An Open-Label, Randosized, Crossover Study to Assess the Pharmacokinetic and Pharmacodynamic Profiles of Once-Daily and Twice-Daily Dose Regimens of recombinant human Parathyroid Hormone (rhPTH[1-84]) Administered Subcutaneously to Subjects with Hypoparathyroidism (SHP634-101)

First published: 25/04/2016

Last updated: 23/05/2024

Study Finalised

Administrative details

EU PAS number

EUPAS13269

Study ID

46482

DARWIN EU® study

No

Study countries

- [ ] Canada
- [ ] United States

Study description

Prior to 2015, in the absence of an approved PTH replacement therapy, management of hypoparathyroidism consisted of supplemental oral calcium and active vitamin D in pharmacological doses sufficient to maintain the serum calcium level without the disabling symptoms of hypocalcemia. Additional calcium load that results from supplementation with exogenous calcium and active vitamin D contributes to the hypercalciuria and renal risks often noted in patients with hyperparathyroidism. In an effort to limit the extent and effect of hypercalciuria, thiazide diuretics can be helpful since they promote renal calcium reabsorption. However, thiazides are associated with their own adverse events including hypokalemia and, more importantly, have no proven long-term effect to reduce hypercalciuria or kidney damage or established safety profile. The investigational product (rhPTH1-84) is a recombinant human PTH that is identical in structure to endogenous human PTH, a single-chain polypeptide consisting of 84 amino acid residues and is manufactured using a strain of Escherichia coli modified by recombinant DNA technology. rhPTH(1-84) was approved for marketing in the United States on 23 January 2015 under the brand name Natpara® as a once-daily injectable dose as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism. The present study is being conducted to characterize the effects of twice-daily administration of rhPTH(1-84) on pharmacokinetics, pharmacodynamics, safety and tolerability over the course of 24 hours as compared with the current once-daily dosing regimen.

Study status

Finalised

Research institutions and networks

Institutions

Shire

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Contact details

Study institution contact

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Study contact

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Primary lead investigator

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Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 26/04/2015

Actual: 01/03/2016

Study start date
Planned: 01/04/2015

Actual: 04/03/2017

Date of final study report
Planned: 01/04/2018

Actual: 20/02/2020

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Shire

Study protocol

SHP634-101_Protocol Amendment 5_redacted_A.pdf (2.54 MB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Methodological aspects

Study type

Study topic:

Disease /health condition

Human medicinal product

Study type:

Clinical trial

Main study objective:

To assess the pharmacokinetic profile and pharmacodynamic effects (control of serum calcium and urinary calcium excretion) of rhPTH(1-84) administered as SC doses of 25µg administered twice-daily, 50µg administered twice-daily, and 100µg administered once-daily, as well as the effect of supplemental oral calcium intake, in subjects with hypoparathyroidism.

Study Design

Clinical trial regulatory scope

Pre-authorisation clinical trial

Clinical trial phase

Human pharmacology (Phase I)

Clinical trial randomisation

Randomised clinical trial

Clinical trial types

Low-intervention clinical trial

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

PARATHYROID HORMONE (RDNA)

Medical condition to be studied

Hypoparathyroidism

Population studied

Short description of the study population

Each subject must participate in the informed consent process and provide written informed consent/assent before any procedures specified in the protocol are performed.

Inclusion Criteria

The subject will not be considered eligible for the study without meeting all of the criteria below.

Subjects cannot be enrolled or randomized before all inclusion criteria (including test results) are confirmed.

1. An understanding, ability, and willingness to fully comply with study procedures and restrictions.
2. Ability to voluntarily provide written, signed, and dated informed consent as applicable to participate in the study.
3. Adult men or women aged ≥18 years at the time of consent. The date of subject signature of the informed consent is defined as the beginning of the Screening Period. The Screening Period for this study may encompass both the Administrative Screening Period (if needed) and the Clinical Screening Period. For purposes of this inclusion criterion, age will only be assessed at the time the informed consent is first signed by the study subject.

