EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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EMA/180882/2017
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Natpar

International non-proprietary name: parathyroid hormone

Procedure No. EMEA/H/C/003861/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

1,25(OH)2 vitamin D	1,25-dihydroxyvitamin D
25(OH) vitamin D	25-hydroxyvitamin D
aBMD	Areal BMD
ACR	Acute calcemic response
ACSC	Albumin-corrected total serum calcium
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
AUC	Area under the concentration-time curve
AUC0-24	Area under the concentration-time curve from 0 to 24 hours
AUC0-8	Area under the concentration-time curve from 0 to 8 hours
AUC0-∞	Area under the concentration-time curve from 0 time point to infinity
AUC0-last	Area under the concentration-time curve from 0 time point to last
AUCt	Area under the concentration-time curve to time t
BA	Bioavailability
BCE	Bone collagen equivalents
BE	Bioequivalence
BLA	Biologics License Application
BMD	Bone mineral density
BMI	Body mass index
BSAP	Bone specific alkaline phosphatase
BTM	Bone turnover marker
Ca	Calcium
CAP [Study]	Study CL1-11-008
CASR	Calcium sensing receptor
CI	Confidence interval
CL	Plasma clearance
CL/F	Apparent total body clearance
ClCr	Creatinine clearance
CLd	Distributional clearance
Cmax	Maximum plasma concentration
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
CTD	Common Technical Document
CTx	Collagen type 1 cross-linked C-telopeptide
CV	Coefficient of variation
Cyclic AMP	Cyclic adenosine monophosphate
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
ECL	Electrochemiluminescence
ECLIA	Electrochemiluminescent immunoassay
EOT	End of Treatment
FDA	Food and Drug Administration
FECa	Fractional excretion of calcium
FEMg	Fractional excretion of magnesium

FEP	Fractional excretion of phosphate
GFR	Glomerular filtration rate
hPTH	Human parathyroid hormone
ID	Intradermal
IIT	Investigator initiated trial
IRMA	Immunoradiometric assay
ISI	Integrated Summary of Immunogenicity
ISS	Integrated Summary of Safety Data
ITT	Intent-to-Treat
IV	Intravenous
LL	Lower limit
LOQ	Limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Meso-scale discovery
N, n	Sample size
Natpar, Natpara	Recombinant human parathyroid hormone (rhPTH[1-84]), EU and US proprietary names, respectively
NIH	US National Institutes of Health
NPS	NPS Pharmaceuticals, Inc.
NPSP558	Most recent compound code for rhPTH(1-84)
NTx	Cross-linked N-terminal telopeptide of type 1 collagen
P1NP	Procollagen amino-terminal peptide
PaTH [Study]	NIH sponsored study N01-AR-9-2245 NIAMS-045
PD	Pharmacodynamic
PK	Pharmacokinetic(s)
Pop PK	Population pharmacokinetic(s)
PP	Per Protocol (Population)
PREOTACT	Parathyroid hormone [rDNA origin] for injection
PSUR(s)	Periodic Safety Update Report(s)
PT	Preferred term
PTH	Endogenous parathyroid hormone
PTH(1-34)	N-terminal region of parathyroid hormone
PTH(1-84)	Parathyroid hormone full length peptide [assay-measured peptide]
QD	Once daily
QT	QT interval from electrocardiogram
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RACE	rhPTH(1-84) Study PAR-C10-008
RELAY	rhPTH(1-84) Study PAR-C10-007
REPEAT	rhPTH(1-84) Study PAR-C10-009
REPLACE	rhPTH(1-84) Study CL1-11-040
rhPTH	Recombinant human parathyroid hormone (1-84)
rhPTH(1-84)	Recombinant human parathyroid hormone full length peptide
SAE(s)	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SC	Subcutaneous
s-CTx	Serum carboxy-terminal telopeptide of type I collagen
SD	Standard deviation

SE	Standard error
SF-36	Short Form-36 questionnaire
SQTS	Short QT syndrome
t1/2	Terminal elimination half-life
tmax	Time to maximum concentration
TmP/GFR	Renal maximal tubular reabsorption of phosphate per liter glomerular filtrate
TOP [Study]	Study ALX1-11-93001
TRAP	Tartrate-resistant acid phosphatase
TRCa	Tubular reabsorption of calcium
TSC	Total serum calcium
UL	Upper limit
ULN	Upper limit of normal
US	United States
vBMD	Volumetric BMD
Vz/F	Apparent volume of distribution

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Shire Pharmaceuticals Ireland Limited submitted on 5 November 2014 an application for marketing authorisation to the European Medicines Agency (EMA) for Natpar, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

Natpar was designated as an orphan medicinal product EU/3/13/1210 on 18 December 2013 in the following condition: Treatment of hypoparathyroidism

The applicant applied for the following indication:

Natpar is a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of adult patients with hypoparathyroidism.

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Natpar as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Human medicines/Rare disease designation.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Natpar was considered to be a known active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/205/2014 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/205/2014 not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request(s) for consideration

Conditional marketing authorisation

In accordance with Article 3(2) of Regulation EC No 507/2006, the CHMP proposed the application to be considered for a Conditional Marketing Authorisation.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Bart Van der Schueren Co-Rapporteur: Greg Markey

- The application was received by the EMA on 5 November 2014.
- The procedure started on 26 November 2014.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 February 2015.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 February 2015.
- The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 20 February 2015.
- During the meeting on 12 March 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 26 March 2015, the CHMP agreed on the consolidated List of Questions to be sent to the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2015.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 September 2015.
- During the PRAC meeting on 10 September 2015, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During a meeting of a Biologics Working Party on 16 September 2015, experts were convened to address questions raised by the CHMP.
- During the CHMP meeting on 24 September 2015, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 March 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 7 April 2016.
- During the PRAC meeting on 14 April 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.

- During the CHMP meeting on 28 April 2016, the CHMP agreed on a 2nd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 June 2016
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the 2nd List of Outstanding Issues to all CHMP members on 1 July 2016.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a 3rd list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 1 September 2016.
- During the CHMP meeting on 15 September 2016, the CHMP agreed on a 4th list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 24 January 2017.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 9 February 2017.
- During the PRAC meeting on 9 February 2017, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 20-23 February 2017, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Natpar 23 February 2017.

