A Phase 3, Multicenter Study Designed to Evaluate the Efficacy and Safety of a Long Acting hGH Product (MOD-4023) in Adult Subjects with Growth Hormone Deficiency

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Primary objective:* Demonstrating clinical superiority of MOD-4023 compared to placebo in terms of reduction of fat mass (FM) in adults persons with GHDSecondary objectives:* Determining the efficacy of MOD-4023 compared to placebo in other body…

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

Summary

ID

NL-OMON38522

Source
ToetsingOnline

Brief title
Prolor CP-4-005 - MOD-4023

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Growth Hormone Deficiency

Research involving
Human

Sponsors and support

Primary sponsor: PROLOR Biotech Ltd.
Source(s) of monetary or material Support: PROLOR Biotech Ltd.

Intervention

Keyword: Efficacy, Growth Hormone Deficiency, MOD-4023, Phase 3

Outcome measures

Primary outcome

Primary endpoint:

Changes in trunk FM, expressed in kilos measured by DXA, from baseline to week

26

Secondary outcome

Secondary endpoints:

Changes in body composition:

* Change in total FM, expressed in kilos measured by DXA, from baseline to week

26 and 52

* Change in lean body mass, expressed in kilos measured by DXA, from baseline

to 26 and 52 weeks

* Change in trunk FM, expressed in kilos measured by DXA, from baseline to 52

weeks

* Change in trunk FM, expressed as % change from baseline, measured by DXA,

from baseline to 26 and 52 weeks

Change in Biochemical markers:

* Change in IGF-I and IGF-I SDS levels over the visits

* Change in IGFBP-3 levels over the visits

* The proportion of the subjects who have achieved normalisation of the IGF-I

level during and at the end of the study (Week 26 and Week 52).

Additional measurements:

* Change in QoL

* Change in waist-hip ratio

* Change in lipid profile: Fasted HDL cholesterol, LDL cholesterol,

triglycerides, Lp(a)

Safety and tolerability

* Adverse events and local tolerability (injection site reaction)

* Parameters of glucose metabolism:

- Fasting insulin level

- Fasting glucose levels

- HbA1c levels

* Immunogenicity

- Occurrence of anti-MOD-4023 neutralising antibody

* IGF-I levels

* MOD-4023 levels

* Status of other hormonal axes

- Thyroid hormones (Free T4, T3 and TSH)

- Cortisol levels in the morning

- Prolactin levels (screening, 6 months, 12 months)

* Other lab parameters, including serum chemistry profile, liver enzymes,

haematology and urinalysis

* ECG (screening, 6 months, 12 months)

* Fundoscopy for the occurrence of raised intracranial pressure

Study description

Background summary

Human growth hormone (hGH) is a pituitary protein that stimulates hepatic production and release of insulin-like growth factor-I (IGF-I) into the systemic circulation. IGF-I is instrumental in the promotion of linear growth in children and in the control of metabolism and body composition in adults.

A GH deficiency (GHD) results in inadequate circulating IGF-I levels and is manifested as abnormal linear growth in children. Adult GHD results in decreased lean body mass, increased fat mass, weakness, reductions in exercise capacity, muscle mass/strength, cardiac performance and bone density and in neuropsychological disturbances

The majority of currently available hGH products require daily or every other day subcutaneous or intramuscular injections to maintain hGH blood levels within the effective therapeutic window. The burden of daily administration and its concomitant side effects (e.g., injection site discomfort, transient edema and arthralgia) cause a reduction in compliance and can limit the therapeutic utility of existing formulations.

Prolor produced a long-acting hGH (MOD4023), which may obviate the need for the numerous injections currently required in marketed
hGH products. As demonstrated in animal models and clinical studies, MOD-4023 may be injected once per week resulting in similar clinical efficacy as compared to daily injections of r-hGH.

