Protocol

Study ID:

CROITRE Registry :French registry of children treated with Norditropin® for short stature associated with Noonan Syndrome (PASS)

Redacted protocol
Includes redaction of personal identifiable information only.

.

Study information

Title	French registry of children treated with Norditropin® for short stature due to Noonan Syndrome (PASS)
Protocol authors	[redacted], Novo Nordisk France [redacted]
Protocol version identifier	9.0
Date of last version of protocol	15 February 2022
EU PAS Register number	Study not yet registered
Active substance	Somatropin (ATC code :H01AC01)
Medicinal product	Norditropin®
Product reference	
Procedure number	GH-4831
Marketing authorisation holder(s)	Novo Nordisk
Joint Post Authorisation Safety Study (PASS)	Yes
Research question and objectives	The present study has been designed to develop a French registry of children treated with Norditropin® for short stature due to Noonan Syndrome (NS). The primary objective is to describe the long-term change of height in children treated with Norditropin® for short stature due to NS over a 4-year period* in routine clinical practice in France. The secondary objectives apply to children treated with Norditropin® for short stature due to NS: • To describe the long-term safety profile of Norditropin® in children with short stature due to NS • To describe the socio-demographic and clinical characteristics of NS children treated with Norditropin® • To describe the therapeutic care of NS children treated with Norditropin®

* The follow-up period in this study is 4 years with possibility of extension for patients who did not reach adult height.

	○ Describe GH treatment patterns ○ Describe other NS treatments • To describe the characteristics of NS in children treated with Norditropin® in terms of auxological characteristics, diagnosis, and NS comorbidities • To describe the change of health-related quality of life (HRQoL) of NS children treated with Norditropin® and their parents/Legally Acceptable Representative (LAR) The exploratory objectives are as follows: • To identify driving factors that are associated with HRQoL • To identify driving factors that are associated with change in height (SDS) over a 4-year period*
Country of study	France

*The follow-up period in this study is 4 years with possibility of extension for patients who did not reach adult height.

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List of abbreviations

ADHD	*Attention deficit hyperactivity disorder*
AE	*Adverse Event*
ADR	*Adverse Drug Reaction*
AMH	*Anti-Müllerian Hormone*
BMI	*Body Mass Index*
CBC	*Complete Blood Count*
CI	*Confidence Interval*
CNIL	*French Data Protection Agency*
CPP	*Committee for Protection of Persons*
CRF	*Case Report Form*
CRO	*Contract Research Organisation*
CT	*Transparency Committee*
CTCAE	*Common Terminology Criteria for Adverse Events*
CV	*Coefficient of variation*
GAS	*Growth Analysis Set*
ECG	*Electrocardiogram*
EDC	*Electronic Data Capture*
eCRF	*Electronic Case Report Form*
EU PAS	*The EU electronic register of post-authorisation studies maintained by the European Medicines Agency*
FAS	*Full Analysis Set*
FSH	*Follicle-Stimulating Hormone*
FT4	*Free Thyroxine*
(rh)GH	*(recombinant human) Growth Hormone*
GHD	*Growth Hormone Deficiency*
GPP	*Good Pharmacoepidemiology Practice*
GVP	*Good Pharmacovigilance Practice*
HAS	*French National Authority for Health*
Hb	*Haemoglobin*
HbA_{1c}	*Haemoglobin A_{1c}*
HDL	*High-density lipoproteins*

(HR)QoL	*(Health Related) Quality of Life*
Ht	*Haematocrit*
IEC	*Independent Ethics Committee*
IRB	*Institutional Review Board*
IGF-1	*Insulin-like growth factor 1*
IGFBP-3	*IGF Binding Protein-3*
ISPE	*International Society for Pharmacoepidemiology*
LAR	*Legally Acceptable Representative*
LDL	*Low-density lipoproteins*
LH	*Luteinizing Hormone*
LVES	*Left Ventricular Ejection Fraction*
LVFS	*Left Ventricular Fractional Shortening*
MAH	*Marketing Authorisation Holder*
MedDRA	*Medical Dictionary for Regulatory Activities*
MCH	*Mean Corpuscular Haemoglobin-*
NAH	*Near Adult Height*
NIS	*Non-interventional Study*
NS	*Noonan Syndrome*
PASS	*Post Authorisation Safety Study*
PMP	*Project Management Plan*
PT	*Prothrombin Time*
PTT	*Partial Thromboplastin Time*
SAE	*Serious Adverse Event*
SADR	*Serious Adverse Drug Reaction*
SAS	*Safety Analysis Set*
SDS	*Standard Deviation score*
SMR	*Service Medical Rendu*
TSH	*Thyroid-Stimulating Hormone*
ULIS	*Units localized for school inclusion*

2 Responsible parties

In this document physician refers to the individual overall responsible for the conduct of the Non-Interventional Study (NIS) at a study site.

3 Abstract

- **Title:** French registry of children treated with Norditropin® for short stature due to Noonan Syndrome-NS (PASS)

Planned milestones:

Milestone	Planned date
Start of data collection (FPFV)	March 2022
Last Patient First Visit (LPFV)	March 2024
Last Patient Last Visit (LPLV)	March 2028
Study progress reports	Monthly update during implementation, inclusion & follow-up
Interim report of study results	October 2025
Final report	August 2028

Background and Rationale:

Norditropin® (NN-220; somatropin; Novo Nordisk A/S, Denmark), a recombinant human growth therapy (rhGH) produced by genetic recombinant technology, is currently the sole approved medication for the treatment of short stature due to NS in France. In October 2020, the Transparency Committee (CT- *Commission de Transparence*) rated the actual clinical benefit (SMR- *Service Medical Rendu*) of Norditropin® as "important" and issued a favourable opinion for inclusion of Norditropin® on the list of reimbursed proprietary medicinal products in NS children with short stature (< -2 SDS)(1).

Despite the existing literature documenting the effect of GH therapy on height outcomes, long-term effectiveness and safety data associated with Norditropin® treatment is needed. Furthermore, information on quality of life in NS patients remains scarce. Hence, the CT has requested the development of a national registry of NS children with short stature and treated with Norditropin® until adulthood. Data should be available within five years. This registry shall provide information on long-term clinical evolution of these patients (e.g adult height and quality of life) and on the safety profile of Norditropin® (notably the risk of tumour, effect on glucose metabolism and cardiac defects). The CT has also recommended that data collection be defined in collaboration with French reference and competence centres.

To respond to the CT request, Novo Nordisk will establish a French registry of NS children treated with Norditropin® for short stature to assess the long-term growth evolution and safety of

Norditropin®. Children will be followed-up for 4 years (with possibility of extension for patients who did not reach adult height) in hospital setting notably in French reference/competence centres specialized in the care of short stature due to NS (the rare endocrine disorders network referred as FIRENDO). This registry also aims to collect data on quality of life, clinical, genetic, and other relevant NS characteristics.

Objectives:

The primary objective is to describe the long-term change of height in children treated with Norditropin® for short stature due to NS over a 4-year period* in routine clinical practice in France.

All secondary objectives (as follows) apply to children treated with Norditropin® for short stature due to NS:

- To describe the long-term safety profile of Norditropin®
- To describe the socio-demographic and clinical characteristics of patients
- To describe the therapeutic care of patients:
  - Describe GH treatment patterns
  - Describe other NS treatments
- To describe the NS in terms of auxological characteristics, diagnosis, and NS comorbidities
- To describe the change in health-related quality of life (HRQoL) of patients and their parents /Legally Acceptable Representative (LAR)

The exploratory objectives are as follows:

- To identify driving factors that are associated with HRQoL
- To identify driving factors that are associated with change in height (SDS) over a 4-year period†

Description of type of study and treatment of patients

This study is a PASS. This is a non-interventional registry of children treated with Norditropin® for short stature due to NS. This study presents both a prospective and retrospective design. Data will be collected for 3 groups of patients:

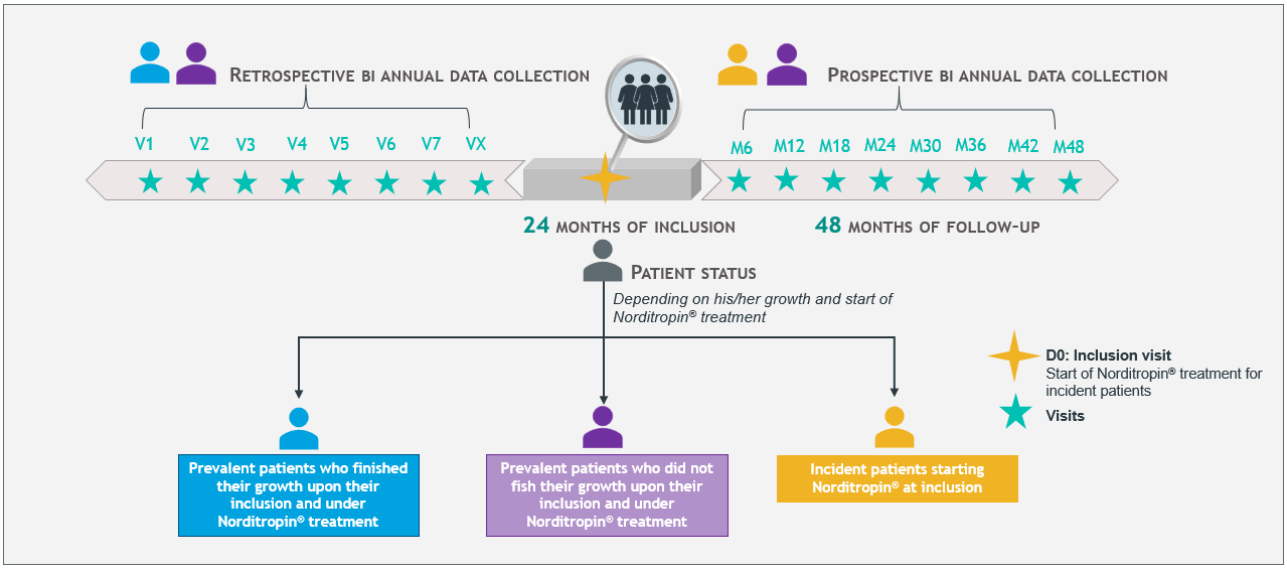
- Incident patients: Children initiating Norditropin® upon their inclusion in the study
- Prevalent patients: Children who were already treated with Norditropin® before their inclusion in the study and finished their growth upon their inclusion. For these patients, all data will be collected retrospectively from medical records

* The follow-up period in this study is 4 years with possibility of extension for patients who did not reach adult height.

