A Randomized, Double-blind, Placebo-controlled, Adaptive Study to Evaluate Symptom Improvement and Metabolic Control Among Adult Subjects With Symptomatic Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone [rhPTH(1-84)]

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Ethical review	Approved WMO
Status	Completed
Health condition type	Endocrine and glandular disorders NEC
Study type	Interventional

Summary

ID

NL-OMON55679

Source
ToetsingOnline

Brief title
SHP634-401

Condition

- Endocrine and glandular disorders NEC

Synonym
Insufficient thyroid function

Research involving
Human

Sponsors and support

Primary sponsor: Shire Human Genetic Therapies, Inc.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Hypoparathyroidism, Metabolic Control, Parathyroid, Symptom Improvement

Outcome measures

Primary outcome

The primary objective is to test the hypothesis that rhPTH(1-84) treatment can result in superior improvements in the symptoms of hypoparathyroidism as assessed by the Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale compared with standard therapy.

Secondary outcome

The key secondary objectives are to test the hypotheses that rhPTH(1-84) treatment can result in superior improvements in:

- Fatigue as assessed by the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) compared with standard therapy.

- The physical component summary (PCS) derived from the 36-Item Short Form Health Survey version 2 (SF-36v2) acute version compared with standard therapy.

Study description

Background summary

Chronic hypoparathyroidism is a rare disease characterized by hypocalcemia and insufficient levels of parathyroid hormone (PTH).

Until recently, standard therapy for hypoparathyroidism consisted of calcium and vitamin D supplementation, which only addresses the hypocalcemia characteristic of this disorder. Other metabolic disorders associated with hypoparathyroidism are not addressed by standard therapy.
The pivotal Phase 3 clinical study in the rhPTH(1 84) program demonstrated that rhPTH(1-84) is effective in maintaining serum calcium levels and enabling significant decreases in active vitamin D and oral calcium doses, when administered subcutaneously once daily for 6 months. Long-term, open label studies have supported these findings with subjects maintaining the physiologic benefit derived from rhPTH(1-84) treatment .
A review of safety data across the hypoparathyroidism program indicated that rhPTH(1 84) is safe for use for the treatment of hypoparathyroidism.

Study objective

The primary objective is to test the hypothesis that rhPTH(1-84) treatment can result in superior improvements in the symptoms of hypoparathyroidism as assessed by the Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale compared with standard therapy.

Study design

This is a randomized, double-blind, placebo-controlled, 2-arm, adaptive study in a minimum of 92 to no more than 150 adult subjects with symptomatic chronic hypoparathyroidism on standard therapy. The study periods will be as follows: a 3-week screening period; a 16-week dose-titration period; a 10-week maintenance-dosing period with minimal change in investigational product dose; and a 4-week safety follow-up period that includes an end-of study contact for all subjects 30 days following the last dose of investigational product. The safety follow-up period includes weekly visits for subjects discontinuing rhPTH(1-84) treatment after the end-of-treatment visit (Week 26) or early termination visit. Subjects transferring to commercial rhPTH(1-84) who experienced a treatment gap of >7 day after the EOT (Week 26) visit will proceed with weekly follow-up visits for every week that there is an interruption in rhPTH(1-84) dosing until receiving commercial rhPTH(1-84) or until a maximum of 30 days has elapsed.
Immediately before dosing at the baseline visit (Week 0), eligible subjects will be randomized in a 1:1 ratio to 1 of 2
treatment arms:
•rhPTH(1-84) as adjunctive treatment with active vitamin D and/or calcium supplements
•*Placebo with active vitamin D and/or calcium supplements.

Investigational product [rhPTH(1-84) or placebo] will be administered each day in the morning by SC injection into the thigh, alternating the left and right thighs each day, via a multidose injection pen device. Subjects and site

personnel will remain blinded to the treatment assignments for the duration of the study. Active vitamin D and calcium supplements will be provided by the sponsor or designee or study site.
Dosing of investigational product and active vitamin D and calcium supplements will be adjusted for each subject to
achieve specified biochemical target levels. Investigational product doses are intended to remain stable during the last
12 weeks of the treatment period.

