Exploratory endpoints

Endpoint title	Time frame	Unit
AGHD Work Study Impact (WSI)	From baseline (week 0) to end of study*	-10 to +10 Annual rate of sick days and physician visits
Number of anti-diabetic medications for patients with diabetes mellitus type 2 at baseline	From baseline (week 0) to end of study*	count of ATC code

*End of study will differ from patient to patient, but can be between 1 week and a maximum of 10 years

9.1.2 Treatment of patients

Patients will be treated with commercially available Sogroya® (somapacitan) according to routine clinical practice at the discretion of the treating physician. The decision to treat a patient with Sogroya® (somapacitan) must be made prior to and independently from the decision to include the patient in this study.

Novo Nordisk will not provide any medicinal products during the conduct of the study.

9.2 Setting

9.2.1 Study population

Patients for this study will be included globally from centres in countries where patients will be treated with Sogroya® within the planned recruitment timelines of the study.

Planned number of patients to be included globally: 400

Planned number of patients to complete the study: 400

Anticipated number of patients to be included in each country: depending on availability and commercial uptake of Sogroya® in relevant countries.

Planned time period for the study: 15 Dec 2022-15 Dec 2032

9.2.2 Inclusion criteria

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

1. Signed consent obtained before any study-related activities (study-related activities are any procedure related to recording of data according to the protocol).
2. The decision to initiate treatment with commercially available Sogroya® (somapacitan) has been made by the patient and the treating physician before and independently from the decision to include the patient in this study.
3. Male or female, age above or equal to 18 years assigned to Sogroya® (somapacitan) treatment at the time of signing informed consent.
4. Diagnosis of adult growth hormone deficiency (AGHD) as per local practice

9.2.3 Exclusion criteria

For an eligible patient, all exclusion criteria must be answered “no”.

1. Previous participation in this study. Participation is defined as signed informed consent
2. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation
3. Patients with hypersensitivity to the active substance or to any of the excipients.
4. Patients with active malignancy or in treatment for active pre-existing malignancy.
5. Patients with acute critical illness, suffering from complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions per investigator judgement.

9.2.4 Rationale for selection criteria

The study population is comprised of adult patients diagnosed with GHD and treated with commercially available Sogroya® (somapacitan). The study population will include patients naïve and non-naïve to any GH replacement therapy (including Sogroya® (somapacitan)) at time of study enrolment and will also include patients with severe hepatic impairment, patients with New York

Heart Association class 2 heart failure and woman on oral oestrogen treatment who are diagnosed with AGHD.

The few inclusion and exclusion criteria of this study will greatly reduce selection bias. As a multicentre, multinational population has been selected the generalizability of the study is evaluated as high. The study is global and can include all ethnic groups.

The study population is characterized through the inclusion criteria:

Criterion no. 1 is included in accordance with Good Pharmacoepidemiology Practices (GPP)[5].

Criterion no. 2 is included in accordance with Good Pharmacovigilance Practice (GVP) and for the purpose of reflecting local clinical practice[6].

Criterion no. 3 is included to reflect the population for which Sogroya® (somapacitan) is approved.

Criterion no. 4 is included to ensure that adults enrolled in the study are GH deficient and reflect the population for which Sogroya® (somapacitan) is approved and marketed in the respective countries.

The study population is characterized through the exclusion criteria:

Criterion no. 1 is to ensure that a patient only counts once in the data analyses.

Criterion no. 2 serves to protect patient safety and rights.

Criterion no. 3 is to exclude patients with hypersensitive to Sogroya® (somapacitan) or any of its excipients in accordance with the summary of product characteristics (SmPC)

Criterion no.4 is to exclude patients with any evidence of active malignancy. Any pre-existing malignancy should be inactive, and its treatment complete prior to instituting therapy with Sogroya® (somapacitan) in accordance with the SmPC.

Criterion no.5 is to exclude patients with increased risk of mortality, in accordance with the SmPC.

9.2.5 Withdrawal criteria

The patient may withdraw at will at any time.

In case of withdrawal, the physician should attempt to collect any outstanding data. The primary reason (withdrawal of consent, lost to follow up or other) for discontinuation should be specified in the Case Report Form (CRF).

9.2.6 Visit procedures

9.2.6.1 Study flow chart

	Section	Baseline	Visits	Follow-Up
Visit		Visit 1	Visit 2, 3, 4 etc	End of Study
PATIENT RELATED INFORMATION AND ASSESSMENTS				
Informed Consent & Demography	10.1 9.2.8.1	X		
In/exclusion Criteria	9.2.2 9.2.3	X		
Body Measurements	9.2.8.2	X	X	X
Tobacco use	9.2.8.4	X	X	X
Medical history / Concomitant illness	9.2.8.5 9.2.8.6	X		
Concomitant medication	9.2.8.7	X	X	X
Dosing and titration	9.2.8.8		X	X
Adverse event	11		X	X
Physical examination	9.2.7.3	X	X	X
Vital Signs	9.2.8.3	X	X	X
ECG	9.2.7.4	X	X	X
Biochemistry	9.2.7.2	X	X	X
Lipid profile	9.2.7.2	X	X	X
Glucose metabolism	9.2.7.2	X	X	X
Body Composition	9.2.7.6	X	X	X
Biomarkers	9.2.7.5	X	X	X
PRO questionnaires	9.2.8.9	X	X	X
Clinical response evaluation	9.2.8.10		X	X
End of study	9.2.6.2			X

9.2.6.2 Study visits

Patients should receive treatment and care at their respective clinic in accordance with normal clinical practice. For each clinical visit and clinical patient contact (e.g., phone call etc) the site personnel should enter all available information in the eCRF as specified in the below sections.