- Prevalent patients: Children who were already treated with Norditropin® before their inclusion in the study and who did not finish their growth upon their inclusion. For these patients, data will be collected both retrospectively and prospectively

HRQoL data will be collected on incident patients only. The inclusion period will last for 24 months and patients will be followed-up for 4 years, with possibility of extension for patients who did not reach adult height. This will allow to provide interim results on October 2025 to the French National Authority for Health (HAS). A total of 9 visits (1 inclusion visit: D0 and 8 follow-up visits: M6, M12, M18, M24, M30, M36, M42, M48) are planned. Each visit is allowed within one-month window. All information will be collected as per physicians' routine of care.

The design of the registry is displayed below :



Eligibility criteria .

Inclusion criteria

- Patients with a clinical and/or genetic diagnosis of NS
- Patients who are treated with Norditropin® (already treated or initiating) and who are followed in a participating centre
- The decision to initiate treatment with commercially available Norditropin® has been made by the patient/parents/Legally Acceptable Representative (LAR) and the treating physician before and independently from the decision to include the patient in this study.

Exclusion criteria

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

- Patients/Parents/LAR opposed to the collection and processing of their children's medical data.
- Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation

Withdrawal criteria

- Patient withdrawal (opposition)
- Lost to follow-up
- Death

Key assessment variables

Norditropin® treatment patterns

- Date at start (baseline)
- Dose at Norditropin® treatment start in mg/kg/day (baseline)
- Date at the end of treatment (at one of the follow-up visit)
- Dose of Norditropin® in mg/kg/day at the end of follow-up (at one of the follow-up visit)

Auxological characteristics

- Age at gestational age in weeks (baseline)
- Weight at birth, 1 year, 2 years and 3 years of age in kg (baseline)
- Length at birth, 1 year, 2 years and 3 years of age in cm (baseline)
- Head circumference at birth, 1 year, 2 years and 3 years of age in cm (baseline)
- Mother's height in cm (baseline)
- Father's height in cm (baseline)
- Adult height (AH) in SDS (at one of the follow-up visit)

Health-Related Quality of Life

- PedsQL score (from baseline until end of follow-up)

Data sources

The data required to address the registry objectives come from the medical records, prescription records, laboratory and questionnaires administered to patients (patient reported outcomes-PROs). Study investigators (or clinical research associates (CRAs) will capture data through an e CRF.

HRQoL will be collected directly from incident patients and their parents by using a self-administered validated quality of life questionnaire (PedsQL).

- **Number of patients to be studied**

According to experts' input, a maximum of 50 eligible incident patients could be included during the 24 months inclusion period. It is expected that the number of eligible patients initiating Norditropin® before 2020 would be lower since that there was no market authorisation for this indication yet and would not exceed 30 patients per year. Considering that eligible prevalent patients initiated Norditropin® from 2010, that 79% of solicited sites will be participating in the study (30 sites over 38) and that 80% of eligible patients will be included (excluding opposition, patient not regularly followed by this site), it is estimated that a maximum of 221 patients will be included in the registry.

Finally, the proportion of evaluable patients for the primary criteria (patients that have height measurements until the end of their 4 years follow-up or until they reach adult height (AH)) is planned to be 80%. Therefore, it is estimated that this study will enrol a maximum of 177 patients evaluable for the primary criteria.

Data analysis

There are 3 patients population considered in this study:

- Overall population: All patients included in the eCRF.
- Full Analysis Set (FAS): All patients included in the eCRF and meeting all selection criteria. All secondary analyses will be performed on FAS.
- Growth Analysis Set (GAS): All patients from the FAS for which the primary criteria can be evaluated, i.e. height measurements available until the end of the 4-year follow-up or AH is reached, whatever occurs first.

A descriptive analysis will be conducted on all study endpoints for which data has been collected both on FAS (GAS for primary endpoint) and per subgroups of interest as long as that the sizes of the subgroups are relevant for statistical estimations.

4 Amendments and updates

None.

5 Milestones

Table 1 Milestones

Milestone	Planned date
Start of data collection (FPFV)	March 2022
Last Patient First Visit (LPFV)	March 2024
Last Patient Last Visit (LPLV)	March 2028
Study progress reports	Monthly update during implementation, inclusion & follow-up

Milestone	**Planned date**
Interim report of study results	October 2025
Final report	August 2028

6 Rationale and background

6.1 Background

Norditropin® (NN-220; somatropin; Novo Nordisk A/S, Denmark), a recombinant human growth hormone (rhGH) produced by genetic recombinant technology, is currently the sole approved medication for the treatment of short stature due to NS in France. In October 2020, the Transparency Committee (CT- *Commission de Transparence*) rated the actual clinical benefit (SMR- *Service Medical Rendu*) of Norditropin® as "important" and issued a favourable opinion for inclusion of Norditropin® on the list of reimbursed proprietary medicinal products in NS children with short stature (< -2 SDS)(1). The CT has recommended that Norditropin® treatment be initiated under following conditions:

- After resolution of feeding difficulties associated with (or not) underweight, given that these disorders are common before the age of 2. Thus, clinical data on efficacy and safety should be evaluated in paediatric patients aged at least 3 years.
- After genetic diagnosis confirmation to optimize NS management.
- At the lowest dosage of RCP (0.033 mg/kg/day). The dosage should be tailored to each patient and adjusted every six months based on clinical response (growth velocity and height) and treatment tolerance (IGF-1 monitoring).

6.2 Study Rationale

Given the complexity of NS management and potential risks associated with Norditropin® administration, the CT has also advised that Norditropin® be solely prescribed by paediatric endocrinologists and that the follow-up of NS children be coordinated by French reference/competence centres of NS (1).

Despite the existing literature documenting the effect of GH therapy on height outcomes, long-term effectiveness and safety data associated with Norditropin® treatment is needed. So far, data on use of Norditropin® treatment in NS children with short stature remain limited and arise mostly from observational studies with small number of patients and restricted follow-up, notably until adult height. This is of importance when considering that GH therapy should be initiated early, and for a prolonged time. Furthermore, information on quality of life in NS patients remains scarce, while literature has shown that short stature has been associated with lower HRQoL. To our knowledge, no study has specifically assessed the evolution of HRQoL in NS children with short stature and under GH treatment.

Hence, the CT has requested the development of a national registry of NS children with short stature and treated with Norditropin® until adulthood. Data should be available within five years. This registry shall provide information on long-term clinical evolution of these patients (e.g adult height and quality of life) and on the safety profile of Norditropin® (notably the risk of tumour, effect on

glucose metabolism and cardiac defects). The CT has also recommended that data collection be defined in collaboration with French reference and competence centres.

To respond to the CT request, Novo Nordisk will establish a French registry of NS children treated with Norditropin® for short stature to assess the long-term growth evolution and safety of Norditropin®. Children will be followed-up for 4 years (with possibility of extension for patients who did not reach adult height) in hospital setting notably in French reference/competence centres specialized in the care of short stature due to NS (the rare endocrine disorders network referred as FIRENDO). This registry also aims to collect data on quality of life, clinical, genetic and other relevant NS characteristics.

A committee of experts (referred as the scientific committee) was constituted to provide support in the data to be collected in the registry. This scientific committee consists of physicians practicing in reference/competence centres of the FIRENDO network.

7 Research question and objectives

The present study has been designed to develop a French registry of children treated with Norditropin® for short stature due to NS.

7.1 Primary objective

The primary objective is to describe the long-term change of height in children treated with Norditropin® for short stature due to NS over a 4-year period* in routine clinical practice in France.

7.2 Secondary objectives

All secondary objectives (as follows) apply to children treated with Norditropin® for short stature due to NS:

- To describe the long-term safety profile of Norditropin®
- To describe the socio-demographic and clinical characteristics of patients
- To describe the therapeutic care of patients
    - Describe GH treatment patterns
    - Describe other NS treatments
- To describe the NS in terms of auxological characteristics, diagnosis, and NS comorbidities
- To describe the change in health-related quality of life (HRQoL) of patients and their parents /Legally Acceptable Representative (LAR)

* The follow-up period in this study is 4 years with possibility of extension for patients who did not reach adult height.