4. History of hypoparathyroidism for ≥12 months, post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia with concomitant serum intact PTH concentrations below the lower limit of the laboratory normal range.
5. Requirement for supplemental oral calcium treatment ≥1000 mg elemental calcium per day.
6. Requirement for therapy with active forms of vitamin D at a minimum dose of ≥0.25µg per day (ie, ≥0.25µg calcitriol or equivalent per day).
7. Serum calcium level within the laboratory normal reference range based on clinical chemistry lab results at the Clinical Screening Visit (based on central and/or local lab results) and Treatment Period 1, Day -2 (based on central and/or local lab results), or if outside of normal range, considered not clinically significant by the investigator.
8. Urinary calcium excretion ≥200mg (5mmol)/24h, based on a 24-hour collection, collected anytime during the Clinical Screening Period, but prior to check-in to the CRC at Treatment Period 1, Day -2 (based on central and/or local lab results).
9. Serum magnesium level within the laboratory normal range at the Clinical Screening Visit or, if outside of normal range, considered not clinically significant by the investigator.
10. Serum thyroid function tests within normal laboratory limits at the Clinical Screening Visit, or, if outside of normal range, considered as not clinically significant by the investigator.
11. Serum 25(OH)D level between the lower limit of normal and 1.5-fold the laboratory upper limit of normal, or, if outside of this range, considered not clinically significant by the investigator, at the Clinical Screening Visit.
12. Serum creatinine <1.5 mg/dL (<133µmol/L) AND estimated creatinine clearance >60 mL/minute (>1.002mL/s) at the Clinical Screening Visit, and serum creatinine <1.5 mg/dL (<133µmol/L) at Treatment Period 1, Day -2.
13. Male or non-pregnant, non-lactating female who agrees to comply with any

applicable contraceptive requirements of the protocol or females of non-childbearing potential.

Exclusion Criteria

Subjects are excluded from the study if any of the following exclusion criteria are met:

1. Participation in any other investigational drug study in which the last dose of investigational drug occurred within 3 months prior to Day 1 of Treatment Period 1 (or within 5 half-lives, if elimination half-life is greater than 18 days).
2. Presence or history of a clinically significant disorder involving the cardiovascular, respiratory, renal, gastrointestinal, immunologic, hematologic, endocrine (with exception of the condition under study), or neurologic system(s) or psychiatric disease as determined by the investigator.
3. Known history of hypoparathyroidism resulting from an activation mutation in the CaSR gene or impaired responsiveness to PTH (pseudohypoparathyroidism).
4. Any disease that might affect calcium metabolism or calcium-phosphate homeostasis other than hypoparathyroidism, including but not limited to, active hyperthyroidism; poorly controlled insulin-dependent diabetes mellitus or type 2 diabetes mellitus; severe and chronic cardiac, liver or renal disease; Cushing's syndrome; neuromuscular disease such as rheumatoid arthritis; myeloma; pancreatitis; malnutrition; rickets; recent prolonged immobility; active malignancy, bone metastases or a history of skeletal malignancies; primary or secondary hyperparathyroidism; a history of parathyroid carcinoma; hypopituitarism, acromegaly; or multiple endocrine neoplasia types 1 and 2, as determined by the investigator.
5. In male and female rats, parathyroid hormone caused an increase in the incidence of osteosarcoma (a malignant bone tumor). The occurrence of osteosarcoma was dependent on parathyroid hormone dose and treatment duration. This effect was observed at parathyroid hormone exposure levels

ranging from 3 to 71 times the exposure levels in humans receiving a 100µg dose of rhPTH(1-84). Therefore, subjects who are at increased baseline risk for osteosarcoma such as subjects with Paget's disease of bone or unexplained elevations of alkaline phosphatase, pediatric and young adult subjects with open epiphyses, subjects with hereditary disorders predisposing to osteosarcoma or subjects with a prior history of external beam or implant radiation therapy involving the skeleton are excluded.

6. Subjects who have a known history of hypercalcemia during initiation of treatment with PTH, PTH analogues or fragments of PTH.

7. Subjects who have a known history of hypocalcemia following abrupt withdrawal of treatment with PTH, PTH analogues or fragments of PTH.

8. Subjects dependent on regular parenteral calcium infusions (eg, calcium gluconate) to maintain calcium homeostasis within 3 months prior to enrollment, as determined by the investigator.