The physician should keep a patient enrolment log.

Baseline (visit 1)

Relevant data available in the patient's medical record at the time of the baseline visit may be used as baseline data and should be entered in the eCRF after having obtained informed consent. All relevant data necessary for evaluating whether a patient can be enrolled in the study e.g. inclusion/exclusion criteria, see section 9.2.2 and 9.2.3, must be available prior to enrolling a patient.

Relevant data regarding the assessments listed in the flow chart for visit 1 must be entered in the eCRF, if available.

Visits 2, 3, 4 etc

At each contact with the site during the study, the patient should be asked about possible adverse events since the last contact. This may be done by posing a simple question such as "have you experienced any problems since the last contact?"

Relevant data regarding the assessments listed in the flow chart must be entered in the eCRF, if available.

In case a patient contacts the site (phone, virtual etc) during his/her participation in this study all relevant study information, i.e., reported AEs, should be entered in the patient's medical records and subsequently in the eCRF in accordance with the flowchart.

End of study

This visit will take place no later than the planned study LPLV date.

Relevant data regarding the assessments listed in the flow chart must be entered in the eCRF, if available.

9.2.7 Assessments for safety and other clinical parameters

9.2.7.1 Adverse Events

All AEs, either observed by the physician or reported by the patient following the patient's enrolment (signing informed consent) into the study and until the end of study for each patient must be recorded and evaluated by the physician. At each contact with the site during the study, the patient should be asked about possible AEs since the last contact. Please refer to section 11 for AE definitions, collection, recording, and reporting.

9.2.7.2 Local Laboratory

Blood samples obtained from local laboratory in accordance with normal clinical practice should be recorded in the eCRF if available and may include:

Applicable local laboratory reference ranges must be collected and shared with Novo Nordisk.

- **Biochemistry**
  - Creatinine
  - High-Sensitive C-Reactive Protein
  - Alkaline phosphatase

    Liver function:
  - Aspartate Aminotransferase (AST)
  - Alanine Aminotransferase (ALT)
  - Gamma-Glutamyltransferase (GGT)
  - Bilirubin

- **Lipid profile**
  - Total Cholesterol
  - Low Density Lipoprotein cholesterol (LDL-Cho)
  - High Density Lipoprotein cholesterol (HDL-Cho)
  - Triglycerides

- **Glucose metabolism**

Samples should preferably be obtained in a fasting state

  - Insulin,
  - Blood glucose
  - HbA1c

Laboratory data obtained a maximum of 6 months before informed consent have been signed can be used for baseline data if evaluated still to be valid by the physician. If data from more than one previously obtained sample is available, the latest one should be used.

9.2.7.3 Physical examination

It is recommended to perform physical examination at every visit. The examination may include:

- Head, ears, eyes, nose, throat, neck
- Respiratory system
- Cardiovascular system
- Gastrointestinal system incl. mouth
- Musculoskeletal system
- Central and peripheral nervous system
- Skin
- Lymph node palpation

Results from physical examination should be recorded in the eCRF at baseline and at each visit throughout the study if available.

Data obtained a maximum of 6 months before informed consent has been signed can be used for baseline data if evaluated still to be valid by the physician. If data from more than one previously examination is available, the latest one should be used.

9.2.7.4 ECG

Results from ECG should be recorded in eCRF at baseline and at each visit throughout the study if available. ECG classified as abnormal and clinically significant at baseline should be recorded as medical history. Worsening of ECGs will be recorded as AE if they are evaluated as abnormal and clinically significant at a time after baseline.

Data obtained a maximum of 6 months before informed consent has been signed can be used for baseline data if evaluated still to be valid by the physician. If more than one previously obtained ECG is available, the latest one should be used.

9.2.7.5 Biomarkers

Samples obtained from local laboratory in accordance with normal clinical practice should be recorded in the eCRF if available:

- IGF-I
- IGFBP-3
- IGF-I standard deviation score (SDS)

Local Assay method and reference ranges must be collected and shared with Novo Nordisk.

Data obtained a maximum of 6 months before informed consent is signed can be used for baseline data if evaluated still to be valid by the physician. If more than one previously obtained data is available, the latest one should be used.

9.2.7.6 Body Composition

Results from body composition measurement by DXA or bioimpedance should be recorded in the eCRF at baseline and at each visit throughout the study if available.

Data obtained a maximum of 6 months before informed consent is signed can be used for baseline data if evaluated still to be valid by the physician. If more than one previously obtained data is available, the latest one should be used.

- Bone density
- Bone mineral content (hip or spine)
- Total body fat-mass
- Truncal fat mass
- Lean body mass
- Body fat percentage
- Visceral adipose tissue compartments (VAT)

9.2.8 Other assessments

9.2.8.1 Demography

Information about date of birth, sex, race, and ethnicity will be recorded in the eCRF according to local regulations.