2. Scientific discussion

2.1. Problem statement

Physiology of parathyroid hormone

Parathyroid hormone is an 84-amino acid protein that is secreted by four parathyroid glands that lie behind each of the upper and lower poles of the thyroid gland. Each gland weighs approximately 30–50 mg and is supplied by blood from the thyroid arteries which may be disrupted during thyroid surgery.

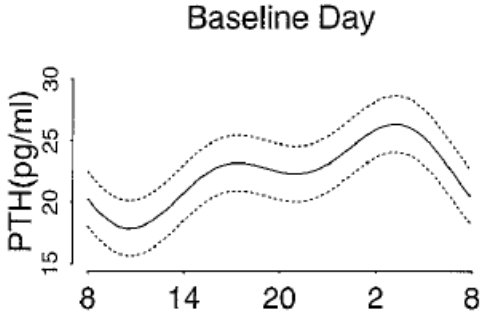
Parathyroid hormone regulates bone metabolism and serum concentrations of calcium and phosphate. Changes in circulating Ca2+ concentrations are detected by the cells of the parathyroid glands and alter parathyroid hormone secretion via a negative feedback system. Under normal conditions, if the serum calcium concentration is low then the parathyroid glands increase secretion of parathyroid hormone and when the serum calcium concentration is high then secretion of parathyroid hormone is reduced.

Parathyroid hormone stimulates 1-α-hydroxylase activity in the kidney that converts 25(OH) vitamin D into 1,25-dihydroxyvitamin D (calcitriol): this active metabolite of vitamin D facilitates the absorption of calcium and phosphate from the intestine. Parathyroid hormone reduces calcium excretion and promotes phosphate excretion in the urine.

Parathyroid hormone also has a role in maintaining the skeletal content of calcium mineral.

Parathyroid hormone follows a bimodal diurnal pattern in the circulation. A primary peak occurs at 4am and a secondary peak occurs at 4pm. The primary and secondary nadirs take place at 10am and 9pm respectively (times are approximate). The underlying rhythm is endogenous. Life style factors and nutritional intake modulate the pattern of secretion. The diurnal variation of parathyroid hormone is shown in the following figure:

Figure 1:



Estimated population mean rhythm curves (±2 SD) for plasma PTH on baseline day. (Fuleihan GE et al. J Clin Endo Metab 1997; 82:281-6)

The parathyroid hormone concentration recorded is dependent upon the assay used. Subjects with postmenopausal osteoporosis do not display the nocturnal increase in circulating parathyroid hormone. Serum [Ca++] does not display a diurnal variation.

Hypoparathyroidism

Hypoparathyroidism is a rare endocrine deficiency that is characterized by absent or inappropriately low circulating PTH levels, secreted normally by the parathyroid glands. The most common aetiology is permanent damage / removal of parathyroid glands or their blood supply during neck surgery (70 % - 80 %), for instance total thyroidectomy, but also thyroid resection for benign thyroid disease, parathyroidectomy for treatment of primary hyperparathyroidism, etc. Other causes include autoimmune conditions, congenital absence, genetic mutations, iron overload syndromes, radiation damage.

The parathyroid glands sense the level of extracellular calcium at the surface of the parathyroid cell and adjust the synthesis and secretion of PTH accordingly. The relationship between ionized extracellular calcium and PTH secretion is a steep sigmoidal curve where small variations in calcium level lead to significant changes in PTH secretion. Calcium sensing is initiated by the binding of calcium to a calcium "sensing" receptor (CASR for calcium sensing receptor) that is present at high levels on the plasma membrane of the parathyroid cells. The CASR, a member of the G-protein-coupled receptor superfamily, is activated by calcium binding to it that, in turn, induces intracellular signals and, through largely unknown mechanisms, regulates the synthesis and secretion of PTH. The net physiological effects are an increase in circulating PTH levels when the extracellular calcium decreases and a decrease in PTH levels when the extracellular calcium increases.

Clinical presentation and current management of hypoparathyroidism

Hypoparathyroidism results in hypocalcaemia and hyperphosphataemia, while in the urine there is increased calcium excretion and decreased phosphate excretion. Serum magnesium concentration usually is not abnormal. Because CASR is widely distributed in the human body, a fluctuation in calcium may lead to multiple and very diverse symptoms, although these hypocalcaemia symptoms are generally reversible. The key symptoms involve the neuromuscular system: numbness: paraesthesias, twitching, tetany. Seizures, cardiac arrhythmias, cardiomyopathy, laryngeal spasm are more serious and potentially life-threatening effects, and difficulties in concentrating ("brain fog") and effects on mood and ideation are also described.

In the PARADOX study, a cross-sectional web-based observational study of 374 subjects with hypoparathyroidism [Hadker N, et al.. Endocr Pract. 2014;20(7):671-679; initiated by the applicant, the Hypoparathyroidism Association (USA) and the Mayo Clinic (Rochester, USA)], in which most patients (66.6%) took a combination of oral calcium and active vitamin D [Including some treated with PTH] respondents were asked about 38 symptoms that were physical, emotional or cognitive.

Physical symptoms experienced by more than 50% of the respondents were: fatigue (82%); muscle pain or cramping (78%); paraesthesia (76%); tetany (70%); joint or bone pain (67%); and pain, heaviness, or weakness in extremities (53%).

Emotional symptoms were anxiety, fear, or inner unrest (59%) and feeling sad, down, blue, or depressed (53%).

Cognitive symptoms were brain fog or mental lethargy (72%), inability to focus or concentrate (65%), memory loss or forgetfulness (62%), and sleep disturbances (57%).

Current management of hypoparathyroidism

Current management of hypoparathyroidism consists of calcium (carbonate/citrate) and active vitamin D (calcitriol/alphacalcidol) in pharmacological doses sufficient to maintain serum calcium levels just below or at the low end of the normal range, to protect the kidneys from hypercalciuria and to prevent long-term damage from a high calcium-phosphate product. Risk of the use of large amounts of calcium and active vitamin D are nephrocalcinosis or nephrolithiasis, hyperphosphatemia, parenchymal renal

calcifications. Long-term this can lead to renal impairment (renal complications ranging from 15 to 41% of patients studied). Thiazide diuretics can be helpful, promoting renal calcium reabsorption. These thiazides have however their own adverse events including hypokalaemia, and have no proven long-term efficacy. Deposition of calcium-phosphate complexes in other organs or precipitation in soft tissues are also risks of the current management. The balance between too little and too much is the challenge. Too little would lead to hypocalcaemia (potentially life-threatening), too much could lead to symptomatic hypercalcaemia (also life-threatening). The required amounts vary widely across patients and there is even great intra-patient variability. Therefore, constant vigilance and monitoring is required. Some patients require magnesium supplementation and phosphate binders further increasing the pill burden.

