foresiGHt: A multicenter, randomized, parallel-arm, placebo- controlled (double-blind) and active-controlled (open-label) trial to compare the efficacy and safety of once-weekly lonapegsomatropin with placebo and a daily somatropin product in adults with growth hormone deficiency

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Primary: To evaluate the efficacy of once-weekly lonapegsomatropin compared to placebo at 38 weeks in adults with growth hormone deficiency (GHD). Secondary: 1. To evaluate the safety and tolerability of once-weekly lonapegsomatropin in adults with...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Interventional

Summary

ID

NL-OMON52023

Source
ToetsingOnline

Brief title
foresiGHt

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Lack of growth hormone in the body ; Adult Growth hormone deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Ascendis Pharma Endocrinology Division A/S
Source(s) of monetary or material Support: Ascendis Pharma Endocrinology division A/S

Intervention

Keyword: adult growth hormone deficiency, lonapegsomatropin, multinational, weekly dosing

Outcome measures

Primary outcome

Primary Efficacy Endpoint:

Change from baseline in trunk percent fat (as assessed by dual-energy x-ray

absorptiometry [DXA]) at Week 38.

Secondary outcome

Secondary Efficacy Endpoints:

• Change from baseline in trunk fat mass at Week 38 (as assessed by DXA)

• Change from baseline in total body lean mass at Week 38 (as assessed by DXA)

Study description

Background summary

Although there are various causes of AGHD, current standard treatment aims for growth hormone replacement by daily injections of recombinant human growth hormone (rhGH). Recombinant human growth hormone was first approved in the 1980*s and hassince been on the market from
different manufacturers for various indications.Lonapegsomatropin contains the same active substance (rhGH) as currently marketed daily growth
hormone products but being a long-acting growth hormone product (LAGH) with the advantage of only requiring one injection per week, hence reducing the number

of injections per week from seven to one.

Study objective

Primary:
To evaluate the efficacy of once-weekly lonapegsomatropin compared to placebo at 38 weeks in adults with growth hormone deficiency (GHD).
Secondary:
1. To evaluate the safety and tolerability of once-weekly lonapegsomatropin in adults with GHD
2. To evaluate the pharmacokinetics (PK) of once-weekly lonapegsomatropin in adults with GHD
3. To evaluate the pharmacodynamics (PD) of once-weekly lonapegsomatropin in adults with GHD

Study design

This is a randomized, parallel-arm, placebo-controlled, active-controlled trial and designed to evaluate efficacy of lonapegsomatropin versus placebo. The daily somatropin product arm is included as a calibration arm to assist clinical judgement on the trial results.

The trial will consist of:
• Screening Period - up to approx. 4 weeks to establish eligibility (approx. 2 weeks may be added between randomization and the first dose to allow for logistics and shipments)

• Treatment Period - (38 weeks in total), consisting of: * Dose Titration Period - 12 weeks of dose titration, scheduled dose titration visits will occur at Week 4, Week 8, and Week 12
* Dose Maintenance Period - 26 weeks of maintenance treatment, trial visits will occur at Week 17, Week 28, and Week 38

• Follow-up Period - (4 weeks in total), treatment free period, AEs/SAEs will be collected via phone 2 weeks after Week 38 (Week 40), an ADA sample will be taken 4 weeks after Week 38 (Week 42)

Intervention

Randomized subjects will receive the study drug as assigned according to randomization and dosing group.
Lonapegsomatropin will be provided as a lyophilized powder in single-use glass vials requiring reconstitution with 1 mL sterile water for injection (sWFI) and administered by subcutaneous (SC) injection via syringe and needle The placebo for lonapegsomatropin drug product will contain the same excipients as lonapegsomatropin drug product but does not contain lonapegsomatropin

itself.Norditropin FlexPro or NordiFlex (somatropin) 5 mg/1.5 mL will be provided as a commercially approved solution for injection in a pre-filled pen for SC administration.

Study burden and risks

For decades, hGH has been used all over the world for different types of growth problems in children, and for controlling metabolism and body composition in adults, and has been shown to be safe and effective. Lonapegsomatropin has been investigated in healthy volunteers and patients with GHD (both in children and in adults) and no major concerns have been observed. It has been shown to be safe and well tolerated at the dose used for this study. However, like with all medications, lonapegsomatropin, placebo and Norditropin may exert side effect. The side effects that have been seen with growth hormone medications are the following: local injection site reactions, lipoatrophy and scarring, reduced insulin sensitivity and increased blood sugar levels, development of anti-growth hormone antibodies, impaired thyroid and adrenal function, intracranial hypertension, water retention, allergic reaction, pancreatitis, and headache. Lonapegsomatropin has not been studied in pregnant or nursing women. Therefore, administration of lonapegsomatropin may involve unknown risks to an embryo, foetus or nursing infant.
The following assessments will be performed during the study: blood drawing (9 times), MRI and CT assessments (once during the study, if needed), ECG (3-4 times), DXA scan (4 times), fundoscopy (2 times). A total of approximately 50 mL of blood will be taken during Screening Period, a total of approximately 60 mL will be taken during Dose Titration Period and a total of approximately 45 mL will be taken during dose maintenance period. Most visits will take up to approximately 2 - 3 hours.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Age between 23 and 75 years, inclusive, at screening.
2. AGHD Diagnosis Criteria
For adult-onset AGHD: documented history of structural hypothalamic-pituitary disease, hypothalamic-pituitary surgery, cranial irradiation, 1-4 non-GH pituitary hormone deficiencies, a proven genetic cause of GHD, or traumatic brain injury (TBI).
Subjects with childhood-onset GHD must have had GH axis re assessed at final height.
In subjects with TBI as a cause of GHD, GHD must be confirmed by GH stimulation testing performed at least 12 months after the injury.
For all subjects, documentation of test results must be available before randomization. Stimulation test protocols and results are subject to review and approval by the Medical Monitor.
A. For all countries except Japan: Subjects must satisfy at least one of the following criteria:
a. Insulin tolerance test: peak GH <=5 ng/mL
b. Glucagon stimulation test according to body mass index (BMI)
i. BMI <=30 kg/m2: peak GH <=3 ng/mL
ii. BMI >30 kg/m2: peak GH <=1 ng/mL
c. Three or four pituitary axis deficiencies (ie, adrenal, thyroid, gonadal, and/or vasopressin; not including GH) with IGF-1 SDS <= -2.0 at screening as measured by central laboratory,
d. Macimorelin test: peak GH <=2.8 ng/mL
e. Growth hormone-releasing hormone (GHRH) + arginine test according to BMI:
i. BMI <25 kg/m2, peak GH <11 ng/mL
ii. BMI >=25-<=30 kg/m2, peak GH <8 ng/mL
iii. BMI >30 kg/m2, peak GH <4 ng/mL
B. For Japan only: Subjects with adult-onset AGHD and deficiency of one or more other pituitary hormones need to satisfy at least one of the following