Serum calcium, albumin, phosphate, magnesium, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D will be measured
at specified time points to assess efficacy and to provide information for adjustment of investigational product and
supplement doses. Urine calcium, phosphate, magnesium, creatinine, sodium, and citrate excretion, markers of bone
turnover, and bone mineral density will be measured at specified time points to assess efficacy. Renal ultrasound
scans will be performed and fibroblast growth factor (FGF)-23 measured as exploratory assessments of drug effect.
Subjects will be asked to complete neurocognitive assessment and patient-reported outcome (PRO) instruments.
Healthcare utilization will also be recorded.

Safety measures will include adverse event (AE) recording, serum chemistry, hematology, urinalysis, vital signs,
electrocardiograms (ECGs), physical examinations, and measurement of parathyroid hormone (PTH) antibodies.
Subjects who discontinue treatment with rhPTH(1-84) (gap >7days) following completion of the end-of-treatment (or early termination) visit and are not immediately continuing treatment with commercial rhPTH(1-84) will enter a weekly safety follow up period with serum calcium measurements until the subject is able to begin outpatient rhPTH(1-84) treatment or until a maximum of 30 days has elapsed. All subjects will complete an EOS contact (Week 30 visit), a safety follow up site visit who discontinued treatment with rhPTH(1-84) or is a telephone call initiated by the site staff to document any serious adverse events (SAEs), adverse events (AEs), and concomitant treatments for subjects treated with commercial rhPTH(1-84).

Intervention

There is a chance of 50% that the patient will receive rhPTH(1-84) and a chance of 50% of recieving placebo. Both groups will be taking calcium and active vitamin D supplements during the study.

Study burden and risks

The study drug and study procedures are associated with certain risks. These are described in the ICF. The study drug and the study procedures and the combination thereof, can also lead to other unknown risks. The subjects are carefully monitored. If necessary, the study drug dosage will be decreased of administration will be stopped.

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. Has an understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Is able to voluntarily provide a signed and dated informed consent form before any study-related procedures are performed.
3. Is an adult male or female 18 to 85 years of age, inclusive.

4. In subjects 18-25 years of age, has radiological evidence of epiphyseal closure based on bone age X-ray (single posteroanterior X-ray of left wrist and hand)
5. Has chronic hypoparathyroidism with onset 12 months or more before screening. The diagnosis of hypoparathyroidism is established based on hypocalcemia in the setting of inappropriately low serum PTH levels., 6. During the Week -3 screening visit, the subject reports by history at least 2 of the following symptoms related to hypoparathyroidism occurring within the 2 weeks before Week -3 visit: muscle cramps, muscle spasms or twitching, tingling, numbness, heaviness in arms or legs, physical fatigue, or slowed or confused thinking (brain fog)., 7. The subject must have a Hypoparathyroidism Symptom Diary (HPT-SD) symptom subscale Sum Score of >=10 during the 14-day period immediately prior to the baseline (Week 0) visit (Day -14 to Day -1). In addition, the subject must have at least 4 HPT-SD diaries completed in the first 7 day period and at least 4 HPT-SD diaries completed in second 7 day period. See Appendix 3 for the calculation of the sum score., 8. Must be treated with active vitamin D (calcitriol or alfacalcidol) alone or in conjunction with calcium supplements for at least 4 months prior to the screening visit.
• The subject must be taking >=0.5 µg/day of calcitriol or >=1.0 µg/day of alfacalcidol.
• If the subject is treated with a lower dose of active vitamin D the subject must also be taking calcium supplements of at least 800 mg/day of elemental calcium, 9. Has thyroid-stimulating hormone (TSH) results within normal laboratory limits at screening for all subjects not receiving thyroid hormone replacement therapy. For subjects on thyroid hormone replacement therapy, the thyroid hormone dose must have been stable for at least 4 weeks before screening, and serum TSH level must be within the central laboratory the normal range. A serum TSH level below the lower limit of the normal range but not undetectable in subjects treated with thyroid hormone may be allowed if there is no anticipated need for a change in thyroid hormone dose during the trial., 10. Has serum 25-hydroxyvitamin D levels >=50 nmol/L (20 ng/mL) and <1.5 times the upper limit of normal (ULN) for the central laboratory normal range., 11. Has estimated glomerular filtration rate (eGFR) >30 ml/min/1.73m2., 12. Prior to randomization, is able to perform daily SC self-injections of study medication (or have a designee perform injection) via a multidose injection pen into the thigh., 13. Willing to use oral active vitamin D and calcium supplements provided for the study unless directed to remain on the supplements used prior to enrollment in the current study by the investigator after consultation with the medical monitor., 14. With regard to female subjects: women who are postmenopausal (12 consecutive months of spontaneous amenorrhea and age more than or equal to 51 years) and women who are surgically sterilized can be enrolled. Women of childbearing potential must have a negative pregnancy test at
randomization and be willing to comply with any applicable contraceptive requirements of the protocol and pregnancy testing for the duration of the

study.