In the absence of PTH, bone is not renewed normally with a resultant gradually accrual of bone: leading to an increased bone mineral density (BMD), which is not a benefit because the bone is typically hypermature: greater cancellous bone volume, greater trabecular and cortical bone widths, reduced mineralizing surface and bone formation rate. Although this abnormal bone quality is not felt/visible by the patient, this makes the calcium stored in the bones (99% of the calcium content in the body) unavailable. Low endogenous levels of calcitriol leads to the disability to properly absorb dietary calcium/phosphate and associated impairment of vitamin D-dependent bone and renal regulatory mechanisms.

In the PARADOX study, about 70% of the patients reported having suffered from other severe medical conditions directly related to their hypoparathyroidism, as shown in the following table:

Table 1: Comorbid conditions experienced by hypoparathyroidism patients - paradox study.

Condition	Experienced Any Time Since Diagnosis	Experience Within the Past Year
	n (%)	n (%)
Experienced any diagnosis	259 (69.3)	138 (36.9)
Heart arrhythmias	172 (66.4)	83 (60.1)
Kidney stones	92 (35.5)	36 (26.1)
Elevated bone mineral density	58 (22.4)	30 (21.7)
Decreased bone mineral density	53 (20.5)	24 (17.4)
Seizures/convulsions	46 (17.8)	11 (8.0)
Bone fractures	41 (15.8)	7 (5.1)

n = number

Note: Percentages are based on the total number of patients participating in this survey (n = 374).

Source: Hadker et al, 2014

Other sources confirm morbidities associated with treated hypoparathyroidism. Published studies from the Danish National Patient Registry and prescription databases suggest that post-surgical subjects with hypoparathyroidism show an increased risk of infection, psychiatric illness, kidney stones and seizures [Underbjerg et al. J Bone Miner Res. 2013;28:2277-85; Underbjerg et al. J Bone Miner Res. 2014;29:2504-10.].

Because hypoparathyroidism is more than hypocalcaemia alone and includes multiple organ and system abnormalities, it is not unexpected that the current disease management fails to manage comorbid conditions, since it does not address the root cause of hypoparathyroidism, namely lack of PTH. The maintenance of serum calcium levels that do not lead to hypocalcaemic symptoms requires patients to adhere to a strict routine of taking multiple pills to avoid an always possible "crash" into

severe hypocalcaemic symptoms that may limit their family, professional, and social lives. Hypoparathyroidism (even though treated with the optimum medical management) can be associated with on-going symptoms that impair the quality of life. It is acknowledged that there is an unmet clinical need for parathyroid hormone replacement therapy in subjects with hypoparathyroidism.

About the product

The active pharmaceutical ingredient, recombinant human parathyroid hormone (1-84) [rhPTH(1-84)], is identical to the full-length human 84-amino acid protein. In the application, rhPTH(1-84) is also referred to as NPSP558, and also as PTH(rDNA), PTH, PTH(1-84), hPTH, hPTH(1-84), rhPTH, rhPTH(1-84), rPTH, and rPTH(1-84). rhPTH(1-84) was originally developed and authorised for the treatment of osteoporosis. The current development program is for the treatment of hypoparathyroidism . The product is referred to as NPSP558 in the 4 Efficacy and Safety Studies in Hypoparathyroidism.

Natpar (parathyroid hormone [rDNA]) powder and solvent for solution for injection is supplied as a multiple dose, glass dual-chamber cartridge which is available in 4 nominal dosage strengths (25, 50, 75, or 100 µg). Depending on the dosage strength, each medication cartridge contains 0.40, 0.80, 1.21, or 1.61 mg rhPTH(1-84), 4.5 mg sodium chloride, 30 mg mannitol, and 1.26 mg citric acid monohydrate as a sterile lyophilized powder, with 1.13 mL of a sterile 3.2 mg/mL aqueous solution of m-cresol as the reconstitution diluent. Reconstitution results in a nominal solution concentration of 0.35 mg/mL (25 µg/dose), 0.70 mg/mL (50 µg/dose), 1.05 mg/mL (75 µg/dose) or 1.40 mg/mL (100 µg/dose).

The applicant proposed, during the procedure, the use of the reusable Shire Q-Cliq Pen, referred to as the Natpar pen. This reusable pen customized for delivery of Natpar requires external reconstitution of the powder and solvent contained in the glass dual-chamber cartridge. For that purpose, the cartridge is designed to be used in conjunction with an ancillary mixing device, i.e. the Duoject mixing device. Since the pen injector is reusable (i.e. the cartridge in the cartridge holder inside the pen will be replaced when empty), the pen is not considered as an integral part of the medicinal product and as such is a medical device, requiring a CE certificate. Using the pen injector, each medication cartridge delivers 14 doses; each dose contains 25, 50, 75, or 100 µg of rhPTH(1-84) depending on the product dosage strength.

Recombinant human PTH(1-84) is self-administered once daily by subcutaneous (SC) injection into alternating thighs. The recommended starting dose is 50 µg daily. Based on calcaemic response, rhPTH(1-84) can be titrated at approximately 2- to 4-week intervals upward to doses of 75 µg and then 100 µg daily. Downward titration to a minimum of 25 µg/day can occur at any time. In the case of a missed dose, the next dose should be administered as soon as reasonably feasible and additional exogenous calcium should be taken based on symptoms. Recombinant human PTH(1-84) should not be administered intravenously or intramuscularly.

A replacement therapy with physiological levels of parathyroid hormone could be expected to normalise serum calcium and phosphate levels, while concomitantly controlling renal calcium and phosphate handling, supplying active vitamin D, restoring suppressed bone turnover to normal and improving abnormal bone structure. Unfavourable alterations in serum calcium-phosphate dynamics could be less pronounced and therefore the risk of soft tissue calcifications could be reduced. rhPTH(1-84) treatment could mimic the physiological effect of the endogenous hormone, beyond regulation of serum calcium levels.

