A study comparing the effect and safety of once weekly dosing of somapacitan with daily Norditropin® as well as evaluating long-term safety of somapacitan in a basket study design in children with short stature either born small for gestational age or with Turner syndrome, Noonan syndrome, or idiopathic short stature

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55970

Source
ToetsingOnline

Brief title
REAL 8

Condition

- Other condition
- Endocrine and glandular disorders NEC

Synonym
Growth disorder, Short stature

Health condition

groeistoornis

Research involving
Human

Sponsors and support

Primary sponsor: Novo Nordisk
Source(s) of monetary or material Support: Novo Nordisk

Intervention

Keyword: basket study, Norditropin®, somapacitan

Outcome measures

Primary outcome

Height velocity reported for each indication separately. From baseline (week 0)

to visit 7 (week 52) in cm/year

Secondary outcome

Key secondary endpoints

- Change in Height SDS reported for each indication separately. From baseline

(week 0) to visit 7 (week 52). Unit: -10 to +10

- Change in IGF-I SDS reported for each indication separately. From baseline

(week 0) to visit 7 (week 52). Unit: -10 to +10

- Change in fasting plasma glucose reported for each indication separately.

From screening (visit 1) to visit 7 (week 52) in mmol/L

- Change in fasting plasma glucose reported for each indication separately.

From screening (visit 1) to visit 15 (week 156) in mmol/L

- Weekly average somapacitan concentration (Cavg) based on population PK

analysis. From visit 3 (week 4) to visit 7 (week 52) in ng/mL

Study description

Background summary

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

Treatment of short stature
GH increases growth by both a direct action on the growth plates as well as by stimulating IGF-1 secretion, mainly in the liver. Human GH (hGH) also has important effects on the metabolism of proteins, lipids and carbohydrates, not only during childhood, but also throughout adult life. It is critically important to maximize height with GH therapy before the onset of puberty. The earlier GH is commenced, the more likely the child is to achieve a height that is appropriate for the target height.
In children who have a deficiency of endogenous GH (GHD), the use of GH replacement therapy stimulates linear growth and increases growth rate. In 1985, when biosynthetic GH became available on a large-scale, a large number of clinical studies investigating the effect of GH in various indications

associated with short stature and normal GH secretion were initiated. In the years that followed, recombinant human GH (rhGH) treatment was approved for use in various other indications. It was first approved for treatment of children with chronic renal insufficiency in 1993, Turner syndrome (TS) in 1990, Prader-Willi syndrome (PWS) in 2000, short children born small for gestational age (SGA) in 2001, children with idiopathic short stature (ISS) in 2003, and children with Noonan syndrome (NS) in 2007. The rationale for this treatment is based on the empirical observation of growth acceleration in response to GH administration, rather than on a pathophysiological approach.

Study objective

This study has been transitioned to CTIS with ID 2023-506927-27-00 check the CTIS register for the current data.

Primary objective
The primary objective of this study is to confirm non-inferiority of once-weekly somapacitan compared with once-daily Norditropin® in terms of longitudinal growth measured by height velocity at week 52 in children with each of the four indications SGA, TS, NS or ISS.

Key secondary objectives
The key secondary objectives of this study are to evaluate both other aspects of longitudinal growth and to evaluate safety, including long-term safety, of once-weekly somapacitan compared with once-daily Norditropin® in terms of safety parameters measured by glucose metabolism in children with each of the four indications SGA, TS, NS or ISS.
Furthermore, it is to evaluate the steady state pharmacokinetics of once-weekly somapacitan in children with each of the four indications: SGA, TS, NS or ISS.

Study design

This is an interventional, multi-national, multi-centre, randomised, open-labelled, active comparator, phase 3 basket study designed to compare the effect and safety of once weekly dosing of somapacitan versus daily Norditropin® after 52 weeks in GH treatment naïve children with short stature in each of the indications SGA, TS, NS or ISS. The main treatment phase will be followed by 104 weeks extension to further evaluate safety. The study includes four sub-studies - one for each of the above listed indications.

The study consists of:
• an up to 3-week screening period (Up to 6 weeks for TS and NS)
• a 52-week intervention period
• a 104-week extension period
• a 30-day follow-up period

Intervention

SGA: Eligible participants will be randomised in a 2:1:1 manner to receive either somapacitan 0.24 mg/kg/week (2 out of 4 participants), Norditropin® 0.035 mg/kg/day (1 out of 4) or Norditropin® 0.067 mg/kg/day (1 out of 4).