7.3 Exploratory objectives

The exploratory objectives are as follows:

- To identify driving factors that are associated with HRQoL
- To identify driving factors that are associated with change in height (SDS) over a 4 year* period

8 Research methods

8.1 Study design

This study is a PASS. This is a non-interventional registry of children treated with Norditropin® for short stature due to NS. This study aims to provide data on long-term growth evolution and safety of Norditropin® as well as HRQoL data. This registry will include the entirety of children treated with Norditropin® for short stature due to NS over the inclusion period. In consequence, this registry will enroll both patients who received Norditropin® before its marketing authorization for short stature due to NS in France and patients who received Norditropin® after its approval.

This study presents both a prospective and retrospective design. Data will be collected for 3 groups of patients:

- Incident patients: Children initiating Norditropin® upon their inclusion in the study.
- Prevalent patients:
    - Children who were already treated with Norditropin® before their inclusion in the study and finished their growth upon their inclusion. For these patients, all data will be collected retrospectively from medical records.
    - Children who were already treated with Norditropin® before their inclusion in the study and who did not finish their growth upon their inclusion. For these patients, data will be collected both retrospectively and prospectively.

HRQoL data will be collected on incident patients only.

The inclusion period will last for 24 months and patients will be followed-up for 4 years with possibility of extension for patients who did not reach AH. This will allow to provide interim results on October 2025 to the HAS.

All information will be collected as per physicians' routine of care and as this study is non-interventional, neither clinical interventions nor laboratory assessments will be imposed as per this protocol.

* The follow-up period in this study is 4 years with possibility of extension for patients who did not reach adult height.

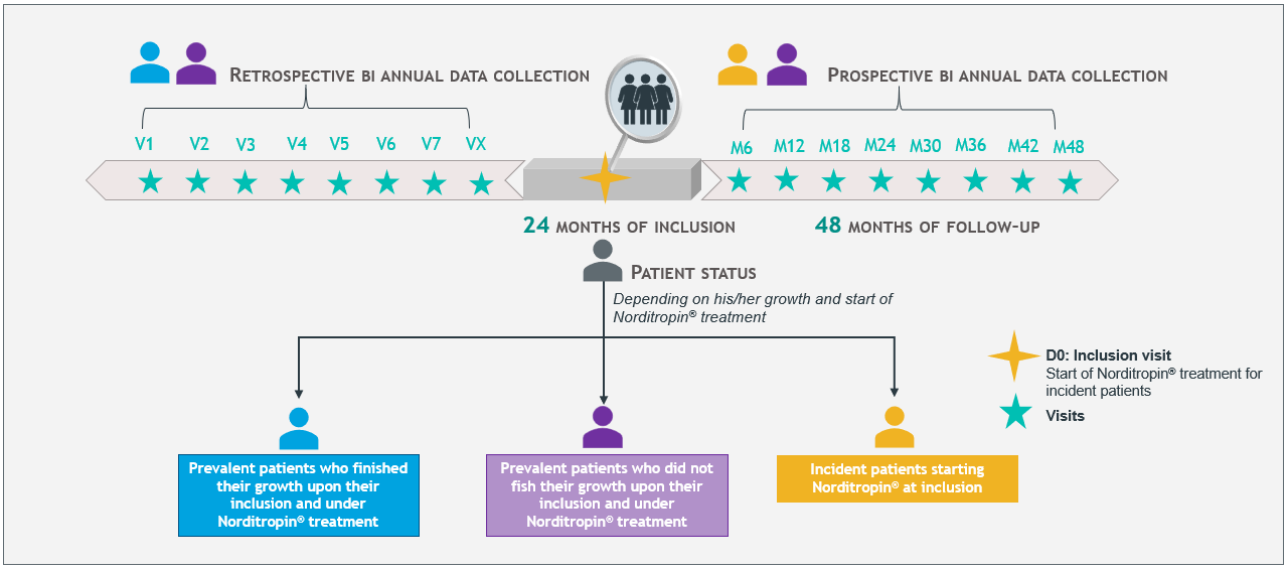
For incident patients, a visit schedule is provided based on the standard clinical practice for GH treatment in NS. We anticipate that each child included in this registry sees his/her enrolling physician every 6 months based on recommendations. A total of 9 visits (1 inclusion visit: D0 and 8 follow-up visits: M6, M12, M18, M24, M30, M36, M42, M48) are planned. Each visit will be allowed within one- month visit. However, no follow-up visits will be mandated by this study and the enrolling physician may not strictly comply with the schedule provided if considered as not relevant.

For prevalent patients who finished their growth upon their inclusion, all data will be collected retrospectively from medical records bi-annually from the start of Norditropin®.Visits will be referred as V1, V2, V3… VX.

For prevalent patients who did not finish their growth upon their inclusion, data will both be collected retrospectively from medical records bi-annually from the start of Norditropin® and prospectively every 6 months following the inclusion visit.

The design of the registry is displayed in Figure 8-1. This is a PASS.

Figure 8-1 Study design



8.1.1 Endpoint(s)

All endpoints are assessed during long-term routine use of Norditropin® treatment and apply to children treated with Norditropin® for short stature due to NS.

Assessments at baseline (such as sex, age at start of Norditropin® etc.) and at single time points are included in 8.2.10 section.

8.1.1.1 Primary endpoint

Table 2 Primary endpoint

Title of endpoint	Time frame	Unit
Change in height standard deviation score	From start of Norditropin® treatment until end of follow-up	SDS

The change in height in SDS (measured in scores -10 to +10) will be derived from recent national growth chart reference(2).

8.1.1.2 Secondary endpoints

Secondary objective-1: To evaluate the long-term safety profile of Norditropin®.

All drug related adverse reactions (ADR), serious adverse drug reactions (SADR), serious adverse events (SAE) and adverse events (AE) will be recorded and described up to the end of growth development or end of follow-up if earlier**.** The endpoints related to the secondary objective-1 are listed in Table 3 **.**

Table 3 Secondary endpoints in relation to secondary objective 1

Title of endpoint	Time frame	Unit
Number of adverse drug reactions (ADR)	From start of Norditropin® until end of follow-up	Count of events
Number of serious adverse drug reactions (SADR),	From start of Norditropin® until end of follow-up	Count of events
Number of serious adverse events (SAE)	From start of Norditropin® until end of follow-up	Count of events
Number of adverse events (AE)	From start of Norditropin® until end of follow-up	Count of events

Secondary objective-2: To describe the socio-demographic and clinical characteristics of patients. The endpoints related to the secondary objective-2 are listed in Table 4.

Table 4 Secondary endpoints in relation to secondary objective 2

Title of endpoint	Time frame	Unit
Socio-demographic		
Education	From start of Norditropin® treatment until end of follow-up	NA
School level	From start of Norditropin® treatment until end of follow-up	NA
Educational measures	From start of Norditropin® treatment until end of follow-up	NA
Clinical characteristics		

Title of endpoint	Time frame	Unit
Tanner stage	At all visits	NA
Change in pulse rate	From start of Norditropin® treatment until end of follow-up	Beats per minute
Change in diastolic blood pressure	From start of Norditropin® treatment until end of follow-up	mm Hg
Change in systolic blood pressure	From start of Norditropin® treatment until end of follow-up	mm Hg
Change in corrected QT-interval (Electrocardiogram)	From start of Norditropin® treatment until end of follow-up	msec
Change in echocardiogram parameters	From start of Norditropin® treatment until end of follow-up	mm (Left ventricular interventricular septal maximum thickness in diastole) mm (Left ventricular end diastolic diameter) % (Left Ventricular Fractional Shortening (LVFS)) % (Left Ventricular Ejection Fraction (LVEF) Cm/s (Diastolic function (Ea)) Cm/s (Diastolic function (Aa))
Change in complete blood count (CBC)	From start of Norditropin® treatment until end of follow-up	g/dL (Haemoglobin-Hb) G/L (White blood cells) G/L (Lymphocytes) G/L (Monocytes) G/L (Platelets)
Change in IGF-1 level	From start of Norditropin® treatment until end of follow-up	ng/ml and SDS
Change in HbA_{1c} level	From start of Norditropin® treatment until end of follow-up	%
Change in fasting insulin level	From start of Norditropin® treatment until end of follow-up	mg/dL or mUI/L
Change in fasting blood glucose level	From start of Norditropin® treatment until end of follow-up	mg/dL or g/L or mmol/L

Title of endpoint	Time frame	Unit
Change in fasting total cholesterol	From start of Norditropin® treatment until end of follow-up	mg/dl or g/L or mmol/L
Change in fasting triglycerides	From start of Norditropin® treatment until end of follow-up	mg/dL or g/L or mmol/L
Change in fasting HDL cholesterol	From start of Norditropin® treatment until end of follow-up	mg/dL or g/L or mmol/L
Change in fasting LDL cholesterol	From start of Norditropin® treatment until end of follow-up	mg/dL or g/L or mmol/L
Change in fasting total cholesterol/HDL ratio	From start of Norditropin® treatment until end of follow-up	NA
Change in inhibin B	From start of Norditropin® treatment until end of follow-up	pg/mL
Change in AMH	From start of Norditropin® treatment until end of follow-up	mg/mL
Change in LH (female from 8 years old and male from 9 years old)	From start of Norditropin® treatment until end of follow-up	mg/mL
Change in FSH (female from 8 years old and male from 9 years old))	From start of Norditropin® treatment until end of follow-up	UI/L or mUI/mL
Change in oestradiol (female from 8 years old and male from 9 years old))	From start of Norditropin® treatment until end of follow-up	pg/mL
Change in testosterone (female from 8 years old and male from 9 years old)	From start of Norditropin® treatment until end of follow-up	ng/mL

Secondary objective-3: To describe the therapeutic care of patients
The endpoints related to the secondary objective-3 are listed in Table 5.