Teriparatide [PTH(1-34)] has an identical sequence to the 34 N-terminal amino acids of the 84-amino acid human parathyroid hormone and is authorised in the EU since 2005 for the treatment of osteoporosis in postmenopausal women, in men at increased risk of fracture and in osteoporosis

associated with sustained glucocorticoid use in women and men. The use is limited to 24-months total exposure. Teriparatide is not approved for the treatment of hypoparathyroidism.

Originally, rhPTH(1-84) was developed for the treatment of osteoporosis in post-menopausal women at a high risk of bone fracture.

The Marketing Authorization Application (MAA) for osteoporosis was submitted in the EU in 2005, and the product was authorised as Preotact in 2006. On request of the marketing authorisation holder, the marketing authorisation for this product was withdrawn in 2014. In parallel rhPTH(1-84) was developed for the treatment of hypoparathyroidism together with a new pen injector system. NPSP558 was the chosen designation for rhPTH(1-84) to distinguish the development program for the treatment of hypoparathyroidism from the previous one in osteoporosis. The safety and efficacy studies in both osteoporosis and hypoparathyroidism used the same drug formulation.

Orphan designation for recombinant human parathyroid hormone for the treatment of hypoparathyroidism was granted by the European Commission on 16 January 2014 (EU/3/13/1210).

2.2. Quality aspects

2.2.1. Introduction

The active substance contained in Natpar is a non-glycosylated recombinant human parathyroid hormone (PTH) produced in *E. coli* and consisting of 84 amino acids (rhPTH(1-84)). The protein is analogous to the full-length PTH naturally produced by the parathyroid glands. PTH is a major regulator of calcium in the body and acts to increase the concentration of calcium in the blood.

The finished product Natpar is a powder and solvent for solution for injection in a cartridge. The lyophilised powder contains rhPTH, sodium chloride, mannitol, citric acid monohydrate and sodium hydroxide. The solvent (i.e. solvent for reconstitution) contains m-cresol in water for injections. The finished product is provided in 4 different strengths, i.e. 25 µg/dose, 50 µg/dose, 75 µg/dose and 100 µg/dose, filled in multiple dose glass dual-chamber cartridges. The cartridges inside their cartridge holders are to be used with a mixing device for reconstitution and a reusable pen-injector (i.e. the Natpar pen) as delivery system. Each cartridge contains 14 doses to be injected subcutaneously.

2.2.2. Active Substance

General Information

The active substance is a single-chain protein containing 84 amino acid residues with a sequence that is identical to the native human parathyroid hormone (PTH). There are no disulfide bonds, no glycosylation sites and no post-translational modifications.

Manufacture, characterisation and process controls

Manufacturing process

Recombinant human parathyroid hormone is produced by recombinant DNA technology in *E. coli* as a fusion protein containing the *ompA* leader sequence and the full sequence of PTH. The manufacturing process of the active substance comprises steps in which the protein is expressed in *E. coli* bacteria (fermentation), recovered and purified (several chromatographic steps and filtration/filling) and storedBased on the currently available information the manufacturing process of the rhPTH(1-84) active substance at the proposed Boehringer Ingelheim (BI) RCV GmbH & Co KG manufacturing site is

sufficiently defined and controlled. The purification process shows a good consistency in the elimination of both process-related and product-related impurities. Critical manufacturing process steps have been defined and in-process controls are in place throughout the process. The complete control strategy including all process parameters and in-process controls and accompanying details has been provided. Hold time periods for the intermediates during purification have been investigated.The starting materials used for production of rhPTH(1-84) have been well described and tests have been implemented to ensure the microbial safety throughout the production process. A two-tier cell banking system is used and the generation of the initial construct and the master cell bank (MCB) and working cell bank (WCB) have been described in detail.

Process validation

Validation encompassed the fermentation, recovery and downstream process. The prospective process validation of rhPTH(1-84) production process was performed.Validation data demonstrate that rhPTH(1-84) active substance produced according to the parameters described in the batch production records meets all predetermined quality attributes and specifications.

Manufacturing process development

Adequate comparability studies have been performed to bridge the manufacturing process changes made throughout development of the product.

Characterisation

The active substance rhPTH(1-84) has been characterised using a variety of test methods. These methods investigated the size, charge, primary, secondary and tertiary structure, aggregative properties, purity and biological activity of the protein.

Specification

The proposed active substance release specification covers identity, purity, potency and other general tests. The current reference standard has been well-characterised and is acceptable.

Stability

Long-term stability results show a good stability profile for the active substance under the proposed storage conditions. The claimed shelf life period at the recommended storage conditions. The stability commitment complies with the regulatory requirements and is acceptable.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product Natpar is a powder and solvent for solution for injection in a cartridge. The finished product is supplied as a multiple dose dual-chamber cartridge inside a cartridge holder. One chamber (“Chamber 1”) contains the sterile lyophilised powder and the other chamber (“Chamber 2”) contains the sterile solvent for reconstitution. The lyophilised powder contains rhPTH, sodium chloride, mannitol, citric acid monohydrate and sodium hydroxide and the solvent for reconstitution contains m-cresol in water for injections. The dual-chamber cartridge is provided in four different nominal dosage strengths (i.e. 25 µg/dose, 50 µg/dose, 75 µg/dose and 100 µg/dose) that differ only in the concentration of the active substance.

The dual-chamber cartridge inside the cartridge holder is made from type I glass with 2 bromobutyl rubber stoppers and a crimp cap (aluminium) with a bromobutyl rubber seal.

The dual-chamber cartridge inside the cartridge holder is designed for use with a mixing device for reconstitution and a reusable pen injector, i.e. the Natpar pen, for delivery of a targeted fixed-dose volume of 71.4 µl. Each cartridge contains 14 doses to be injected subcutaneously.

The composition of Natpar finished product is presented in Tables below.