Study objective

Primary objective:
* Demonstrating clinical superiority of MOD-4023 compared to placebo in terms of reduction of fat mass (FM) in adults persons with GHD

Secondary objectives:
* Determining the efficacy of MOD-4023 compared to placebo in other body composition variables (such as lean body mass and waist-hip ratio)
* Evaluating the safety and tolerability of MOD-4023 compared to placebo in adult subjects with GHD
* Determining the IGF-I and IGFBP-3 serum levels

Study design

This will be a randomised, double-blind, placebo-controlled, parallel-group, multi-centric study in adult subjects with GHD. The initial dose of the study medicine will differ by gender, age and oestrogen treatment (the latter is only applicable to women);

The study will consist of two treatment periods, as follows:
Treatment period I: 26-week double-blind, placebo-controlled (DBPC) period
Treatment period II: 26-week, long-term, open-label extension period (OLE) with a two-week wash-out period; in this period, all subjects will receive MOD-4023 with the primary aim of collecting addition data concerning safety and efficacy. The same subjects in each dose stratification group will participate in both study periods, unless they terminate the study early.

Intervention

MOD-4023 is administered once per week as a subcutaneous (SC) injection in the thighs or abdomen. Injection sites must be rotated.

Placebo is administered once per week as an SC injection in the thighs or abdomen. Injection sites must be rotated.

The initial volume for weekly administration of placebo will be consistent with the equivalent MOD-4023 volume at a concentration of 5, 10 or 20 mg/ml. In order to maintain the blinding, dose adjustments will also be introduced for the placebo patients.

Study burden and risks

During the trial the patient performs 17 visits to the hospital. During these visits vital signs will be measured and blood will be collected, no more than 30mL per visit. A questionnaire for quality of life will be completed. At home, the patient needs to complete a patient diary.

MOD-4023 is an investigational product and can cause expected or unexptected side effects.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Men and women between the age of 23 to 70 years old at screening, inclusive;2. GHD subjects as defined in the Consensus guidelines for the diagnosis and treatment of adults with GH deficiency II (2007). The following cutoff values for the diagnosis of GHD will be used ;* Insulin tolerance test or glucagon test, the validated cutoff for GHD in adults is a peak GH response * 3 µg/L;* Growth-hormone-releasing hormone (GHRH) + arginine: for those with a body mass index:;- BMI <25 kg/m2, a peak GH *11 µg/L; ;- BMI 25*30 kg/m2 (included), a peak GH*8 µg/L; ;- BMI >30 kg/m2, a peak GH*4 µg/L.;3. Subjects using hormonal replacement therapy(s) for deficiencies of other hypothalamo-pituitary axes must be on an optimized and stable treatment regimen (hormone levels within normal ranges on screening) for at least three months prior to screening:;* Temporary adjustment of glucocorticoid replacement therapy, as appropriate, is acceptable. ;* Peripheral thyroid hormones (FT4) within the normal range of the central lab.;* Adrenal insufficiency * subjects that are

sufficient with documented test in last 6 months or on stable replacement. ;4. Subjects with Diabetes Insipidus should be on stable treatment for at least 6 months;5. No rhGH replacement therapy or use of GH secretagogues for at least 9 months with any registered or investigational rhGH or GH secretagogue product.;6. The IGF-I level at screening *-1 SDS of the age and sex normal ranges according to the central laboratory measurements.;7. For patients treated for Cushing's, at least two years elapsed since pituitary surgery and in biochemical remission without current medical therapy for the condition, documented within 6 months of study entry;8. Body Mass Index (BMI, kg/m2) of 23.0 to 35.0 kg/m2, both inclusive;9. Confirmed to be negative for anti r-hGH antibodies at the time of screening. ;10. Women of childbearing potential must agree to use appropriate contraceptive methods. For the purposes of this protocol, a history of tubal ligation, bilateral oophorectomy or hysterectomy, or post-menopausal women constitutes non-fertility. Fertile men must agree to use a barrier contraceptive (condom). Vasectomy older than 6 months is also acceptable.;11. Women of childbearing potential must have a negative serum pregnancy test at inclusion. ;12. Up to date cancer screening according to Dutch Screening Guidelines for the Early Detection of Cancer ('bevolkingsonderzoek') for breast, cervical, colon. Up to date cancer screening for prostate cancer (through PSA measurement at screening) and skin cancer through physical examination at screening.
13. Subjects who are on a stable diet and exercise regime and do not have plans to modify their diet or exercise for at least 12 months.;14. Subject had a DXA screening and the results are interpretable according to the study plan.;15. Willing and able to provide written informed consent prior to performing any study procedures.