9.2.8.2 Body Measurements

Height should be recorded in the eCRF at baseline only. Bodyweight, waist circumference and hip circumference should be recorded in the eCRF at all visits if available. Waste-hip ratio should be calculated and reported in eCRF at all visits if available.

For the baseline visit, height details in the medical records can be used, if evaluated as still relevant. For body weight, waist circumference and hip circumference data obtained a maximum of 6 months before signed informed consent can be used as baseline data, if evaluated as still relevant. For both men and woman, a waist hip ratio of 1.0 or higher is considered “at risk” for heart disease.

9.2.8.3 Vital Signs

Blood pressure and pulse rate will be measured according to local clinical practice, preferably after the patient has rested comfortably for 3 minutes. Measurements of each individual patient should, if possible, be performed using the same method and position (e.g. sitting) throughout the study.

9.2.8.4 Tobacco use

Information on tobacco use should be recorded in the eCRF at baseline and each visit throughout the study if available.

9.2.8.5 Concomitant illness

Any clinically significant illness that is present at baseline will be recorded as concomitant illness. The information collected for concomitant illness will include diagnosis. In case a concomitant illness worsening during the study, an AE must be recorded and reported according to section 11.

9.2.8.6 Medical History

The information collected for medical history should include diagnosis, date of resolution, as applicable and be recorded at the baseline visit based on discussion with the patient and/or based on medical records. In the event a diagnosis is unknown, the description of symptoms should be recorded.

At least history of cancer/intracranial tumour, history of GHD (childhood onset, adult onset, idiopathic, organic) should be recorded in the eCRF, if available.

To enable intra-personal comparison on dose of previous GH treatment, IGF-I/IGFBP-3 values, measures of body composition and bone health and oral oestrogen treatment status, 12 months of retrospective data (i.e., from medical charts, where available) will be collected at study enrolment. The severity of the GH deficiency (IGF-I level) from when the patient was GH treatment naïve should be collected as part of medical history, if available.

9.2.8.7 Concomitant medication

Definition of concomitant medication: any other medication, including other hormone replacement treatment, than Sogroya® (somapacitan) that is taken during the study, including at baseline (visit 1)

Details of all concomitant medication must be recorded at study entry (i.e. at baseline, visit 1) in the eCRF. Any changes in medication must be recorded at each visit (assessment visits, phone visits and end of study visit) in the eCRF.

The information collected for each concomitant medication should preferably include trade name or generic name, indication, start and stop date or continuation. For medications containing oestrogen also the route of administration must be recorded. If a concomitant medication is taken because of an adverse event this must be listed in the eCRF.

9.2.8.8 Dosage, titration, and adherence

The Sogroya® (somapacitan) dosing information at study entry and any changes to the dosing during the study must be recorded in the eCRF. For patient naïve to Sogroya® (somapacitan)

treatment when entering the study, details of titration regimen of Sogroya®(somapacitan) should be recorded in the eCRF when available. Patients' adherence will be recorded in the eCRF at each visit by an average missed dose per 2 months (≤1 dose, 1< and <3 doses or 3 doses ≤) based on physician asking the patient.

9.2.8.9 Patient reported outcomes

Patient reported outcomes (PRO) questionnaires will be used to assess patient functioning and well-being, sick days and physician visits, impact on work and study productivity and the ability to do regular daily activities in patients on Sogroya® (somapacitan) treatment.

The PRO questionnaires should be completed by patients preferably at baseline visit, each subsequent visit and at the end of the study visit. PRO questionnaires should preferably be completed at a visit before any other study-related activities.

The questionnaires will be provided in local language and take approximately 10 minutes to complete.

After completion, the PROs must be reviewed by the physician on the same day for potential AEs, including any overall change in health and concomitant medication. When reviewing the PRO questionnaires for AEs the investigator should not influence nor question the patient on the content of the patient's response to PRO questions.

If clarification of entries in the PRO questionnaires is needed, the patient should be questioned, and a conclusion made in the patient's medical record. Only the subject can make changes in the PRO. Care should be taken not to bias the patient. Filled in questionnaires will be entered in the eCRF by physician/site staff.

TRIM-AGHD

Treatment Related Impact Measure-Adult Growth Hormone Deficiency (TRIM-AGHD) is a disease specific questionnaire which measures the impact of GH treatment on the functioning and well-being of adults with growth hormone deficiency [7]. The four concepts covered by the questionnaire are physical health, energy levels, cognitive ability and psychological health. TRIM-AGHD has 27 items and a total score as well as domain specific scores can be derived. TRIM-AGHD is scored so that a lower score indicates a better health state. Scale range: 0 (best) - 100 (worst)

AGHD WSI

AGHD Work Study Impact (AGHD-WSI) is a disease specific questionnaire which measures the number of sick days and visits to a physician, the impact on work and study productivity and the ability to do regular daily activities of Sogroya® (somapacitan) treatment. The questionnaire has two parts: the patient will complete the first part at the first visit, and the second part at all subsequent visits. For the questions on impact of AGHD on productivity at work or school, and the ability to do regular daily activities, it is measured so that a lower score indicates a better health state. Scale range 0 (best) - 10 (worst).