TS, NS and ISS: Eligible participants will be randomised in a 2:1 manner to receive either somapacitan 0.24 mg/kg/week (2 out of 3 participants) or Norditropin® 0.05 mg/kg/day (1 out of 3).

Treatments will be administered subcutaneously. The 52 weeks treatment period will be followed by a 2-year 1-arm extension period with once-weekly dosing of somapacitan 0.24 mg/kg/week to evaluate safety.

Study burden and risks

Benefit assessment
Information gained from this study will support the development of a growth hormone product with clinical advantages over currently available products to children with SGA, TS, NS and ISS.
For most of the participating children the administration of study intervention during the study most likely reduces the treatment burden compared to current available therapy as somapacitan is administered once weekly.
It is expected that many participating children will experience increased height velocity compared to pre-study experience.
Both children receiving somapacitan and Norditropin® might benefit from the increased attention during the participation of the study which might lead to an increase in treatment adherence.

Overall benefit-risk conclusion
Overall, the safety profile of somapacitan is similar to the well-known safety profile of daily growth hormone products e.g., Norditropin® and no new safety concerns have been found during the conduct of the somapacitan study program.
There are well known risks associated with administration of injectable medication as well as procedural risks as described in table *2 1. In this study the risks associated with administration of trial product as well as the risks associated with the study procedures are expected to be comparable to what is seen in routine clinical practice.
More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AE) of somapacitan and Norditropin® may be found in the respective IBs or any updates hereof.
Taking into account the measures taken to minimise risk and burden to children participating in this study, the potential risks identified in association with somapacitan are justified by the anticipated benefits that may be afforded to children with SGA, TS, NS and ISS.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Informed consent of parent or legally acceptable representative of participant and child assent, as age appropriate must be obtained before any study-related activities. Studyrelated activities are any procedures that are carried out as part of the study, including activities to determine suitability for the study.
2. No prior exposure to growth promoting therapy, including but not limited to growth hormone, IGF-I and ghrelin analogues.

Applicable to children with SGA:
3. Born small for gestational age (birth length below -2 SDS OR birth weight below -2 SDS OR both) (according to national standards).
4. Prepubertal children:

a) Boys:
• Age above or equal to 2 years and 26 weeks and below 11.0 years at screening.
• Testis volume below 4 mL
b) Girls:
• Age above or equal to 2 years and 26 weeks and below 10.0 years at screening.
• Tanner stage 1 for breast development: No palpable glandular breast tissue)
5. Impaired height defined as at least 2.5 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.
6. Impaired height velocity defined as annualised height velocity below the 50th percentile for chronological age and sex according to the standards of Prader calculated over a time span of minimum 6 months and maximum 18 months prior to screening.
7. Body Mass Index below the 95th percentile according to Centers for Disease Control and Prevention, Body Mass Index-for-age growth charts.

Applicable to girls with TS:
8. Confirmed diagnosis of TS by 30-cell (or more) lymphocyte chromosomal analysis.
9. Prepubertal girls:
• Age above or equal to 2 years and 26 weeks and below 10.0 years at screening.
• Tanner stage 1 for breast development: No palpable glandular breast tissue)
10. Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.
11. Historical height measured 6-18 months prior to screening.
12. Thyroid hormone replacement therapy should be adequate and stable for at least 90 days prior to randomisation, if applicable.

Applicable to children with NS:
13. Clinical diagnosis of NS according to van der Burgt score list
14. Prepubertal children:
a) Boys:
• Age above or equal to 2 years and 26 weeks and below 11.0 years at screening.
• Testis volume below 4 mL
b) Girls:
• Age above or equal to 2 years and 26 weeks and below 10.0 years at screening.
• Tanner stage 1 for breast development: No palpable glandular breast tissue)
15. Impaired height defined as at least 2.0 standard deviations below the mean height for chronological age and sex at screening according to the standards of Centers for Disease Control and Prevention.
16. Historical height measured 6-18 months prior to screening.
17. Thyroid hormone replacement therapy should be adequate and stable for at least 90 days prior to randomisation, if applicable.