Composition of Natpar finished product (prior to reconstitution)

Ingredient	Amount per Cartridge				Function	Quality Standard
	25 mcg/dose strength	50 mcg/dose strength	75 mcg/dose strength	100 mcg/dose strength		
Chamber 1						
rhPTH(1-84)					Active Ingredient	In-house Standard
Nominal	0.40 mg	0.80 mg	1.21 mg	1.61 mg		
Overage[a]	0.016 mg	0.032 mg	0.048 mg	0.032 mg		
Sodium Chloride	4.5 mg				Tonicity Agent	Ph Eur
Mannitol	30 mg				Bulking Agent/ Cryoprotectant/ Tonicity Agent	Ph. Eur.
Citric Acid Monohydrate	1.26 mg				Buffering Agent	Ph. Eur.
Sodium Hydroxide[b]	q.s. to pH 5-6				pH Adjustment	Ph. Eur.
Water for Injection	(-)[c]				Solvent	Ph. Eur.
Nitrogen	(-)[d]				Inerting Agent	Ph. Eur.
Chamber 2						
m-Cresol	3.62 mg				Preservative	Ph. Eur.
Water for Injection	q.s. to 1.13 g				Solvent	Ph. Eur.
Nitrogen	(-)[d]				Inerting Agent	Ph. Eur.

rhPTH(1-84) = recombinant human parathyroid hormone; q.s. = quantity sufficient; Ph. Eur. = European Pharmacopoeia.
[a] The 25, 50, and 75 mcg/dose strengths are manufactured with an overage of 4% and the 100 mcg/dose strength is manufactured with an overage of 2%, as discussed in Section 3.2.P.2.2.2.
[b] Charged as an aqueous solution during compounding.
[c] Added as a solvent during the compounding operation; removed during the freeze drying operation as part of manufacturing.
[d] Used as an inerting agent during the compounding and lyophilization steps.

Composition of Natpar finished product (after reconstitution)

Ingredient	Concentration				Function	Quality Standard
	25 mcg/dose strength	50 mcg/dose strength	75 mcg/dose strength	100 mcg/dose strength		
rhPTH(1-84)	0.35 mg/mL[a]	0.70 mg/mL[a]	1.05 mg/mL[a]	1.40 mg/mL[a]	Active Ingredient	NPS In-house Standard
Sodium Chloride	3.9 mg/mL				Tonicity Agent	Ph. Eur.
Mannitol	26 mg/mL				Bulking Agent/ Cryoprotectant/ Tonicity Agent	Ph. Eur.
Citric Acid Monohydrate	1.10 mg/mL[b]				Buffering Agent	Ph. Eur.
Sodium Hydroxide	q.s. to pH 5-6				pH Adjustment	Ph. Eur.
m-Cresol	3.15 mg/mL				Preservative	Ph. Eur.

Ingredient	Concentration				Function	Quality Standard
	25 mcg/dose strength	50 mcg/dose strength	75 mcg/dose strength	100 mcg/dose strength		
Water for Injection	q.s. to 1.15 mL				Solvent	Ph. Eur.

NPS = NPS Pharmaceuticals, Inc.; rhPTH(1-84) = recombinant human parathyroid hormone; q.s. = quantity sufficient; Ph. Eur. = European Pharmacopoeia.
[a] The 25, 50, and 75 mcg/dose strengths are manufactured with an overage of 4% and the 100 mcg/dose strength is manufactured with an overage of 2%, as discussed in Section 3.2.P.2.2.2.
[b] Expressed on an "as charged" basis during compounding and equivalent to 1.0 mg/mL citric acid in the reconstituted solution.

The manufacturing process development for the Natpar finished product is well described.

Manufacture of the product and process controls

The manufacturing process of the Natpar finished product is sufficiently described. No novel excipients have been proposed and the rationale provided for the use of excipients is considered acceptable.

Product specification

The specifications established for the finished product are acceptable. The proposed finished product release specification tests cover identity, purity, potency and other general tests.

Stability of the product

A shelf life of 36 months at 2°C to 8°C is proposed and supported by sufficient real-time stability data for all four product strengths. On the basis of totality of the data and justification provided by the Applicant, an in-use shelf life of 14 days after reconstitution is considered acceptable.

Adventitious agents

The risk of potential contamination with adventitious agents in the finished product is negligible. There is no significant risk of contamination with adventitious agents such as mammalian viruses or

mycoplasma. Therefore, viral clearance studies have not been performed, which is acceptable since no human or animal cell lines are used. Taking into account the nature of the product, sufficient information is presented with regard to the risk management for potential contamination with adventitious agents in terms of control of materials, control of production process, certification of materials of animal origin and testing of active substance and finished product. These controls ensure that the product does not contain adventitious agents.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

It should be noted that the Applicant has proposed the reusable Shire Q-Cliq pen (i.e. the Natpar pen)for product administration. The Natpar pen is designed to be used in conjunction with an ancillary mixing device, i.e. the Duoject mixing device. The Duoject mixing device was CE marked at the time of submission, whereas the Natpar pen was not. The Shire Q-Cliq pen and the medicinal product do not form a single integral product as defined in the Medical Devices Directive 93/42/EEC as amended. As a consequence, the Applicant was asked to provide proof of CE marking to support the use of the proposed Shire Q-Cliq pen. This issue was raised as a Major Objection due to the legal obligation under Directive 2001/83/EC to provide such evidence before adoption of a CHMP Opinion for this marketing authorisation application. With their response, the Applicant submitted the corresponding CE certificate issued by the Notified Body and the Declaration of Conformity. Therefore the issue was considered resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Natpar is considered to be in line with the quality of other approved recombinant DNA products. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall quality of Natpar is considered acceptable when used in accordance with the conditions defined in the SmPC.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

Non-clinical data for this application was in part derived from previous studies undertaken for the approval of rhPTH(1-84) for the treatment of osteoporosis (Preotact; approved in the EU in 2006 and withdrawn in 2014).