Table 5 Secondary endpoints in relation to secondary objective 3

Title of endpoint	Time frame	Unit
Norditropin® treatment patterns		
Change in dose of Norditropin® treatment	From start of Norditropin® treatment until end of follow-up	mg/kg/day
Frequency of injections of Norditropin® treatment per week	From start of Norditropin® treatment until end of follow-up	Count of events
Number of modifications (change in dosage/ temporary stop)	From start of Norditropin® treatment until end of follow-up	Count of events
Reasons for treatment modifications	From start of Norditropin® treatment until end of follow-up	NA
Duration of temporary stop	From start of Norditropin® treatment until end of follow-up	Months

Title of endpoint	Time frame	Unit
Total duration of Norditropin® treatment	From start of Norditropin® treatment until end of follow-up	Years
Total cumulative dose of Norditropin® treatment	From start of Norditropin® treatment until end of follow-up	mg/kg
Other NS treatments		
Type and number of concomitant treatments	At all visits	Count of events
Type and number of concomitant treatments linked to an adverse event	At all visits	Count of events

Secondary objective-4: To describe the NS in terms of auxological characteristics, diagnosis and NS comorbidities.
The endpoints related to the secondary objective-4 are listed in Table 6.

Table 6 Secondary endpoints in relation to secondary objective 4

Title of endpoint	Time frame	Unit
Auxological characteristics		
Change in weight	From start of Norditropin® treatment until end of follow-up	SDS
Change in body mass index (BMI)	From start of Norditropin® treatment until end of follow-up	Kg/m^2
Change in bone age	From start of Norditropin® treatment until end of follow-up	year
Change in height velocity	From start of Norditropin® treatment until end of follow-up	cm/year and SDS/year
Type and number of NS comorbidities	At all visits	NA

Secondary objective-5: To evaluate the evolution of Health-Related Quality of Life (HRQoL) of patients/Legally Acceptable Representative (LAR).
The endpoints related to the secondary objective-5 are listed in Table 7.

Table 7 Secondary endpoint in relation to secondary objective 5

Title of endpoint	Time frame	Unit
Change in HRQoL score (PedsQL)	From start of Norditropin® treatment until end of follow-up	NA

8.1.1.3 Exploratory endpoints

Table 8 Exploratory endpoints

Title of endpoint	Time frame	Unit
Improvement of HRQoL (PedsQL score)	End of follow-up	Y/N
Height at end of follow-up >-2SDS	End of follow-up	Y/N

8.1.2 Treatment of patients

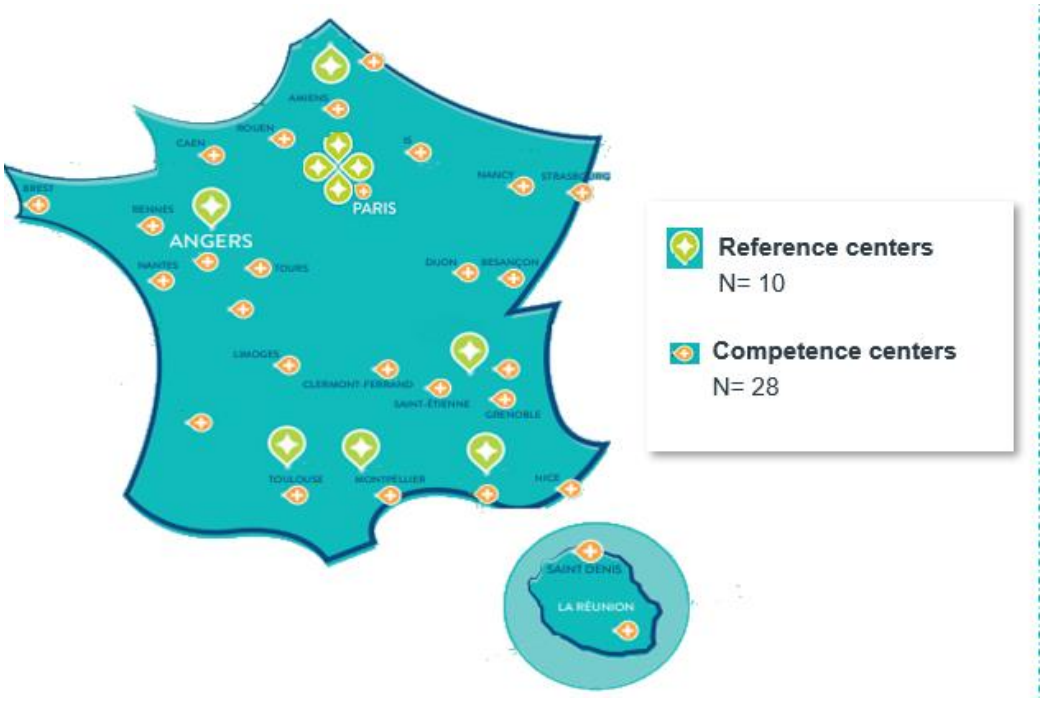
Patients will be treated with commercially available Norditropin® (NN-220; somatropin; Novo Nordisk A/S, Denmark) according to routine clinical practice at the discretion of the treating physician.

8.2 Setting

8.2.1 Sites

French reference centres for the care of short stature due to NS are gathered within the FIRENDO network. This network fulfils national missions around rare endocrine including growth and development disorders with the aim of improving the care of patients, coordinating and encouraging research and developing training and information. All the sites (reference and competence) from the FIRENDO network will be contacted to participate in the study (Figure 8-2).

Figure 8-2 French reference and competence centres of the FIRENDO network



8.2.2 Participating physicians

The population of enrolling physicians consists of paediatric endocrinologists practicing in hospital setting comprising French reference/competence centres of the FIRENDO network (Figure 8-2). A principal investigator (PI) will be designed in each site and study investigators will enrol patients into the study as per routine practice according to the inclusion and exclusion criteria defined below.

8.2.3 Study population

Planned number of patients to be included: 224

Planned number of patients to complete the study: 168

Planned time period for the study: 24 months inclusion period and 4 years follow-up (with possibility of extension for patients who did not reach their adult height)

8.2.4 Inclusion criteria

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

1. Patients with a clinical and/or genetic diagnosis of NS.
2. Patients who are treated with Norditropin® (already treated or initiating) and who are followed in a participating center.
3. The decision to initiate treatment with commercially available Norditropin® has been made by the patient/parents/Legally Acceptable Representative (LAR) and the treating physician before and independently from the decision to include the patient in this study.

8.2.5 Exclusion criteria

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

1. Patients/Parents/LAR opposed to the collection and processing of their children's medical data.
2. Mental incapacity, unwillingness or language barriers precluding adequate understanding or cooperation.

8.2.6 Rationale for selection criteria

The inclusion criteria have been defined for the purpose of developing a French registry of children treated with Norditropin® associated with Noonan syndrome in real clinical setting (no limitations on age neither bone age to reflect on clinical practices). The third inclusion criterion complies with the non-interventional type of the study, which must not interfere with the routine practice.

The first exclusion criterion complies with French regulatory requirements related to NIS (RIPH3), which does not require explicit consent from the patient. The second exclusion criterion prevents patients who cannot be fully informed (due to language barriers, mental incapacity etc.) to be included into the study.

Representativeness of the study population as regards to the source population (NS patients treated with Norditropin® for short stature) will be ensured at the national level by requiring from physicians to include in a consecutive and exhaustive manner all eligible patients seen during a consultation over the inclusion period .