9.2.8.10 Clinical Response evaluation

At each visit the physician will evaluate the clinical response and record whether there is a satisfactory clinical response as Yes or No in the eCRF.

9.3 Variables

Data within safety (AEs), clinical parameters and PRO questionnaires will be collected. Data and results from assessments and laboratory analyses will be recorded if performed according to routine clinical practice at the participating sites.

Ongoing monitoring will ensure that all collected data will be transferred to the eCRF as relevant.

9.4 Data sources

It is the intention of this non-interventional PASS to observe long-term routine treatment of the individual patient. Data and results available in the patient's medical record and from assessments and laboratory analyses performed according to routine clinical practice at the participating sites will be recorded in the eCRF.

Data sources are patients medical record, eCRF, paper PROs, paper CRF form (Pregnancy and pregnancy outcome form) and local laboratory data. The systems used for this is validated according to internal Novo Nordisk procedures.

9.5 Study sample size

Sample size calculations

The following table shows the 95% confidence interval for an incidence between 0% and 5%, like e.g. the incidence of neoplasm:

Table 1 Sample size calculations

Sample size		Observed incidence					
	0%	0.5%	1%	2%	3%	4%	5%
100	<3	-	0 – 5.4	0.2 – 7.0	0.6 – 8.5	1.1 – 9.9	1.6 – 11.3
200	<1.5	0 – 2.8	0.1 – 3.6	0.5 – 5.0	1.1 – 6.4	1.7 – 7.7	2.4 – 9.0
400	<0.75	0.1 – 1.8	0.3 – 2.5	0.9 – 3.9	1.6 – 5.2	2.3 – 6.4	3.1 – 7.6
600	<0.50	0.1 – 1.5	0.4 – 2.5	1.0 – 3.5	1.8 – 4.7	2.6 – 5.9	3.4 – 7.1

Using the observed incidence for neoplasm of 2% in the NordiNet® IOS with somatropin as reference values[2], a sample size of about 400 patients would be required to rule out the doubling of incidence for neoplasm. In general, the table shows that the precision, i.e. the change for the upper limit of the confidence interval, is having a large decrease when changing from 200 to 400 patients,

while the change from 400 to 600 patients is not having the same impact on the precision. Therefore, the study is planned for the sample size of 400 patients.

9.6 Data management

Data management is the responsibility of Data Management at Novo Nordisk.
Novo Nordisk will provide paper/electronic Case Report Forms (CRFs/eCRFs) for capture of study specific patient data. Instructions for completion and correction of CRFs/eCRF will be provided.
The following will be provided as paper Case Report Forms (CRFs):

- Pregnancy and pregnancy outcome form

The following will be provided as paper CRFs to be used when access to the eCRF is revoked or if the eCRF is unavailable:

- NIS Safety form

The physician must ensure that study specific patient data is entered in the CRFs/eCRF as soon as possible, preferably within 5 working days after the visit for non-safety forms. The CRFs will be source data verified, as applicable, on behalf of Novo Nordisk. Once data has been entered, it will be available to Novo Nordisk for data verification and validation purposes.

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.

The system for Electronic Data Capture (EDC) and support services for the system will be supplied by EDC system supplier. The activities of EDC system supplier will be under the direction and supervision of Novo Nordisk.

An audit trail will be maintained in the EDC application containing as a minimum: identification of the person entering the data, date and time of the entry and reason for the correction, the original entry, and the corrected entry.

By signing the casebook, the physician confirms that the information in the CRF/eCRF is complete and correct.

If corrections are made by the physician’s authorised staff after the date of the physician’s signature on the casebook, this must be signed again by the physician.

Available local laboratory data and PRO data will be entered in the eCRF by the physician/site staff.

Site specific eCRF data must after the study database is locked be downloaded by site in an electronic readable format of site’s choice. Hereafter access to the study specific EDC will be removed.

9.7 Data analysis

9.7.1 Definition of analysis sets

The safety analysis will be based on the Safety Analysis Set (SAS). The SAS will consist of all patients exposed to Sogroya® (somapacitan) during study period. Two observation periods are defined:

- on-treatment: from first administration until last study contact, discontinuation of Sogroya®, or withdrawal of informed consent, whichever comes first
- in-study: from first administration until last study contact, or withdrawal of informed consent, whichever comes first

9.7.2 Statistical methods

9.7.2.1 Analysis of primary endpoints

The primary endpoints are the number of Adverse Drug Reactions (ADRs), incident neoplasms, and incident T2D from baseline (week 0) up to end of study (week 520).

Frequencies of 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 event and event rate (events per 100 patient-years of exposure).

The primary objective of the study is to evaluate safety of once weekly dosing of Sogroya® (somapacitan) in AGHD patients over a study period up to 10 years, and analysis of ADRs will be one of the tools for achieving this. Adverse drug reactions will be analysed using descriptive statistics based on the ‘on treatment’ observation period (primary evaluation) and ‘in-study’ observation period (secondary evaluation) within the study period. The ADRs will be summarised by treatment, MedDRA (Medical Dictionary for Regulatory Activities) system organ class and MedDRA preferred term. The descriptive statistics will include the number and percentage of patients who experienced ADRs, the number of events and rate per 100 person years. ADRs will be listed by treatment and patient with information on severity, relationship to study product and demographics. ADRs with onset before first dosing will be reported in a separate listing.