2.3.2. Pharmacology

The Applicant performed different studies to evaluate whether treatment with rhPTH(1-84) induces effects similar to endogenous PTH, being involvement in (1) calcium homeostasis (2) phosphate homeostasis and (3) bone formation. The focus of the pivotal rat and monkey studies has been the effect of rhPTH(1-84) on bone formation in models for osteoporosis, obtained by ovariectomy (OVX). Besides, these monkey studies show that transient increases of serum calcium are obtained after daily administration of rhPTH(1-84), returning to baseline levels within 24h. Thus, pre-dose calcium levels remained stable during the course of the study. For serum phosphate no transient effect of treatment could be seen in the hours after administration of rhPTH(1-84), but at long term a decrease of pre-dose levels was observed. The levels of active vitamin D were increased, as could be expected. The acute and/or chronic effects of rhPTH(1-84) on calcium, phosphate and vitamin D metabolism were also studied in the OVX rat model, but only increases in active vitamin D were observed. The absence of influence on serum calcium levels could be due to the role of calcitonin as a potent anticalcaemic hormone in rats, but not in humans or monkeys.

The Applicant refers to the literature for studies using hypocalcaemic parathyroidectomized and thyroparathyroidectomized rats. Several publications show that treatment with rhPTH(1-84) increases serum calcium levels and urine phosphate levels in these animals shortly after administration, but no long-term data are available.

In normal male and female cynomolgus monkeys, transient increases in serum calcium levels were observed while no long-term effect could be detected. Conversely, no transient serum phosphate level changes were detected while pre-dose levels decreased after long-term treatment.

In OVX rats, treatment with rhPTH(1-84) resulted in a dose-related gain in bone mass at trabecular and cortical bone sites, associated with increased bone strength. In monkeys, treatment increases bone mineral density (BMD) and strength at trabecular bone sites. Increased bone remodelling was also found at cortical bone sites, but this was associated with decreased BMD and strength.

Dose ranges from 1.5 to 30 µg/kg BW were administered in monkeys in the pharmacology studies, with corresponding exposures ranging from 0.2 to 21 ng.hr/mL, covering the human exposure at the maximum recommended dose (100µg/day; or on average 1.66 µg/kg/day).

In conclusion, the nonclinical pharmacology studies in rats and monkeys were originally intended to support the use of rhPTH(1-84) in treating postmenopausal osteoporosis and predominantly investigated the effects of the compound on bone. For this current therapeutic indication they are considered to be secondary pharmacodynamics. No studies dedicated to evaluating the primary PD effects for the current indication have been conducted. The proposed use of Natpar is supported by published literature demonstrating increased serum calcium levels following administration of rhPTH(1-84) in hypocalcaemic animal models. There were no signs of significant tachyphylaxis and desensitisation in long term studies up to 16 months in animals with normal parathyroid function. For

bone markers, long term human data from patients with hypoparathyroidism are very limited. Changes in bone function and structure could be expected.

Safety pharmacology programme

Safety pharmacology studies primarily evaluated cardiovascular effects. The uncertainty about the doses administered in the otherwise GLP compliant in vitro assays for the evaluation of QT-prolongation (hERG - canine cardiac Purkinje fibres) hampers correct interpretation of the negative results of rhPTH(1-84) in these assays. However, the maximal nominal concentration of 300 ng/ml still largely exceeds the human C_{MAX} after dose correction. Therefore, no additional experiments are required.

Two in vivo studies in rat and dog revealed mean arterial blood pressure reduction in rats and no effects in the dog at doses exceeding the intended clinical dose.

Also, no adverse effects on the central nervous system were detected in a functional observation battery conducted in rats, resulting in a exposure-based safety margin of 18-24. Acute effects on the respiratory system were not tested. Given the absence of evidence for adverse effects on the respiratory system in clinical tests performed by the Applicant, no further non-clinical experiments were considered to be required, consistent with the assessment of the safety pharmacology data for the previous approval of Preotact.

2.3.3. Pharmacokinetics

Absorption was evaluated in rats, rabbits, dogs and monkeys in several single dose studies and in the course of the repeated-dose toxicity studies. Absorption after subcutaneous administration was rapid in rats (2-20 min) and monkeys (20-60 min), and the rate of absorption was independent of gender, dose or treatment duration. For both single and repeated doses, peak plasma concentrations and exposure were linearly related to dose, except in monkeys at 25 µg/kg on. In monkeys, single dose exposure was predictive for multiple dose exposure, while in the rat exposure increased during the first weeks of daily treatment. Absolute bioavailability after subcutaneous administration was calculated to be 46% in rats and 39.5% in monkeys, comparable to humans (53%).

Apart from the lacteal excretion study, no conventional distribution studies were conducted. Based on the results of this rat study, the possibility of minimal maternal transfer of rhPTH(1-84) through the milk to offspring cannot be excluded. The volume of distribution is comparable to blood volume in rats, and radio-labelled PTH was shown to be rapidly and widely distributed.

PTH(1-84) is rapidly cleared from plasma in the liver by nonspecific peptidases as its primary clearance pathway and to a lesser extent in the kidney. Excretion studies were not performed. The Applicant refers to literature for identification of major route of elimination, i.e. urinary excretion.

A concern was raised about potential effects on PK and PD of proteinacious particles in the finished product over the 14-day in-use shelf life after reconstitution of Natpar. In a rabbit PK and PD study, dose solutions prepared using reconstituted cartridges having appearance category B or C did affect the pharmacokinetics of the drug in the rabbit while those of category 0 and A have comparable PK profiles. The pharmacodynamics of the drug also appeared to be altered by batch appearance category.

2.3.4. Toxicology

Repeated-dose toxicity studies were conducted in rats (up to 26 weeks), dogs (up to 4 weeks) and Cynomolgus monkeys (up to 26 weeks). Due to sensitivity to rhPTH(1-84)-induced hypercalcaemia, the dog was not considered an appropriate animal model and was replaced by the non-human primate. The most significant target organ in all species was the kidney, characterized by varying degrees of tubular dilation, regeneration and mineralization, which was due to the elevation in serum calcium associated with the pharmacological action of PTH. Male rats appeared to be more sensitive than females (9 deaths compared to 1 death or moribund sacrifices in the high dose group (n=30/sex)), a finding also observed in the carcinogenicity study. As in contrast to the previously authorized indication, Natpar is intended for use in both sexes, concern was raised about the clinical relevance of this apparent gender-based difference in sensitivity. In both non-clinical studies, total systemic exposure is slightly lower in female compared to male rats. Human data with respect to gender effects on PK, efficacy and safety are limited, but no gender difference in exposure of patients was observed so far. Increased toxicity observed in male rats might be explained by a gender-based difference in exposure which is not observed in patients, and might therefore be of no clinical relevance.