criteria, while subjects with isolated GHD and no evidence of intracranial structure disorder (structural hypothalamic-pituitary disease) or with adult-onset AGHD without deficiency of other pituitary hormones need to satisfy at least 2 of the following criteria:
a. Insulin tolerance test: peak GH <=1.8 ng/mL
b. Glucagon test: peak GH <=1.8 ng/mL
c. Growth Hormone-Releasing Peptide-2 (GHRP-2) tolerance test: peak GH <=9 ng/mL
3. IGF-1 SDS <= -1.0 at screening as measured by central laboratory.
4. hGH treatment-naïve or no exposure to hGH therapy or GH secretagogue for at least 12 months prior to screening.
5. For subjects on hormone replacement therapies for any hormone deficiencies other than GH (eg, adrenal, thyroid, estrogen, testosterone) must be on adequate and stable doses for >=6 weeks prior to and throughout screening.
6. For subjects not on glucocorticoid replacement therapy, documentation of adequate adrenal function at screening defined as: morning (6:00-10:00AM) serum cortisol >15.0 ng/mL (measured at central laboratory) and/or Adrenocorticotrophic Hormone (ACTH) stimulation test or ITT with serum cortisol >18.0 ng/mL at or within 26 weeks prior to screening.
7. For males not on testosterone replacement therapy: morning (6:00 10:00AM) total testosterone within normal limits for age as measured by the central laboratory at screening.
8. On a stable diet and exercise regime at screening with no intention to modify diet or exercise pattern during the trial, ie, no weight reduction program intended during the trial or within the last 90 days prior to or through screening.
9. No plans to undergo bariatric surgery during the trial.
10. Normal fundoscopy at screening (without signs/symptoms of intracranial hypertension or diabetic retinopathy stage 2 / moderate or above). For subjects with a diagnosis of diabetes mellitus at screening, this must be documented with a fundus photograph.
11. Able and willing to provide a written Informed Consent Form (ICF) and authorization for protected health information (PHI) disclosure in accordance with Good Clinical Practice (GCP).

Exclusion criteria

1. Known Prader-Willi Syndrome and/or other genetic diseases that may have an impact on an endpoint; individual cases to be discussed by the Investigator with the Medical Monitor.
2. Diabetes mellitus at screening if any of the following criteria are met:
a. Poorly controlled diabetes, defined as HbA1c >7.5% at screening according to central laboratory
b. Diabetes mellitus (defined as HbA1c >=6.5% and/or fasting plasma glucose >=126 mg/dL and/or plasma glucose >=200 mg/dL two hours after oral glucose tolerance test) diagnosed <26 weeks prior to screening

c. Change in diabetes regimen (includes dose adjustment) within <90 days prior and throughout screening
d. Use of any diabetes drugs other than metformin and/or DPP 4 inhibitors for a cumulative duration of greater than 4 weeks within 12 months prior to screening
e. Diabetes-related complications at screening (ie, nephropathy as judged by the investigator, neuropathy requiring pharmacological treatment, retinopathy stage 2 / moderate and above within 90 days prior to screening or during screening)
3. Active malignant disease or history of malignancy. Exceptions to this exclusion criterion:
a. Resection of in situ carcinoma of the cervix uteri
b. Complete eradication of squamous cell or basal cell carcinoma of the skin
c. Subjects with GHD attributed to treatment of intracranial malignant tumors or leukemia, provided that a recurrence-free survival period of at least 5 years prior to screening is documented in the subject*s file based on a Magnetic Resonance Imaging (MRI) result
4. Evidence of growth of pituitary adenoma or other benign intracranial tumor within the last 12 months before screening.
5. Subjects with acromegaly without remission / with documented remission less than 24 months prior to screening.
6. Subjects with Cushing*s disease without remission / with documented remission less than 24 months prior to screening.
7. Subjects with prior cranial irradiation or hypothalamic-pituitary surgery: the procedure took place less than 12 months prior to screening.
8. Any disease or condition that, in the judgement of the investigator, may make the subject unlikely to comply with the requirements of the trial or any condition that presents undue risk from the investigational product or procedures.
9. Participation in another interventional clinical trial involving an investigational compound within 26 weeks prior to screening or in parallel to this trial.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	32
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	LONAPEGSOMATROPIN
Product type:	Medicine
Brand name:	Norditropin FlexPro 5mg/1.5 ml
Generic name:	Somatropin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-02-2021
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-04-2022
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2020-000929-42-NL
ClinicalTrials.gov	NCT04615273
CCMO	NL75768.029.21