In addition, incidence rates will be calculated for the endpoints Neoplasm and Diabetes Mellitus type 2.

Results will be reported separately for treatment-naïve and prevalent users of GH replacement therapy, and patients with a history of neoplasia and diabetes mellitus 2 will be addressed in stratified analyses.

For historical reference the primary evaluation, i.e. the on-treatment analysis, will be compared to the same results reported from the Nordinet® IOS database. It is not expected that there will be big differences in the baseline characteristics between the Nordinet® adult population and the population investigated in this study. If there are big differences between baseline characteristics, a matching procedure will be considered when making the comparison. In addition, a sensitivity analysis will be performed, restricting the primary evaluation to a European population only.

9.7.2.2 Analysis of secondary endpoint(s)

Analyses in the following specific populations of patients will be conducted: Females on oral oestrogen therapy; Adult-onset GHD; Childhood-onset GHD, transition phase from 18 to 25 years and patients switching from daily or other weekly GH treatment after the time of enrolment in the study. Results will be reported separately for treatment-naïve and prevalent users of GH replacement therapy.

Stratified analyses will be performed according to the IGF-I levels (IGF-I SDS [-2, 0], [0, +2] and >+2) at baseline.

Count-data secondary endpoints:

The analyses of the following secondary endpoints will be performed both for the in-study and on-treatment observation period, in the same way as the analysis of the primary endpoint:

- Number of AEs
- Number of SAEs
- Number of medication errors (incorrect dose administration rate)

Continuous secondary endpoints:

For the following secondary endpoints, the change will be estimated by length of follow-up and by treatment duration. Patients on oral oestrogen therapy and patients with childhood-onset GHD will be addressed in stratified analyses. The effect of a previous GH replacement therapy on the health-related quality of life will be checked in stratified analyses.

- Change in IGF-I SDS
- Change in weight
- Change in BMI
- Change in waist circumference
- Change in waist-hip ratio
- Change in lipid profile
- Change in HbA1C
- Change in bone density
- Change in bone mineral content
- Change in total body fat mass
- Change in truncal fat mass
- Change in lean body mass
- Change in body fat percentage
- Change in VAT
- Change in liver function
- Change in PRO score (TRIM-AGHD)

Categorical secondary endpoints:

The binary categorisation of the endpoints Patient achieving IGF-I SDS target (0 -+2) and Patient reaching satisfactory clinical response will be used to calculate the proportion (%) of patients achieving these criteria.

9.7.2.3 Analysis of exploratory endpoint(s)

The number of sick days and physician visits in the AGHD WSI will be converted into visits per year. The impact on productivity and ability to do regular activities will be analysed in the same way as the secondary endpoint Change in PRO score (TRIM-AGHD).

The number of anti-diabetic medications will be presented in descriptive tables for the subgroup of patients with diabetes mellitus type 2 at baseline by length of follow-up and by treatment duration.

9.7.3 Interim analysis

The interim reports are planned with data cut at 3 and 6 years after FPFV respectively and will include the same analytic approach as the final report.

9.7.4 Sequential safety analysis/safety monitoring

Events listed in the endpoints will be reported as SAEs, ARs and AEs, and summarized separately by statistical analysis.

9.8 Quality control

9.8.1 Monitoring procedures

During the course of the study, monitoring should be performed to ensure that the protocol has been adhered to. The extent of source data verification and validation of endpoints will be described in the CRA monitoring plan.

9.8.2 Critical documents

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

- Regulatory approval and/or notification as required
- Documentation of the physician's qualifications as medically qualified (for instance a short CV or authorisation)
- Signed and dated agreement on the final protocol
- Approval/favourable opinion from Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (or other appropriate bodies as required locally) clearly identifying the documents reviewed: the protocol including version, patient information/informed consent form and any other written information to be provided to the patient, patient enrolment procedures
- Copy of IEC/IRB approved patient information/informed consent form/any other written information/advertisement (or document of waiver by IEC/IRB of informed consent)
- Non-interventional study agreement

9.8.3 Retention of study documentation

Novo Nordisk will comply with Good Pharmacoepidemiology Practice (GPP)[5] and relevant national legislation related to archiving of study documentation.

The physician must agree to archive the documentation pertaining to the study in an archive for 5 years after final report/first publication of the study, whichever comes later. The physician should not destroy any documents without prior permission from Novo Nordisk

Novo Nordisk 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.

9.9 Limitations of the research methods

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.

AGHD is characterised by low prevalence, resulting in the need to capture data from many different regions and settings. In addition to the non-interventional nature of the study, 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.

In any non-interventional study, there is a risk of selection bias, affected by the willingness and/or ability of physicians and patients to participate in the study. 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.