Exclusion criteria

1. History of hypoparathyroidism resulting from a known activating mutation in the CaSR gene or impaired responsiveness to PTH (pseudohypoparathyroidism)., 2. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, such as poorly controlled hyperthyroidism; Paget disease; type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus; severe and chronic cardiac, liver (Child-Pugh score >9) (US FDA, 2003), or renal disease; Cushing syndrome; rheumatoid arthritis; myeloma; active pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy (other than low-risk well differentiated thyroid cancer); primary or secondary hyperparathyroidism; or documented parathyroid carcinoma within the previous 5 years, acromegaly, or multiple endocrine neoplasia types 1 and 2.
3. Very low or very high blood calcium level (eg, ACSC <1.87 mmol/L [<7.5 mg/dL] or >=2.97 mmol/L [>=11.9 mg/dL]) at the Week -3 screening visit. Results from the central laboratory must be used for this assessment.
4. If the Blood calcium level is above the ULN at the baseline (Week 0) visit, the analysis can be repeated another day as long as the next date is within the visit window for the baseline visit. If the subject does not met exclusion #4 on the repeat measure the subject may be randomized., 5. Use of prohibited medications, such as loop and thiazide diuretics, phosphate binders (other than calcium carbonate), digoxin, lithium, methotrexate, or systemic corticosteroids, within respective prohibited periods. See Section 5 (Prior and Concomitant Treatment) for a list of prohibited and restricted medications, 6. Participation in any other investigational study in which receipt of investigational drug or device occurred within 6 months before screening for this study. Prior treatment with PTH-like drugs (whether commercially available or through participation in an, investigational study), including PTH(1-84), PTH(1-34), or other N-terminal fragments or analogs of PTH or PTH-related protein, within 3 months before screening., 7. Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets, or cinacalcet hydrochloride, within the prohibited period., 8. Use of oral bisphosphonates within the previous 6 months or intravenous bisphosphonate, preparations within the previous 24 months before screening., 9. Nonhypocalcemic seizure disorder with a history of a seizure within the previous 6 months before screening. Subjects with a history of seizures that occur in the setting of hypocalcemia are allowed., 10. The subject is at increased baseline risk for osteosarcoma, such as those with Paget*s disease of bone or unexplained elevations of alkaline phosphatase, hereditary disorders predisposing to osteosarcoma, or with a prior history of external beam or implant radiation therapy involving the skeleton., 11. Any disease or condition that, in the opinion of the investigator, may require treatment or make the

subject unlikely to fully complete the study, or any condition that presents undue risk from the investigational product or procedures. For example, illness that is anticipated to be chronic and not transient., 12. Pregnant or lactating women., 13. Known or suspected intolerance or hypersensitivity to the investigational product, closely-related compounds, or any of the stated ingredients. Refer to the investigator*s brochure for the list of excipients.
14. History of diagnosed drug or alcohol dependence within the previous 3 years.
15. Poorly controlled short bowel syndrome, bowel resection, tropical sprue, celiac disease, ulcerative colitis, and Crohn disease.
16. Chronic or severe cardiac disease including but not limited to heart failure (according to the New York Heart Association classification Class II to Class IV) (Dolgin and NYHA, 1994), arrhythmias, bradycardia (resting heart rate <50 beats/minute).
17. History of cerebrovascular accident.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	18-09-2018
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Naptar

Generic name:	Recombinant Human Parathyroid Hormone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-11-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-06-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	30-08-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-09-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-12-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	16-01-2019

Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-02-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-11-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-04-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-08-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-09-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-02-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	18-03-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	01-06-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-11-2021
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2017-000284-32-NL
CCMO	NL62879.056.17

Study results

Date completed:	31-01-2022

Results posted: 06-04-2023

First publication
30-11-2022