In contrast to the rat, with a NOAEL of 8.11 µg/kg/day and an animal to human margin of exposure of 8.8, kidney-related abnormalities were detected at levels comparable to the clinical exposure levels in the pivotal monkey repeat-dose toxicity study. Nephrotoxicity is added as a potential risk in the Risk Management Plan.

rhPTH(1-84) tested negative for *in vitro* mutagenic potential in two assays (bacteria and mammalian cells). In a two-year carcinogenicity study in rats, dose-dependent increases in bone tumors including osteosarcoma were observed in males and females. Osteosclerosis was observed in the 26 week repeat dose toxicity study in rats, suggesting that the observed lesions in the carcinogenicity study result from the long duration of treatment and the exaggerated pharmacologic response of the rat skeleton to daily treatment with PTH(1-84). Rat-to-human safety margin based on exposure are 4.8 and 3.3 in male and female respectively. Bone tumors were detected at 26- and 18-fold (male/female) human exposure at the maximum recommended dose. Although a growing body of evidence may be in favour of considering the observed increased risk for osteosarcoma or other bone neoplasms in rats, continued follow-up is recommended (See also Risk Management Plan and Clinical objections). Differences in rat and human bone metabolism may explain the difference in carcinogenic potential in these species. In contrast to humans, the ever growing rat skeleton may be considered to be a developing organ harboring immature and potentially tumorigenic cells that may respond to PTH with uncontrolled behavioral growth. Therefore, this concern remains for children as PTH treatment may have a different impact in developing bone compared to adult bone. In the agreed paediatric investigatiol plan, a juvenile study to address this question is planned.

For evaluation of reproductive and developmental toxicity, conventional studies on fertility and early embryonic development (rat), embryofoetal development (rat and rabbit), and pre- and postnatal development (rats) were performed. A common finding in parental animals was a transient decrease in body weight gain, an observation not identified in repeat-dose toxicity studies. In the FEED rat study, small but significant differences compared to controls were observed in females (reduced number of corpora lutea, implantation sites and live foetuses, increase in gestation duration) and males (reduced prostate and cauda epididymis weights). Reproductive toxicity was also described for rhPTH1-34 (Forsteo), where embryotoxicity (fetal resorption and reduced litter size) occurred in pregnant rabbits administered daily doses of 3 to 100 µg/kg.

The observed foetal effects in rats and rabbits are limited to skeletal variations (reduced number of ossified phalanges in the hindlimb (rat), and incompletely ossified sternal centra, increased number of ossified thoracic vertebrae and ribs, and decreased number of ossified lumbar vertebrae (rabbit). This

could be ascribed to growth retardation induced by maternal toxicity, or to a pharmacological effect. In a peri-/post-natal development study in pregnant rats, male pups given subcutaneous doses of 1000 µg/kg/day showed mild dehydration.

The minor effects observed in the fertility study in rats and in the embryofoetal development studies in rats and rabbits are within historical control data ranges or can be attributed to maternal and paternal toxicity. The observed maternal and paternal toxicity was transient in these studies. No direct effects of rhPTH(1-84) were observed on reproduction and development. The mild dehydration observed in the pre-and postnatal study in rats at the high dose (1000µg/kg/d) is considered of no clinical relevance due to the high exposure margin (123-fold therapeutic dose).

A conventional local tolerance study revealed no rhPTH(1-84)-specific effects after single dose administration by intravenous, perivenous or intra-arterial route. Repeated-dose toxicity studies revealed dose-related changes at injection sites (haemorrhage and fibrosis) suggesting that the rhPTH(1-84) solution was mildly inflammatory.

Repeated administration of rhPTH(1-84) in rats and dogs can elicit weak immune responses, but the frequency of antibody formation is low and had little or no effect on the biological activity of PTH. In monkeys, an isolated immune response was detected. Overall, these responses do not compromise the interpretation of non-clinical studies.

Several impurities identified in the drug substance and product exceed the threshold for qualification according to ICH guideline Q3A/B. The proposed release specifications for PTH(1-80) + PTH(deaminated), Met8[ox]PTH and Met18[ox]PTH are 1, 1 and 1.5 % respectively. For five of the toxicology studies, impurity profiles of drug substance/product have been determined, and a sufficient margin of exposure (animal to human; dose-based) was observed in these repeated-dose and reproductive toxicity studies, both for the tested batches as for the proposed release specifications for the finished product. No genotoxicity study was performed but it is considered unnecessary to conduct further nonclinical studies in support of the qualification of these impurities.

rhPTH(1-84) is non-haemolytic in human whole blood, and compatible with human serum and plasma.

2.3.5. Ecotoxicity / environmental risk assessment

Natpar is a protein and has an identical in structure to the endogenous human 84-amino-acid hormone. It is therefore exempted from the need to provide an environmental risk assessment as this naturally occurring hormone is unlikely to result in significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

The non-clinical pharmacology studies in rats and monkeys were originally intended to support the use of rhPTH(1-84) in treating postmenopausal osteoporosis and predominantly investigated the effects of the compound on bone. For this current therapeutic indication they are considered to be secondary pharmacodynamics. No studies dedicated to evaluating the primary PD effects for the current indication have been conducted. but the intended use is a hormone replacement therapy. Furthermore, the proposed use of Natpar is supported by published literature demonstrating increased serum calcium levels following administration of rhPTH(1-84) in hypocalcaemic animal models. There were no signs of significant tachyphylaxis and desensitisation in long term studies up to 16 months in animals with normal parathyroid function. For bone markers, long term human data from patients with hypoparathyroidism are very limited. Changes in bone function and structure could be expected. The pharmacokinetics of rhPTH(1-84) have been demonstrated to be linear except at the high doses used in toxicology studies. In all species tested (rat, dog, rabbit, monkey), rhPTH(1-84) exhibited rapid