Considering that AGHD is a rare disease, the inclusion of Nordinet® IOS historical comparison group will provide an unique opportunity to evaluate the long-term safety, including the detection of rare adverse events, as well as the clinical parameters of GH replacement therapy across a heterogeneous patient population.[3] Furthermore, patient data in this Sogroya® (somapacitan) prospective NIS (present study) and Nordinet® IOS historical comparison group are considered to be comparable, as natural history of the disease or the management of AGHD, i.e., diagnostic criteria and treatment options over the past 10 years (time-course of data collection in the Nordinet® IOS) has not changed significantly. However, the proposed historical comparator is a finalised non-interventional study and therefore has the same potential limitations as mentioned above. The comparability between the results of the two studies and any limitations in the conclusions will therefore be thoroughly discussed in the final study report.

9.10 Other aspects

Not applicable section, as all aspects of the study is covered by the previous sections.

10 Protection of human subjects

The study will be conducted in accordance with GPP[5], applicable regulatory requirements and in accordance with the declaration of Helsinki.[8]

10.1 Informed consent form for study patients

A voluntary, signed and personally dated informed consent form will be obtained from the patient prior to any study-related activity.

The physician must give the patient information in a form that the patient 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 regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki[8].

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 withdraws the previously given informed consent, the patient's data will be handled as follows:

- Data collected will be used as part of the statistical analysis
- Safety events will be reported to Global Safety, Novo Nordisk/health authorities.

Data will be collected and handled in accordance with local law 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.

In accordance with regulatory requirements, including GVP, the sponsor will inform the health authorities of Sogroya® (somapacitan) ADRs. In certain situations, other adverse events may be subject to expedited reporting, if required by health authorities. In addition, Novo Nordisk will inform the IECs/IRBs (or other appropriate bodies as required locally) of Sogroya® (somapacitan) related serious adverse reactions, in accordance with the local requirements in force.

10.4 Premature termination of the study

The sponsor may decide to stop the study or part of the study at any time. However, the study may only be terminated prematurely after consultation and in agreement with relevant regulatory authorities.

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

11 Management and reporting of adverse events/adverse reactions

11.1 Collection of adverse events and other safety information

Safety definitions and a guideline for evaluation of outcome, severity and causality can be found in Appendix A.

All adverse events including all fatal outcomes on Sogroya® (somapacitan) which occur after informed consent is obtained and until the end of study for each participating patient must be collected and reported to Novo Nordisk.

If the physician becomes aware of events of overdose, abuse, misuse, medication errors, lack of therapeutic effect or occupational exposure related to the study product treatment with or without an associated suspected adverse reaction, this should be reported to Novo Nordisk on the NIS Safety Form and on the medication error, misuse and abuse form (misadministration). These events will be summarised by Novo Nordisk in the interim and final study reports.

For female patients: Pregnancies and pregnancy outcome should be collected including **adverse events** in the pregnant patient, foetus or newborn infant from birth to 12 months of age.

11.2 Reporting of adverse events

Adverse events must be reported by the physician on the NIS Safety Form in EDC.

The physician should record the diagnosis, if available. If no diagnosis is available, the physician should record each sign and symptom as individual adverse events. When a diagnosis becomes available, the diagnosis should be reported, and the signs and symptoms covered by the diagnosis should be described.

Several signs, symptoms or diagnoses can be reported on the same NIS Safety Form if they are part of the same clinical picture. This can be done by filling out one adverse event section per sign, symptom and diagnosis.

The physician must report adverse events (non-serious and serious) to Novo Nordisk within **3 calendar days** of the physician's knowledge of the event. Adverse events must be reported using the NIS Safety Form.

The physician must complete the NIS Safety Form in the EDC application within the above specified timelines of obtaining knowledge about the event(s). The physician must sign the form

within 7 days after completing the forms. If the EDC application is unavailable, paper forms must be filled out and forwarded electronically in an encrypted manner, or by fax or courier copies.

Contact details of Novo Nordisk affiliate safety responsible to which safety events should be reported if not reported through EDC will be supplied to the participating sites.

11.3 Adverse Events requiring additional data collection

The following AEs require additional data collection:

- Neoplasms (including all benign and malignant neoplasms)
- Medication Errors, misuse and abuse (misadministration) related to the study product treatment

For AEs requiring additional data collection, an event specific form should be completed in addition to NIS safety form regardless of seriousness of the event (note that full NIS safety form should be filled in for neoplasms within 3 calendar days regardless of seriousness of the event). Event specific forms should be filled and reported within **14 calendar days** of the physician's knowledge of the event.

11.4 Follow-up on safety information

All serious adverse events, serious adverse reactions and non-serious adverse reactions must be followed until the outcome of the event or reaction is "recovered", "recovered with sequelae" or "fatal" and until all queries have been resolved. Cases of chronic conditions, cancer, serious adverse reactions, serious adverse events or non-serious adverse reactions ongoing at the time of death (that is, the patient dies from another serious adverse event) can be closed with the outcome of "recovering" or "not recovered". Cases can be closed with an outcome of "recovering" when the patient has completed the study and is expected by the physician to recover.

All other non-serious adverse events must be followed until the outcome of the event is "recovering", "recovered" or "recovered with sequelae" or until the end of study, whichever comes first, and until all queries related to these adverse events have been resolved. Adverse events ongoing at time of death (that is, patient dies from another adverse event) can be closed with an outcome of "recovering" or "not recovered".