Exclusion criteria

1. Women who are pregnant or breast-feeding (at least 6 months delay from childbirth or lactation);2. Evidence of growth benign intracranial tumor within the last 12 months (determined by comparing a previous MRI to a new one obtained no more than 6 months prior to study entry to clarify dynamics of growth).;3. History of any cancer. Exceptions to this exclusion criterion include resected in situ carcinoma of the cervix and squamous cell or basal cell carcinoma of the skin with complete local excision. Patients with GHD attributed to treatment of intracranial malignant lesions in childhood or adulthood (or, tumors) or leukemia may also be enrolled into the study provided that a recurrence-free survival period of at least 5 years is well documented in the study record.;4. Signs of intracranial hypertension at screening;5. Heart insufficiency, NYHA class > 2 ;6. History of overt diabetes mellitus (including currently treated, well-controlled DM) defined according to the American Diabetes Association (ADA) Criteria. A history of gestational diabetes, resolved after childbirth, is not exclusionary. ;7. Impaired liver function defined as: ;a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than three times the upper limit of normal (ULN) at Screening visit in a patient without prior history of elevated LFTs 5(non-alcoholic fatty liver disease is not excluded, but requires etiological clarification prior to eligibility confirmation);OR;b. Total bilirubin greater than 2 times the ULN at Screening;8. Subjects with severe renal failure at the Screening visit (defined by GFR < 30 mL/min using MDRD Study Equation);9. History of Acromegaly;10. For patients treated for Cushing's, biochemical, documented evidence of possible recurrence within 2 months of study entry according to

2008 Endocrine Society Guideline ;11. Active Carpal tunnel syndrome suspected on a recent history (last 6 months) or ongoing symptoms such as: Numbness, or tingling in hand and/or finger, pain in the arm, palm or forearm, both occurring also at night and with intensive use of the hand; trouble gripping objects and weakness in the thumb.;12. Systemic corticosteroids other than in replacement doses within the 3 months before study entry (temporary adjustment of glucocorticoids, as appropriate, is acceptable);13. Anabolic therapy or supplements (subject to Medical Monitor's decision) other than gonadal steroid replacement therapy within 2 months before study entry;14. History of non-compliance with medications, un-cooperativeness or drug abuse;15. Subjects who, based on the investigator*s judgment, have a clinically significant or unstable medical or surgical condition that may preclude safe and complete study participation. Conditions may include cardiovascular, peripheral vascular, pulmonary, hepatic, renal, or neurological disease, as determined by medical history, physical examination, laboratory tests or ECG.;16. Subjects who participated in any study and had administration of an investigational medicinal product (IMP) within the last 2 months. Subjects with previous participation in investigational studies must have recovered from all adverse effects. ;17. Subjects who participated within the last 12 months in any clinical trial involving the use of medicinal products (investigational or approved) that impact insulin levels, or that included specific dietary or physical activity requirements are excluded;18. History of positive serology to HBC, HBV and HIV (patients that have been previously vaccinated and therefore have positive serology are not excluded);19. Subjects with genetic causes of familial lipodystrophy.

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:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	MOD-4023
Generic name:	MOD-4023

Ethics review

Approved WMO Date:	29-07-2013
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-01-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	31-07-2014
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
EudraCT	EUCTR2013-000830-37-NL
CCMO	NL45383.078.13