8.2.7 Withdrawal criteria

The patient or the parents may withdraw from the study at will at any time. Besides, early discontinuation may occur for the following reasons:

- Patient withdrawal (opposition)
- Lost to follow-up
- Death

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

8.2.8 Visit procedures

8.2.8.1 Study flow chart

Table 9 Study flow-chart

	Baseline (M0)	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	**M42**	**M48**
Inclusion/Exclusion criteria	X								
Socio-demographic characteristics									
Year of birth	X								
Sex	X								
Education, school level and educational measures	X	X	X	X	X	X	X	X	X
Clinical characteristics									
Age of onset of puberty	X								
Date of onset of menstruations (female only)	X								
Tanner stage	X	X	X	X	X	X	X	X	X
Comorbidities of interest not related to NS	X								
Pulse rate	X	X	X	X	X	X	X	X	X
Blood pressure (diastolic, systolic)	X	X	X	X	X	X	X	X	X
Echocardiogram parameters	X		X		X		X		X
Corrected QT interval (QTc) (measured by electrocardiogram (ECG)	X		X		X		X		X
Complete blood count (CBC)	X	X	X	X	X	X	X	X	X
Haemostasis parameters	X								
IGF-1 level	X	X	X	X	X	X	X	X	X
IGFBP-3 level	X								
TSH level	X								
FT4 level	X								
HbA_{1c} level	X		X		X		X		X
Fasting insulin blood level	X		X		X		X		X
Fasting glucose blood level	X		X		X		X		X
Fasting total cholesterol	X		X		X		X		X

	Baseline (M0)	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	**M42**	**M48**
Fasting triglycerides	X		X		X		X		X
Fasting HDL level	X		X		X		X		X
Fasting LDL level	X		X		X		X		X
Fasting Ratio total cholesterol/ HDL level	X		X		X		X		X
Parameters of gonadal function (inhibin B, AMH, LH, FSH, oestradiol / testosterone)	X		X		X		X		X
NS characteristics									
Auxological characteristics									
Gestational age at birth	X								
Head circumference at birth, at 1 year, at 2 years and 3 years of age	X								
Weight at birth, at 1 year, at 2 years and 3 years of age	X								
Length at birth, at 1 year, 2 years and 3 years of age	X								
Height velocity in the first year/ 6 months preceding Norditropin® start	X								
Weight at Norditropin® start	X	X	X	X	X	X	X	X	X
Height at Norditropin® start	X	X	X	X	X	X	X	X	X
Father ‘s height	X								
Mother’s height	X								
Adult height (NAH)	X								
Bone age	X		X		X		X		X
Diagnosis									
Familial form of Noonan	X								
Parent affected	X								
Age of clinical diagnosis of NS	X								
Date of molecular diagnosis	X								
Molecular diagnosis (Type of NS-related genes mutated, and variant identified)	X								
NS comorbidities									

	Baseline (M0)	**M6**	**M12**	**M18**	**M24**	**M30**	**M36**	**M42**	**M48**
NS comorbidities	X	X	X	X	X	X	X	X	X
Therapeutic care									
Norditropin® treatment patterns									
Date of start	X								
Dose at start	X								
Dose titration		X	X	X	X	X	X	X	X
Dose at the end of treatment		X							
Frequency of injections per week	X	X	X	X	X	X	X	X	X
Treatment modifications (change in dosage, temporary stop)		X	X	X	X	X	X	X	X
Date of end of treatment		X							
Reasons for treatment modifications		X	X	X	X	X	X	X	X
Other GH treatments									
Previous GH treatments (type, dose at start and total duration)	X								
GH treatment following Norditropin® (type, dose and date of initiation)		X							
Other NS treatments									
Concomitant medications (with a focus on ADHD* medications including methylphenidate, cardiac medications, thyroid hormones, sex steroids comprising testosterone and oestrogens)	X	X	X	X	X	X	X	X	X
HRQoL									
PedsQL	X		X		X		X		X
Safety									
SAR, AR, SAE and AE		X	X	X	X	X	X	X	X
Pregnancy		X	X	X	X	X	X	X	X

*ADHD: Attention deficit hyperactivity disorder

8.2.8.2 Study visits

The physician should keep a patient enrolment log. The routine treatment of the patients enrolled into the registry should not be influenced by recruitment. Therefore, the data collected is only what is collected as part of standard routine and missing data is expected. This registry will collect data on patients during biannual visits (every 6 months) for 4 years, with possibility of extension for patients who did not reach adult height, starting from the inclusion (D0). As so 8 follow-up study visits (M6; M12; M18; M24; M30; M36; M42; M48) are anticipated. The frequency of the visits is based on actual recommendations on the follow-up of NS patients treated with GH therapy for short stature. Nevertheless, this frequency remains determined by the study site/enrolling physician.

D0 (Baseline-Inclusion)

At the initial visit, children and/or their parents will be informed about the registry objectives and overall requirements, and an information notice will be given to them by the enrolling physician. If they do not oppose to the collect and process of their medical data and are eligible to the registry, the physician will enrol the patient to the study and collect his/her data. Medical data will be collected by physicians using an electronic case report form (eCRF) for each patient. QoL data are patient reported outcomes (PROs) and as so will be collected directly from patients using a questionnaire.

Follow-up visits (from M6 until M48 every 6 months)

During follow-up visits, enrolling physicians will assess patients within clinical routine standard of care. QoL data will be collected annually (D0, M12, M24, M36 and M48) on incident patients.

All drug related adverse reactions (ADR), serious adverse drug reactions (SADR), serious adverse events (SAE) and adverse events (AE) will be recorded and described up to the end of growth development or end of follow-up, if earlier.

8.2.9 Assessments for safety and growth

Growth evolution

Growth evolution endpoints of GH treatment (Norditropin®) will be assessed by collecting height characteristics at baseline and at each follow-up visit to derive height variation in SDS, bone age, and height velocity values.

Safety

All children who received at least one administration of Norditropin® will be included in the evaluation for safety. All serious adverse events (SAE), serious adverse drug reactions (SADR), drug related adverse reactions (ADR) and adverse events (AE), regardless of causal relationship and seriousness criteria, and pregnancies that occur during follow-up will be recorded, reported and described.

At every follow-up visit, the enrolling physician ascertains the occurrence of ADR, SADR,SAE, AE and pregnancies. The physician must report ADR, SADR, SAE and AE using the NIS Safety Form to Novo Nordisk or to [redacted] within 3 calendar days of the physician's knowledge of the event. Pregnancy must be reported on the paper pregnancy form within 14 calendar days of the physician's first knowledge of the pregnancy.

Definitions and further details about ADR, SADR,SAE, AE and pregnancies are provided 10 section.

8.2.10 Other assessments

Socio-demographic characteristics

- Sex (baseline)
- Age at start of Norditropin® treatment in years (baseline)

Clinical characteristics

- Age at puberty onset (at baseline or one of the follow-up visit)
- Age at onset of menstruations (female only) (at baseline or one of the follow-up visit)
- IGFBP-3 level (baseline)
- TSH level (baseline)
- FT4 level (baseline)
- Haemostasis parameters

Norditropin® treatment patterns

- Date at start (baseline)
- Dose of Norditropin® at treatment start in mg/k/day (baseline)
- Date at the end of treatment (at one of the follow-up visit)
- Dose of Norditropin® in mg/k/day at the end of follow-up (at one of the follow-up visit)

GH treatment history

- Type and number of previous GH treatments (baseline)
- Duration of GH treatment before Norditropin® in years (baseline)
- Dose of GH treatment before Norditropin® in mg/kg/day (baseline)
- Type of GH treatment following Norditropin® (at one of the follow-up visit)
- Date of start of GH treatment following Norditropin® (at one of the follow-up visit)
- Dose of GH treatment following Norditropin® in mg/kg/day (at one of the follow-up visit)

Auxological characteristics

- Age at gestational age in weeks (baseline)
- Weight at birth, 1 year, 2 years and 3 years of age in kg (baseline)

- Length at birth, 1 year, 2 years and 3 years of age in cm (baseline)
- Head circumference at birth, 1 year, 2 years and 3 years of age in cm (baseline)
- Height velocity in the first year/six months preceding Norditropin® treatment start
- Mother's height in cm (baseline)
- Father's height in cm (baseline)
- AH in SDS (at one of the follow-up visit)

Diagnosis

- Familial form of Noonan (baseline)
- Parent affected (baseline)
- Ageof clinical diagnosis of NS (baseline)
- Molecular diagnosis performed (at one of the follow-up visit)
- Date of molecular diagnosis(at one of the follow-up visit)
- Molecular diagnosis (type of NS-related genes mutated, and variant identified) (at one of the follow-up visit)

NS comorbidities

- Type and number of NS comorbidities (baseline)

Health-Related Quality of Life (PROs): PedsQL

HRQoL will be assessed on incident patients only. They will be asked and their parents to complete the PedsQL questionnaire annually.

The PedsQL is a widely used 23-items generic questionnaire that assesses the HRQoL in children and adolescents (2 18 years) from the child- and parent perspective. This questionnaire is multidimensional measuring physical (8 items), emotional (5 items), social (5 items) and school functioning (5 items). Responses are assessed using a five-point Likert scale (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4=almost always a problem) (3).The PedsQL questionnaire is applicable for healthy school and community populations, as well as paediatric populations with acute and chronic health conditions, which proved satisfactory internal consistency reliability (α = 0.88 child, 0.90 parent report for the total scale score) (4). The PedsQL total score is computed as the sum of all the items. Items will be transformed to 0-100 scale so that higher scores indicate better HRQoL

Evaluation of PedsQL will be performed at baseline visit and at annual follow-up visits. Baseline PedsQL score will be compared with those taken after 12, 24, 36 and 48 months of Norditropin® treatment.