Follow-up information concerning previously reported adverse events must be reported by the physician on the NIS Safety Form **within 3 calendar days of** the physician's knowledge of the follow-up information.

All follow-up information requested by Novo Nordisk must be forwarded to Novo Nordisk within **14 calendar days** from the date specified on the request, unless otherwise specified in the follow-up information request.

The physician must ensure that the worst-case severity and seriousness is kept consistent through the series of forms used for safety reporting. The follow-up information should only include new (update and/or additional) information that reflects the situation at the time of the physician's signature.

11.5 Regulatory reporting requirements for adverse events

Sponsor's assessment of expectedness of adverse events is done according to the Company Core data sheet for Novo Nordisk product(s).

In addition, local expectedness assessment of adverse events is done according to local reference safety information document for reporting to national health authorities where required by local legislation.

11.6 Collection and reporting of technical complaints

Technical complaints on Sogroya® (somapacitan) which is considered related to an, according to study, collected adverse event/serious adverse event or adverse reaction/serious adverse reaction must be reported to Novo Nordisk along with safety information on the NIS Safety Form. Reporting timelines for technical complaints are the same as for reporting of adverse event/serious adverse event or adverse reaction/serious adverse reaction described in section 11.2.

Technical complaints NOT related to an adverse event/serious adverse event or adverse reaction/serious adverse reaction or technical complaints related to an adverse event not covered by the reporting requirements in section 11.1 may be reported to Novo Nordisk affiliate via the spontaneously reporting system.

11.7 Reporting of pregnancies in female patients and adverse events in pregnant patients, foetus or newborn infant

Female patients:

Pregnancy must be reported on the paper pregnancy form **within 14 calendar days** of the physician's first knowledge of the pregnancy.

Elective termination of the pregnancy for medical reasons or any adverse events or pregnancy complications experienced by the pregnant female should be reported as AEs or SAEs on the NIS Safety Form within the timelines specified in section 11.2 for reporting of AEs/SAEs. Spontaneous abortion will always be considered a SAE and should be reported as such.

The outcome of the pregnancy and follow-up information on the newborn including medication during lactation should be reported on the designated pages of the paper pregnancy and pregnancy outcome form. Pregnancy outcome and follow-up information on the newborn should be reported **within 14 calendar days** of the physician's first knowledge of the pregnancy outcome and follow-up information. The physician must follow the newborn infant periodically until at least 12 months of age.

In case of abnormal pregnancy outcome, adverse events experienced by the foetus or newborn infant or adverse reactions in an infant exposed via breast milk then a paper NIS Safety Form should also be filled out using the patient identification of the Female patient (mother) followed by an "x" (e.g. 145060x) The timelines for reporting are the same as the ones specified in section 11.2 for reporting AEs/SAEs.

Paper forms should be sent by fax or encrypted email to: <Novo Nordisk Affiliate address >

11.8 Precautions/Over-dosage

For information concerning precautions and procedures to be observed in the event of overdose of Sogroya® (somapacitan) please see the latest edition of the SmPC or corresponding local product labelling text.

11.9 Novo Nordisk safety committee(s)

Novo Nordisk has an internal somapacitan safety committee that performs ongoing safety surveillance of Sogroya® (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 for regulatory purposes and for the safety surveillance of Sogroya® (somapacitan). All information supplied by Novo Nordisk in connection with this study must remain the sole property of Novo Nordisk and is to be considered confidential information. No confidential information must be disclosed to others without prior written consent from Novo Nordisk. 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.

12.1 Registration of study information

In accordance with Novo Nordisk's commitment to transparency in clinical activities, this study will be registered on `ClinicalTrials.gov´ and www.novonordisk-trials.com no later than at enrolment of the first study participant. At least one study site per participating country will be included in the study registration.

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 European Medicines Agency and accessible through the European Medicines Agency's web portal.

If applicable the study will be registered at national study registries in addition to www.clinicaltrials.gov.

12.2 Communication and publication

Novo Nordisk 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. Novo Nordisk 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 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 physician must ensure submission of the results of the study (either abstracts or full study report) 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 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 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 and physician allows the latter to independently prepare publications based on the study results. Also PASS studies in Europe require Novo Nordisk to communicate to the EMA 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 has discretion to determine who will have access to the database.

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 disease and/or product studied in this study.

13 References

1. Höybye C, Sävendahl L, Christesen HT, Lee P, Pedersen BT, Schlumpf M, et al. The NordiNet® International Outcome Study and NovoNet® ANSWER Program®: rationale, design, and methodology of two international pharmacoepidemiological registry-based studies monitoring long-term clinical and safety outcomes of growth hormone therapy (Norditropin®). Clin Epidemiol. 2013;5:119-27.
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3. Yuen KCJ, Biller BMK, Radovick S, Carmichael JD, Jasim S, Pantalone KM, et al. American Association of Clinical Endocrinologists and American College of Endocrinology guidelines for management of growth hormone deficiency in adults and patients transitioning from pediatric to adult care. Endocr Pract. 2019;25(11):1191-232.
4. Yuen KCJ, Llahana S, Miller BS. Adult growth hormone deficiency: clinical advances and approaches to improve adherence. Expert Rev Endocrinol Metab. 2019:1-18.
5. International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). 2015 2015.
6. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) Module VIII - Post-authorisation safety studies (EMA/813938/2011 Rev 3). 2017.
7. Brod M, Hojbjerre L, Adalsteinsson JE, Rasmussen MH. Assessing the impact of growth hormone deficiency and treatment in adults: development of a new disease-specific measure. J Clin Endocrinol Metab. 2014;99(4):1204-12.
8. World Medical Association. WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. Last amended by the 64th WMA General Assembly, Fortaleza, Brazil. October 2013.