9. Use of the following medications prior to administration of investigational product within:

- 14 days– thiazide diuretics
- 30 days – loop diuretics, lithium, systemic corticosteroids (medical judgment is required by the investigator. Primarily high doses of systemic corticosteroids [eg, prednisone] should be excluded. Stable doses of hydrocortisone [eg, as treatment for Addison's disease] may be acceptable).
- 3 months – calcitonin, cinacalcet hydrochloride, treatment with rhPTH(1-84) or Nterminal PTH or PTH-related peptide fragments or analogs
- For females: changes in hormone replacement therapy within 3 months are excluded. Stable (≥3 months) hormone replacement therapy is acceptable.
- 6 months – fluoride tablets, oral bisphosphonates, methotrexate, growth hormone, digoxin, raloxifene or similar selective estrogen receptor modulators (SERMs)
- 12 months – intravenous bisphosphonates, drug or alcohol abuse, as

determined by the investigator.

10. Presence of any clinically significant results from laboratory tests, vital signs assessments, or electrocardiograms (ECGs), as judged by the investigator.

11. Twelve-lead ECG values (average of triplicate readings) demonstrating QTc>450 msec (males) or >470 msec (females) at the Clinical Screening Visit and/or any time points up to and including predose of Day 1 (Period 1).

12. Any medical condition or prior therapy that, in the opinion of the investigator, would make the subject unsuitable for this study.

13. Positive test result for any of the following viral infections at the Clinical Screening Visit:

- Hepatitis B surface antigen
- Hepatitis C
- HIV

14. Known significant bleeding diathesis that could preclude multiple venipunctures as determined by the investigator.

15. Subjects who have donated a total of 100 mL to 499 mL of whole blood within 30 days prior to dosing, or subjects who have donated a total of more than 499 mL of whole blood within 56 days prior to dosing.

16. A positive screen for drugs of abuse at the Clinical Screening Visit, and/or a positive screen for drugs of abuse and alcohol at check-in to the CRC at Treatment Period 1. Subjects taking prescription medications that might be detected during the urine screen for drugs of abuse may be enrolled per the investigator’s medical judgment.

17. History of a clinically significant illness during the 4 weeks prior to dosing (as determined by the investigator).

18. History of any clinically significant surgery or procedure within the past 8 weeks, as determined by the investigator.

19. History of an allergic response(s) to PTH or PTH analogs, or other clinically significant allergies, as determined by the investigator.

Age groups

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Special population of interest

Other

Special population of interest, other

Hypoparathyroidism patients

Estimated number of subjects

24

Study design details

Outcomes

Pharmacokinetic (Tmax, AUC0-t, AUC0-inf, AUC0-24h, Kel, CL/F, Vz/F and t½), Pharmacodynamic (AUC0-24h, TEmax, Emax) and Parameters representing urinary excretion of each analysis, Adverse Events including episodes of hypo- and hypercalcemia, Laboratory test results (hematology, serum chemistries, creatinine clearance, urinary chemistries (24-hr urinary calcium, sodium, citrate, phosphate, magnesium, and creatinine excretion), immunology (anti-PTH antibody), and urinalysis, ECG and Physical examinations (including vital signs).

Data analysis plan

Pharmacokinetic parameters will be determined from the plasma concentration-time data for PTH and by non-compartmental analysis. Pharmacodynamic parameters will be computed from the individual concentrations of serum calcium (uncorrected and corrected for serum albumin levels), phosphate,

albumin, creatinine,magnesium, 1,25(OH)2D and FGF23 using a non-compartmental approach, AEs will be coded using the Medical Dictionary for Regulatory Activities, Safety data including clinical laboratory tests, physical exams, concomitant medications,adverse events, ECG monitoring and vital signs assessments will be summarized by treatment and time of collection. Descriptive statistics (arithmetic mean, standard deviation, median,minimum and maximum) will be calculated for quantitative safety data as well as for the difference from baseline, if applicable.

Documents

Study results

SHP634-101-clinical-study-report-redact.pdf (3.61 MB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Other

Data sources (types), other

Prospective patient-based data collection

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No