8.3 Variables

Table 10 Variables

Variables	Operational Definition	Measurement
Socio-demographic		
Education	Categorical variable : • Standard education • Education with assistance (special needs assistant, units localized for school inclusion (ULIS classes) and medical and education institute) • Educational measures (physiotherapy, psychomotricity, occupational therapy and speech therapy)	Endpoints
School (education) level	Categorical variable : • Preschool • Elementary school • Secondary school • High school	Endpoints
Educational measures	Categorical variable : • Physiotherapy • Psychomotricity • Occupational therapy • Speech therapy	Endpoints
Age of puberty	Continuous variable	Endpoints
Age of onset of menstruations (female only)	Continuous variable	Endpoints
Tanner stage	3 sub-scales : Pubic hair scale (both females and males) Female breast development scale (for females only) Male external genitalia scale (male only) Categorical variable : • Stage 1 • Stage 2 • Stage 3 • Stage 4 • Stage 5	Endpoints
Clinical		
Comorbidities of interest not related to NS	Categorical variable	Endpoints
Pulse rate	Continuous variable	Endpoints
Diastolic pressure	Continuous variable	Endpoints
Systolic pressure	Continuous variable	Endpoints

Variables	**Operational Definition**	**Measurement**
Echocardiogram (left ventricular interventricular septal maximum thickness in diastole, left ventricular end diastolic diameter, LVFS, LVEF and diastolic function (Ea and Aa))	Continuous variable	Endpoints
corrected QT interval	Continuous variable	Endpoints
Complete blood count (CBC) (Hb, white blood cells, lymphocytes, monocytes and platelets)	Continuous variable	Endpoints
IGF-1 level	Continuous variable	Endpoints
IGFBP- 3 level	Continuous variable	Continuous variable
TSH	Continuous variable	Continuous variable
FT4	Continuous variable	Continuous variable
HbA_{1c} level	Continuous variable	Endpoints
Fasting insulin blood level	Continuous variable	Endpoints
Fasting glucose blood level	Continuous variable	Endpoints
Fasting total cholesterol	Continuous variable	Endpoints
Fasting triglycerides	Continuous variable	Endpoints
Fasting HDL level	Continuous variable	Endpoints
Fasting LDL level	Continuous variable	Endpoints
Fasting ratio total cholesterol/ HDL level	Continuous variable	Endpoints
Inhibin-B	Continuous variable	Endpoints
AMH	Continuous variable	Endpoints
LH	Continuous variable	Endpoints
FSH	Continuous variable	Endpoints
Oestradiol	Continuous variable	Endpoints
Testosterone	Continuous variable	Endpoints
Auxology		
Gestational age at birth	Continuous variable	Endpoints
Head circumference at birth , at 1 year, 2 years and 3 years of age	Continuous variable	Endpoints
Birth weight, at 1 year, 2 years and 3 years of age	Continuous variable	Endpoints
Birth length at 1 year, 2 years and 3 years	Continuous variable	Endpoints
Weight at start of Norditropin®	Continuous variable	Endpoints

Variables	Operational Definition	Measurement
Height at start of Norditropin®	Continuous variable	Endpoints
Parents 'height	Continuous variable	Endpoints
BMI	Continuous variable	Endpoints
Height velocity in the first year/6 months preceding Norditropin® treatment start	Continuous variable	Endpoints
Height velocity	Continuous variable	Endpoints
Adult height (AH)	Continuous variable	Endpoints
Bone age	Continuous variable	Endpoints
Diagnosis		
Familial form of Noonan	Categorical variable • Yes • No	Endpoints
Parent affected (*if yes to familial form of Noonan*)	Categorical variant • Mother • Father	
Age at clinical diagnosis of NS	Continuous variable	Endpoints
Molecular diagnosis performed	Categorical variable • Yes • No	
Date of molecular diagnosis of NS (*if yes to molecular diagnosis performed*)	Continuous variable	Endpoints
Molecular diagnosis (type of NS-related genes mutated and variant identified)	Categorical variable • PTPN1 • KRAS • RAF1 • RIT1 • SHOC2 • SOS1 • SOS2 • Other	Endpoints
NS comorbidities		
NS comorbidities	Categorical variable • Cardiac defects including pulmonary valve stenosis and hypertrophic cardiomyopathy • Orthopaedic issues (pectus, scoliosis) • Anorchia in males	Endpoints
Therapeutic care		
Dose of Norditropin® treatment	Continuous variable Recorded at each study visit	Endpoints

Variables	**Operational Definition**	**Measurement**
Total duration of Norditropin® treatment	Continuous variable From start of Norditropin® treatment until end of follow-up	Endpoints
Total cumulative of Norditropin® dose	Continuous variable Total dose of Norditropin® administered from start of treatment until end of treatment	Endpoints
Frequency of injections per week	Categorical variable • 6 days/7 • 7 days/7 • Other	Endpoints
Type of treatment modifications	Categorical variable • Increase in dosage • Decrease in dosage • Temporary stop • Permanent stop	Endpoints
Duration of temporary stop	Continuous variable	Endpoints
Number of treatment modifications	Categorical variable • From 1 to 5	Endpoints
Reasons for treatment modifications	Categorical variable • Safety (occurrence of ARs or AEs) • Growth too fast • Growth too slow • Patient's or parents/LAR choice • Other	Endpoints
Type of previous GH treatments	Categorical variable	Endpoints
Dose of previous GH treatment at start	Continuous variable	Endpoints
Total duration of previous GH treatment	Continuous variable From start of previous GH treatment until the end of treatment	Endpoints
Type of GH treatment following Norditropin®	Categorical variable	Endpoints
Dose of GH treatment following Norditropin®	Continuous variable	Endpoints
Date of GH treatment following Norditropin®	Continuous variable	Endpoints
Concomitant medications	Categorical variable • ADHD medications including methylphenidate • Cardiac medications • Thyroid hormones • Sex steroids including testosterone and oestrogen	Endpoints

Variables	Operational Definition	Measurement
	• Other	
HRQoL		
PedsQL score	Categorical variable • From 0 to100	Endpoints
Safety		
Incidence rate	Number of new cases per population at risk over the follow-up period (per person-time)	Endpoints
Other co-variates (controls)		
Sites ‘geographic location	Categorical variable : • Ile-De France • North-West • West • East • South-East • South-West	Bias
Sites ‘activity size s	Continuous variable Defined by the number of children treated with Norditropin® for short stature due to NS managed over a year	Bias

8.4 Data sources

The data required to address the registry objectives come from the medical records, prescription records, laboratory and questionnaires administered to patients (patient reported outcomes-PROs). Study investigators (or clinical research associates (CRAs)) will capture data through an e-CRF.

HRQoL will be collected directly from incident patients and their parents by using a self-administered validated quality of life questionnaires (PedsQL). They will complete the questionnaires independently from physicians.

Data will be collected as per routine practice. If the data is not available, it will not be required and collected.

8.5 Study sample size

This study will set up a registry that aims to include all eligible patients treated by Norditropin® for short stature due to Noonan syndrome.

No sample size calculation is required as this registry aims to include all patients fulfilling the sets of selection criteria defined.

According to experts' input, a maximum of 50 eligible incident patients could be included during the 24 months inclusion period. It is expected that the number of eligible patients initiating Norditropin® before 2020 would be lower since that there was no market authorisation for this indication yet and would not exceed 30 patients per year. Considering that eligible prevalent patients initiated Norditropin® from 2010, that 79% of solicited sites will be participating in the study (30 sites over 38) and that 80% of eligible patients will be included (excluding opposition, patient not regularly followed by this site), it is estimated that a maximum of 221 patients will be included in the registry.

Finally, the proportion of evaluable patients for the primary criteria (patients that have height measurements until the end of their 4 years follow-up or adult height) is planned to be 80%. Therefore, it is estimated that this study will enrol a maximum of 177 patients evaluable for the primary criteria.

The height variation (in SDS) after 4 years of treatment has been evaluated in the ANSWER® Program (observational study) at 1,14 (0,13) SDS. The change in height SDS is estimated with a 11,4% coefficient of variation (ratio of standard deviation over mean).

The following table presents the precision in primary criteria measurement (with a 2-sided 95% confidence interval (CI)) for the estimation of mean height variation in SDS considering a 20% coefficient of variation. The primary criteria will be estimated with a 2.95% precision. This high level of precision enables to perform subgroup analysis with also a satisfying precision.

Table 11 Precision of the primary criteria depending on the number of evaluable patients

Sample size	**150**	**160**	**170**	**177**	**190**	**200**
Precision for 95% CI	3.2%	3.1%	3.0%	2.95%	2.85%	2.78%

The sample size (n) is calculated based on the normal approximation using the following formula:

$$N = z_{1-\alpha/2}^2 \frac{cv^2}{\varepsilon^2}$$

where:

- z is the standard normal distribution's quantile (for α=5%),
- CV is the coefficient of variation (20%),
- ε is the precision (i.e., ratio of the mean estimation that determines half width of the 95% CI).

8.6 Data management

[redacted] on behalf of Novo Nordisk will be responsible for the management of data collected in this study.

Novo Nordisk will provide electronic Case Report Forms (eCRFs) for capture of study specific patient data. Instructions for completion and correction of eCRF will be provided in the eCRF completion guidelines.

The physician must ensure that study specific patient data is entered in the eCRF according to the visits schedule (see Table 9), as much as possible. When data is entered it will be available to Novo Nordisk for data verification activities 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.

For eCRFs: The system for Electronic Data Capture (EDC) and support services for the system will be supplied by [redacted] The activities of [redacted] 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 affirmation statement/casebook the physician confirms that the information in the eCRF is complete and correct. The physician has the responsibility to maintain adequate and accurate information entered in the eCRF.