Appendix A
Safety definition and evaluation of outcome, severity, and causality

Abuse

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

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject 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 reaction (AR)

An Adverse reaction (AR) is a response to a medicinal product which is noxious and unintended. This includes AR 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 AR may be associated with the use of a drug, a medical device or both.

An AR 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 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 the Sogroya® (somapacitan)

Hospitalisation

When a patient stays at the hospital for treatment or observation for more than 24 hours. However, medical judgement must always be exercised, and when in doubt, the hospital contact should be regarded as a hospitalisation.

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 AR
- Not associated with an AR
- 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.

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.

Non-serious

An AE or AR that does not fulfil the requirement for being an SAE or SAR.

Occupational Exposure

An exposure to a medicinal product, as a result of one’s professional or non-professional occupation. It does not include the exposure to one of the ingredients during the manufacturing process before the release of a finished product.

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. Example 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.

Outcome categories and definitions

- Recovered/resolved – The patient has fully recovered from the condition, or by medical or surgical treatment the condition has returned to the level observed at the first study related activity after the patient has signed the informed consent.

- Recovering/resolving – The condition is improving, and the patient is expected to recover from the event. This term is only applicable if the patient has completed the study or has died from another AE.

- Recovered/resolved with sequelae – The patient has recovered from the condition, but with a lasting effect due to a disease, injury, treatment or procedure. If a sequela meets a SAE criterion, the AE must be reported as a SAE.

- Not recovered/not resolved – The condition of the patient has not improved, and the symptoms are unchanged, or the outcome is not known.

- Fatal – (only applicable if the patient died from a condition related to the reported AE. Outcomes of other reported AE in a patient before he/she died should be assessed as "recovered/resolved", "recovering/resolving", "recovered/resolved with sequelae", or "not recovered/not resolved". An AE with fatal outcome must be reported as an SAE.

- Unknown – This term should only be used in cases where the patient is lost to follow-up.

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.

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 subject 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 Reaction (SAR)

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

Severity assessment definitions

Mild – No or transient symptoms, no interference with the patient's daily activities.

Moderate – Marked symptoms, moderate interference with the patient's daily activities.

Severe – Considerable interference with the patient's daily activities, unacceptable.

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 adverse event but does not concern the adverse event itself.

ANNEX 1. List of Stand-alone Documents

List of Stand-alone Documents

Number	Document reference number	Title
1	VV-TMF-4377145	Attachment I: Global List of key staff and relevant departments and suppliers of clinical relevance
2	Master Document: VV-TMF-4361535 Local signed documents will be filed for every participating country by the affiliate responsible person	Attachment II: Country list of key staff and relevant departments
3	Master Document VV-TMF-4436069	Agreement on protocol
4	Master document VV-TMF-4388758 Local translated documents will be filed for every participating country by the affiliate responsible person	Participation information and agreement to take part form

ANNEX 2. ENCePP Checklist for Study Protocols

ENCePP Checklist for Study Protocols

Study title:
A multi-national, multi-centre, prospective, single-arm, observational, non-interventional post-authorisation safety study to investigate long-term safety of Sogroya® (somapacitan) in adults with growth hormone deficiency (AGHD) under routine clinical practice

EU PAS Register® number: pending
Study reference number (if applicable): NN8640-4515

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)	☐	☒	☐	
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Study will be registered in the EU PAS Register® prior to First patient first visit

Progress reports will be submitted in line with PSUR.

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 -8.3

[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 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.4 9.7.2.2
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
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.4
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1.1
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:

Not applicable for this study

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	☒	☐	☐	9.1
	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:

Country or origin isn’t relevant for this study

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)	☒	☐	☐	
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)	☒	☐	☐	
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:

Treatment (dosing) according to normal practice and label. All relevant dosing and treatment information will be captured in the eCRF for this study

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 9.2.8
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)	☒	☐	☐	9.2.8.9

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)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

As described in section 9.9. due to the non-interventional nature of the study, potential confounding factors cannot be ruled out. Physicians are asked to monitor and discuss treatment and AEs with patients to ensure complete reporting.

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)	☒	☐	☐	9.7

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)	☒	☐	☐	9.2.8.8
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.2.8
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)	☒	☐	☐	9.2.8.8
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.2.7
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.2.7 9.2.8
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))	☒	☐	☐	4.1.0 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?	☐	☒	☐	9.7.2.1

Comments:

Not applicable for this study

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)	☒	☐	☐	9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
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? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
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:

Not applicable for this study

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:

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

Date: 15/Feb/2022

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

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