Exclusion criteria

1. Known or suspected hypersensitivity to study intervention(s) or related products.
2. Previous randomisation into same sub-study in this study.
3. Receipt of any investigational medicinal product within 3 months before screening or participation in another clinical study at the time of randomisation.
4. Children with suspected or confirmed growth hormone deficiency according to local practice.
5. Children diagnosed with diabetes mellitus or screening values from the central laboratory of
a. fasting plasma glucose above or equal to 126 mg/dL (7.0 mmol/L) or
b. HbA1c above or equal to 6.5%.
6. Current inflammatory diseases requiring systemic corticosteroid treatment for longer than 2 consecutive weeks within the last 3 months prior to screening.
7. Children requiring inhaled glucocorticoid therapy at a dose greater than 400 µg/day of inhaled budesonide or equivalent (i.e., 250 µg/day for fluticasone propionate) for longer than 4 consecutive weeks within the last 12 months prior to screening.
8. Concomitant administration of other treatments that may have an effect on growth, e.g., but not limited to methylphenidate for treatment of attention deficit hyperactivity disorder (ADHD).
9. Diagnosis of attention deficit hyperactivity disorder (ADHD).
10. History or known presence of malignancy including intracranial tumours.
11. History or known presence of active Hepatitis B or Hepatitis C (exceptions to this exclusion criterion is the presence of antibodies due to vaccination against Hepatitis B).
12. Any disorder, which in the investigator*s opinion, might jeopardise participant*s safety or compliance with the protocol.
13. The participant or the parent/legally acceptable representative is likely to be non-compliant in respect to study conduct, as judged by the investigator.
14. Current treatment with sex hormones or aromatase inhibitors.

Applicable to children with SGA:
15. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements, such as, but not limited to:
a. Known family history of skeletal dysplasia.
b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
c. Any other disorder/condition that can cause short stature such as, but not limited to, psychosocial deprivation, nutritional disorders, chronic systemic illness and chronic renal disease.
d. TS (including mosaicism). India: Please see local requirements in Appendix

11.
e. NS.
f. Hormonal deficiencies.
g. Children who are small due to malnutrition defined as -2 standard deviations according to standards. 0¬-5 years: weight for height on World Health Organisation Multicentre Growth Reference Study 2006. Above 5 years: World Health Organisation 2007 Body Mass Index.
h. Known chromosomal aneuploidy or significant gene mutations causing medical *syndromes* with short stature, including but not limited to Laron syndrome, Prader-Willi syndrome, Russell-Silver Syndrome, skeletal dysplasias, abnormal SHOX gene analysis or absence of GH receptors.

Applicable to children with TS:
16. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements, such as, but not limited to:
a. Known family history of skeletal dysplasia.
b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
c. Any other disorder/condition that can cause short stature such as, but not limited to, psychosocial deprivation, nutritional disorders, chronic systemic illness and chronic renal disease.
d. NS.
e. Mosaicism below 10%.
f. TS with Y-chromosome mosaicism where gonadectomy has not been performed.
g. NYHA class II or above or requiring medication for any heart condition.
h. Coeliac disease where participant is not stable on gluten free diet for the previous 12 months prior to screening.

Applicable to children with NS:
17. Any known or suspected clinically significant abnormality likely to affect growth or the ability to evaluate growth with standing height measurements, such as, but not limited to:
a. Known family history of skeletal dysplasia.
b. Significant spinal abnormalities including but not limited to scoliosis, kyphosis and spina bifida variants.
c. Any other disorder/condition that can cause short stature such as, but not limited to, psychosocial deprivation, nutritional disorders, chronic systemic illness and chronic renal disease.
d. TS (including mosaicism). India: Please see local requirements in Appendix 11
e. Noonan-related disorders: Noonan syndrome with multiple lentigines (formerly called *LEOPARD* syndrome), Noonan syndrome with loose anagen hair, cardiofaciocutaneous syndrome (CFC), Costello syndrome, neurofibromatosis type 1 (NF1) and Legius syndrome. Genetic testing results must be available prior to randomisation to exclude these.

f. Coeliac disease where participant is not stable on gluten free diet for the previous 12 months prior to screening.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-06-2023
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Norditropin
Generic name:	somatropine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sogroya
Generic name:	somapacitan

Ethics review

Approved WMO

Date:	02-06-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-09-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-12-2022
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-01-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-06-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-07-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-10-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam

	(Rotterdam)
Approved WMO Date:	13-11-2023
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-506927-27-00
EudraCT	EUCTR2021-005607-13-NL
ClinicalTrials.gov	NCT05330325
CCMO	NL81002.078.22