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

8.7 Data analysis

8.7.1 Definition of analysis sets

The site populations will be defined as follows:

- Contacted sites: all reference and competence centres in France will be solicitated to participate in this study
- Participating sites: all sites that agreed to participate in the study
- Active sites: all sites that included at least one eligible patient

The sites main characteristics (localisation, size) will be compared to ensure that the active sites are representative at the national level.

There are 3 patients population considered in this study:

- Overall population: all patients included in the eCRF,
- Full Analysis Set (FAS): all patients included in the eCRF and meeting all selection criteria. All secondary analyses will be performed on FAS.

- Growth Analysis Set (GAS): all patients from the FAS for which the primary criteria can be evaluated, i.e. height measurements available until the end of the 5-year follow-up or until NAH is reached, whatever occurs first.

The subgroups of interest for analyses are defined as follows:

- Norditropin® treatment duration: depending on age of onset and age at puberty onset, the patients may have shorter or longer time under GH treatment, which may highly influence auxological outcomes
- Mutated gene: PTPN11, SOC2, other

8.7.2 Statistical methods

A descriptive analysis will be conducted on all study endpoints for which data has been collected both on FAS (GAS for primary endpoint) and per subgroups of interest as long as that the sizes of the subgroups are relevant for statistical estimations.

The following statistics will be provided for quantitative variables: number of patients with non-missing and missing values, mean, standard deviation, median, first quartile (Q1), third quartile (Q3), minimum and maximum value, mode (for discrete quantitative variables with limited variability).

For qualitative variables, the number and proportion of each variable modality will be provided together with the number of missing values. Proportions will be computed based on the population with non-missing data. Missing data will not be imputed or replaced.

Exploratory comparison between study subgroups might be considered. Statistical tests will be based on the type and the variables. All comparison tests will be two-tailed with a standard type 1 error threshold of 5% (significance level).

In order to reach the exploratory objectives, logistic regressions will be implemented to identify factors linked to Norditropin® growth evolution (reaching height > -2SDS) and patients' HRQoL. The clinically relevant explanatory variables will be first tested with univariate regression. The selected variables will be processed in the multivariate regression (backward selection) and the odds-ratio with their 95% confidence interval will be used for interpretation when the variable effect is significant (5% threshold for p-value).

In addition, a mixed model will be developed to explore HRQoL scores evolution over the follow-up. Patient effect will be considered as random effect.

The patients will be enrolled in the study over a variable period limited to 24 months. The probability that a patient is included in the cohort is greater when the patient has a higher number of annual visits. This study design therefore presents several biases related to:

- the heterogeneous duration of patients' inclusion which depends on the activity size of each participating site;

- the probability that a patient is included in the cohort which depends on the frequency of annual visits.

In order to take into account the biases associated with this study design and be able to extrapolate results at the national level, adjustments will be made for descriptive analyses over the cohort using weights applied at center and patient level.

8.7.2.1 Analysis of primary endpoint

The main growth evolution endpoint is defined as the change in height Standard Deviation Score (SDS) between baseline and the end of follow-up or GH, whatever occurs first. It will be described overall and depending on the duration of Norditropin® treatment.

Height SDS is defined as the deviation of patient's height from the standard French growth curve (normal values). It is obtained from the patient's height by subtracting the normal mean and dividing by the normal standard deviation.

8.7.2.2 Analysis of secondary endpoint(s)

All secondary endpoints will be described according to the outputs defined in the statistical methods.

8.7.2.3 Analysis of exploratory endpoint(s)

Exploratory endpoints will be assessed through logistic regressions and mixed model. The models detailed characteristics and process will be described in the statistical analysis plan.

8.7.3 Interim analysis

Please refer to 8.7.2.1, 8.7.2.2, 8.7.2.3 and 8.7.4 sections

8.7.4 Sequential safety analysis/safety monitoring

All drug related adverse reactions (ADR), serious adverse drug reactions (SADR), serious adverse events (SAE) and adverse events (AE) will be classified and analysed from the initiation of the study drug until the end of follow-up.

Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher will be used for coding to "Lower Level Term (LLT)", "Preferred Term (PT)", "High Level Term (HLT)", "High Level Group Term (HLGT)" and the associated primary "System Organ Class (SOC)". CTCAE version 5 will be used to provide the grade.

AEs will be analysed as follows:

The number and percentage of patients experiencing:

- at least 1 on-treatment SAE/AE/SADR/ADR (including non-serious and serious irrespective of the relationship with the study treatment)
- at least 1 on-treatment SAE/AE/SADR/ADR related to the study treatment (including serious and non-serious AEs)
- at least 1 on-treatment serious SAE/SADR (regardless the relationship with the study treatment)
- at least 1 on-treatment serious SAE/SADR related to the study treatment
- at least 1 on-treatment SAE/AE/SADR/ADR leading to treatment discontinuation
- at least 1 on-treatment SAE/AE/SADR/ADR leading to treatment interruption/delay
- at least 1 on-treatment SAE/AE/SADR/ADR leading to dose decrease
- fatal on-treatment SAE/AE/SADR/ADR

They will be presented by SOC and preferred term.

Patient will be counted once by AE taking into account the maximum grade. The SOC/PT will be summarized (irrespective of the grade) and by maximum grade CTCAE (grade 1-2 ,3-4 and 5) as well. The incidence rate, corresponding to the number of patients experiencing at least one AE divided by the total person years of follow-up, will be calculated for each AE. A listing will be provided for fatal on-treatment AE. These analyses will be performed for the post-treatment AEs as well.

8.8 Quality control

Data entered in the eCRF will be verified as documented in the Data Validation Plan (DVP). The DVP will describe edit check specifications to ensure data accuracy and validity. A data review meeting will be set-up to resolve data inconsistencies that could not be addressed by the end of data collection. During this meeting, Novo Nordisk and [redacted] will agree on data management conventions. Database lock will occur once data review and all quality assurance procedures have been completed.

Data entered in the eCRFs that are transcribed from original documents must be consistent with the original documents or the discrepancies must be explained.

Audit

Novo Nordisk, its designees, IRBs/IECs or regulatory authorities may audit one or several study site(s), at any time during the study. The quality assurance auditor will have access to all medical records, the investigator's study-related files and correspondence, and the patient information documentation of this study to verify whether the study is being conducted in agreement with Good Pharmacoepidemiology Practices (GPP). The accuracy and integrity of data will also be verified by reviewing the study documents by focusing on key variables collected at each visit. The investigator will permit and provide direct access to all original documents.

8.8.1 Monitoring procedures

During the course of the study, monitoring should be performed to ensure that the protocol has been adhered to.

[redacted] will perform routine remote oversight of the sites' data collection activities and periodic on-site monitoring visits with the aim to:

- Assess the progress of the study,
- Ensure adherence to study protocol,
- Discuss any emergency issues,
- Verify the eCRFs for accuracy and completeness,
- Validate the consistency of the eCRFs against the source documentation.

8.8.2 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 or [redacted]:

- Notification of the declaration to the French Data Protection Agency (CNIL)
- Documentation of the physician's qualifications as medically qualified (for instance a short CV or authorisation)
- Signed and dated agreement on the final protocol
- Signed and dated agreement on any amendment(s), if applicable
- Approval/favourable opinion from the Committee for Protection of Persons (CPP), clearly identifying the documents reviewed: the protocol including version, patient information form and any other written information to be provided to the patient
- Non-interventional study agreement
- Financial contract
- Source document agreement.

8.8.3 Retention of study documentation

Novo Nordisk will comply with Good Pharmacoepidemiology Practice (GPP) 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 at least 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.

8.9 Limitations of the research methods

As this is a non-interventional study, potential confounding factors cannot be ruled out. 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.

The following source of bias will be discussed:

- Selection bias
- Information (measurement) bias

8.9.1 Selection bias

Selection bias arises when the study population is not representative of the exposure or outcome pattern in the source population. Selection bias occurs both early during the recruitment of participants and later during the process of retaining the participants for the duration of the study Registries are likely to be concerned by selection bias due to the fact that the inclusion of patients into a registry may be influenced by multiple factors such as clinical, demographic and socio-economic factors, notably in case the recruitment has not been exhaustive.

Sites' recruitment

All sites of the FIRENDO network will be contacted to participate in the study. We expect that approximately 80% of contacted sites will enrol patients into the registry, ensuring an acceptable representativeness of eligible sites. Still, sites representativeness of active sites (that include at least one eligible patient) will be compared to contacted sites to verify national representativeness (geographic location and activity size).

Patients' recruitment

This registry aims to enrol the entirety of patients treated with Norditropin® for short stature due to NS over the inclusion period and meeting the eligibility criteria. Both prevalent patients (children who were already treated with Norditropin® before their inclusion in the study) and incident patients (children initiating Norditropin® upon their inclusion in the study) will be included in the study.

To reduce the risk for physicians to influence patients' recruitment, we will provide them with clear instructions on the obligation of consecutive enrolment of patients. We expect that around 80% of eligible patients be included into the registry.

Attrition bias

This study will follow-up patients up to 4 years (with possibility of extension for patients who did not reach adult height) and as so is concerned by lost to follow-up. Attrition can threaten sample representativeness if characteristics of patients lost to follow-up differ from the other patients. To

minimize this bias, if a patient is lost to follow-up (due to change in the treating physician, moving up etc.), efforts will be undertaken to collect the data from the previous visit and physicians will be encouraged to contact the patient for AE information. Physicians will also complete a discontinuation CRF to document the reason(s) for discontinuation.

8.9.2 Information bias

Missing data

Missing data can bias the descriptions if data are not missing completely at random . The use of an eCRF that includes online checks for missing information and remote monitoring may reduce the risk of missing data (by limiting to non-existing information and exclude non-reported information).

The use of a mobile application, comprising automatic push notifications, as a tool for filling-in questionnaires (PedsQL) may limit missing data related to PROs.

Social desirability bias

With regard to HRQoL, the social desirability bias refers to the fact that patients may respond to questionnaires in the direction they perceive area of interest, notably to minimize their actual health status severity to please their treating physician. However, we consider this bias to be limited by requiring that completion of questionnaires be done independently from physicians.

8.9.3 Other bias

Another bias may occur by the omission of a variable from a regression model referred as the omitted variables bias. In this study, regression and mixed models will be developed to assess the explanatory endpoints: identify explanatory variables for HRQoL and long-term height evolution. This bias will be mitigated by conducting a literature review to identify all potential factors influencing HRQoL and long-term height evolution, which will be validated by the scientific committee. We expect that most of relevant variables be collected in this study.

8.10 Other aspects

Not applicable.

9 Protection of human subjects

The study will be conducted in accordance with GPP of the International Society for Pharmacoepidemiology (ISPE) Guidelines (5), applicable regulatory requirements, and in accordance of the Declaration of Helsinki.

9.1 Informed consent form for study patients

This non-interventional study will be conducted under the French reference methodology MR-003 "Research in the Field of Health Without Collection of Consent " updated on May 3th,2018 by the deliberation n°2018-154, which does not require explicit consent but individual patient information.

Novo Nordisk or [redacted] undertakes to inform the patients concerned about the processing of personal data within this study in agreement with the General Data Protection Regulation (EU) 2016/679. They will develop and make available to the physicians, an information notice to be given to patients, their parents and/or LAR as the patients may not be of legal age. It is the responsibility of the physicians to inform subjects on the objectives, methods and benefits expected from the study. Subjects will also be informed on their rights to oppose their participation in the study, as well as to as well as to access or to correct their data via their physician, should they choose to participate.

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

In obtaining and documenting non-opposition to data collection, the physician must comply with the applicable regulatory requirement(s) and adhere to the requirements in the Declaration of Helsinki (6).

The task of information can only be performed by the physician or another medically qualified person delegated by the physician, if permitted by local regulation, who must document the patient information and non-opposition on the medical record.

9.2 Data handling

If the patient, the parent or LAR oppose to their participation over the course of the study, 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 and health authorities.

Data will be collected and handled in accordance with local law and IRB/IEC procedures, Institutional Review Boards/Independent Ethics Committee, health authorities and other relevant national institutions/bodies.

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

In France, this study must be approved by the following relevant national bodies :

- The French Data Protection Agency – CNIL: This study will be declared to the CNIL under MR-003 . This declaration is immediate and no waiting time for approval is required. A Privacy Impact Assessment (PIA) shall be developed and submitted to the CNIL.
- The French Medical Council – CNOM: Study investigators will receive a compensation for their participation in the study. Financial agreements to be signed with investigators and study documents (synopsis, protocol and CRF) will be submitted for approval to CNOM (section L. 4113-6 of the Public Health Code).
- The Committee for Protection of Persons-CPP. This study must be approved by the CPP prior enrolling patients in agreement to with the French Law (article L. 1123-6 of the French Public Health Code).

Besides, the protocol, CRF and study reports after completion of the study must be submitted to the HAS as this study aims to address HAS's information requests regarding the use of Norditropin® for short stature due to NS (long-term effectiveness, safety, quality of life of patients etc.).

In accordance with regulatory requirements, including GVP, the sponsor will inform the health authorities of Norditropin® related adverse reactions. In certain situations, other adverse events may be subject to expedited reporting, if required by health authorities. In addition, the sponsor or [redacted] will inform ANSM (or other appropriate bodies as required locally) of Norditropin® related serious adverse reactions, in accordance with the local requirements in force.

9.3 Premature termination of the study

The sponsor may decide to stop the study or part of the study at any time.

An unplanned termination of the study could occur if any serious safety issue arises with the use of Norditropin® in the study population assessed. If a study is prematurely terminated or suspended, information must be provided to the relevant national bodies as required by national regulation and procedures.

9.4 Responsibilities

[redacted] is accountable for the conduct of the study. The conduct and management of the study is performed according to French regulations, Novo Nordisk standard operating procedures (SOPs) and the Project Management Plan (PMP) validated by the Sponsor.

The medical care given to, and medical decisions made on behalf of, patients should always be the responsibility of a qualified physician.

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 unauthorised access to data or any other processing of data against applicable law.

10 Management and reporting of adverse events/adverse reactions

10.1 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 Norditropin® which occur after informed consent is obtained and until the follow-up visit/end of study visit 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 NN on the NIS Safety Form and on the medication error, misuse and abuse form. These events will be summarised by NN 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 1 month of age.

For male patients' pregnant partners effort should be made to collect information about the pregnancy and any **adverse reactions and serious adverse events** in the foetus or newborn infant from birth to 1 month of age. Before collecting any information an ad-hoc informed consent form should be signed by the pregnant partner.

For infants exposed to a medicinal product via breast milk, suspected **adverse reactions** (serious and non-serious) should be collected and reported.

10.2 Reporting of adverse events

All drug related adverse reactions (ADR), serious adverse drug reactions (SADR), serious adverse events (SAE) and adverse events (AE) will be reported by the physician on the NIS Safety Form.

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 or to [redacted] within one (1) working day but no later than three (3) calendar days after Date of Receipt, if the

information is received e.g. during a weekend or on public holidays. Adverse events must be reported using the NIS Safety Forms to the French affiliate email address francesafety@novonordisk.com in an encrypted manner or by fax (to 01 41 97 64 77).

The physician must complete the NIS Safety Form in the eCRF (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.

10.3 Follow-up on safety information

All serious adverse events, serious adverse reactions, adverse events of special interest 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 one (1) working day but no later than three (3) calendar days after Date of Receipt of the follow-up information, if the information is received e.g. during a weekend or on public holidays.

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.

10.4 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) and according to EU Summary of Product Characteristics for non NN 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.

10.5 Collection and reporting of technical complaints

Technical complaints on Novo Nordisk product(s): Norditropin® which occur from the first time of usage of the product(s) until the last time of usage of the product(s), and which is considered related to an according to study collected adverse event/serious adverse event, adverse reaction/serious adverse reaction or adverse event of special interest (cardiac AE) must be reported to Novo Nordisk along with safety information on the NIS Safety Form within the timelines given for reporting of adverse event/serious adverse event, adverse reaction/serious adverse reaction or adverse event of special interest described in section 11.2.

Technical complaints must be reported to the email address francesafety@novonordisk.com or by fax (to 01 41 97 64 77).

10.6 Collection, storage and shipment of technical complaint samples

The physician must collect the technical complaint sample and notify the local study manager within 5 calendar days of obtaining the sample at study site. The local study manager must coordinate initiation of the shipment to Novo Nordisk and ensure that the sample is sent in accordance with local regulations as soon as possible to Novo Nordisk (locally in each country). A copy of the technical NIS safety form describing the complaint must be send with the sample, if available.

The physician must ensure that the technical complaint sample contains the batch or lot number. Storage and shipment of the technical complaint sample should be done in accordance with the conditions prescribed for the product.

10.7 Reporting of pregnancies in female patients or male patients' female partners 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 until at least 1 month 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.

Male patient's female partners:

The pregnancy must be reported **within 14 calendar days of the physician's first knowledge of the pregnancy or as soon as possible after receipt of informed consent**. Adverse reactions and any serious adverse events experienced by the foetus or newborn infant must be collected and reported on the paper NIS Safety Form using the patient identification of the Male patient (father) followed by an "y" (e.g. 145060y). 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 (01 41 97 64 77) or encrypted email to francesafety@novonordisk.com.

10.8 Precautions/Over-dosage

Short-term overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Overdose with somatropin is likely to cause fluid retention. Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the known effects of excess growth hormone (Norditropin® prescribing information last revised 03/2020).

10.9 Novo Nordisk safety committee(s)

Novo Nordisk has an internal Norditropin® safety committee that performs ongoing safety surveillance of the study product(s).

11 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 the Norditropin®. 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. 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.

11.1 Registration of study information

In accordance with Novo Nordisk's commitment to transparency in clinical activities, this study will be registered on `ClinicalTrials.gov´, www.novonordisk-trials.com , and EU PAS Register (ENCePP) 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.

11.2 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.

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 the HAS as requested by the authority. 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.

11.3 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.

12 References

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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 events of special interest (AESI)

An event which in the evaluation of safety has a special focus.

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

Causality is assessed for Norditropin®.

- *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 Norditropin®*

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

Number	**Document reference number**	**Title**
1		CRF
2		Data Management Plan
3		Data Validation Plan
4		Statistical Analysis Plan
5		Patient Information Notices