absorption following subcutaneous administration, a distribution volume that approximated blood volume, and rapid elimination from the systemic circulation. The toxicology programme consisted of the investigation of single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, a complete assessment of reproductive and developmental toxicity, local tolerance and antigenicity. The species used were mice, rats, rabbits, dogs, and monkeys. Since the intended clinical route of administration in the clinic is SC injection, the majority of the studies were performed using that route. Initially, the dog was chosen as the non-rodent species for the toxicology programme. However, the dog was shown to be overly sensitive to the calcaemic effects of rhPTH(1-84) which resulted in pronounced adverse effects on the kidney. The non-rodent species was changed to the non-human primate. Repeated-dose toxicity studies conducted in rats (up to 26 weeks), dogs (up to 4 weeks) and Cynomolgus monkeys (up to 26 weeks) showed that the kidney was the most significant target organ in all test species. In monkeys, kidney-related abnormalities were detected at levels comparable to the clinical exposure levels, which is reflected in the SmPC. Nephrotoxicity is also added as a potential risk in the Risk Management Plan. A 2-year rat carcinogenicity study showed a dose-related increase in bone tumors including osteosarcoma. Although a growing body of evidence seems to indicate the observed increased risk for osteosarcoma to be of little clinical relevance (see clinical section of this report). The negative results in the in vitro genotoxicity studies and the results from the 2-year carcinogenicity study indicate that rhPTH(1-84) is a non-genotoxic carcinogen. In the carcinogenicity study and the rat repeated-dose toxicity study, males appeared to be more sensitive than females. This could be explained by the increased exposure in males, a finding that is not confirmed in patients. The effects on reproduction and embryofoetal development are minor. Those observed in the fertility study in rats and the embryofoetal development studies in rats and rabbits are within historical control data ranges or can be attributed to maternal and paternal toxicity, which was transient in these studies. Mild dehydration observed in the pre-and postnatal study in rats at the high dose (1000µg/kg/d) is considered of no clinical relevance due to the high exposure margin (123-fold therapeutic dose).

2.3.7. Conclusion on the non-clinical aspects

Considering the absence of clinical relevance of the observed toxicities in non-clinical studies, and considering that limited dedicated pharmacodynamics studies are acceptable in view of (1) available nonclinical data in osteoporosis models, (2) published literature on hypocalcaemic animal models and (3) clinical data, the nonclinical testing program is considered adequate to support the safe use of Natpar in human subjects.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the European Union were carried out in accordance with the ethical requirements of Directive 2001/20/EC.

The rhPTH(1-84) clinical development program includes 13 clinical pharmacology studies, 4 efficacy and safety studies in hypoparathyroidism, and a supporting development program consisting of 7 osteoporosis studies.

5 studies are conducted in hypoparathyroidism subjects (4 efficacy and safety studies, 1 clinical pharmacology study). Among these studies, the pivotal study, CL1-11-040 was randomized, double-blind, and placebo-controlled. It provided robust, statistically significant differences in efficacy between rhPTH(1-84) and placebo and is the primary registration study.

In addition to the 4 efficacy and safety studies in the clinical development program, 1 investigator-initiated trials (IITs) was reported studying the use of rhPTH(1-84) in subjects with hypoparathyroidism. This study was conducted in Denmark by Dr. Leif Mosekilde with a total of 62 subjects. NPS has obtained a right of reference only to the Mosekilde pharmacokinetic (PK)/pharmacodynamic (PD) substudy.

The clinical development program also included a total of 13 clinical pharmacology studies: 7 comparative bioavailability and bioequivalence studies (PAR-C10-005, PAR-C13-004, CL1-11-007, CL1-11-012, CL1-11-013, CL1-11-017, and SH-PTH-0001), 2 healthy subject PK and initial tolerability studies (PBR930811 and PBR930812), 2 patient PK and initial tolerability studies in subjects with hypoparathyroidism (C09-002 and the Mosekilde PK/PD substudy), and 2 intrinsic-factor PK studies in subjects with hepatic (CL1-11-009) and renal impairment (CL1-11-010).

In addition to the efficacy and safety studies in hypoparathyroidism and the clinical pharmacology studies, the safety of rhPTH(1-84) for the treatment of hypoparathyroidism is supported by nonclinical safety data, the premarketing and postmarketing safety data on the use of rhPTH(1-84) in patients with osteoporosis, and the results of a literature search pertaining to the safety of rhPTH(1-84) and the use of PTH(1-34).

Tabular overview of clinical studies

Table 2: bioavailability / bioequivalence studies in the Natpara development program

Study Title (Number) Sponsor	Study Objectives	Design	Formulation[a] Delivery Information[b]	Dosage (µg) and Route (Site of Administration)	Subjects Randomized
Phase I study performed for the hypoparathyroidism development					
A Randomized, Open-label, Two-treatment, Two-period Crossover Study to Determine the Bioequivalence of NPSP558 Administered Subcutaneously With the Ypsomed and Haselmeier Injection Pens in Healthy Volunteers (PAR-C10-005) NPS Pharmaceuticals, Inc.	Determine BE after SC administration by Ypsomed and Haselmeier injection pens	Randomized, open-label, single-dose, 2-treatment, 2-period crossover, 3-day washout	B Ypsomed pen for SC injection Haselmeier pen for SC injection	100 SC (alternating thighs)	50 healthy volunteers
A Randomized, Open-label, Single-dose, Two-treatment, Two-period Crossover Study to Determine the Bioequivalence of NPSP558 Administered Subcutaneously With the Ypsomed and Scandinavian Health Ltd (SHL) Pens in Healthy Volunteers (PAR-C13-004) NPS Pharmaceuticals, Inc.	Determine BE after SC administration by Ypsomed and SHL injection pens	Randomized, open-label, single-dose, 2-treatment, 2-period crossover, 3-day washout	B Ypsomed pen for SC injection SHL pen for SC injection	100 SC (alternating thighs)	58 healthy volunteers

Phase I supportive studies from the osteoporosis development					
A Pharmacokinetic and Bioavailability Study of ALX1-11 (rhPTH[1-84]) Administered to Healthy Postmenopausal Women by Intravenous Infusion or Subcutaneous Injection (CL1-11-013) NPS Allelix Corp.	Determine PK after IV and absolute BA after SC administrations	Open-label, randomized, 2-way crossover, 1-week washout	B IV infusion Disetronic pen for SC injection	100 IV (15 min) SC (abdomen)	12 healthy postmenopausal women
A Phase I, Randomized, Three-way Crossover Bioavailability Study of ALX1-11 in Normal Healthy Postmenopausal Women (CL1-11-007) NPS Allelix Corp.	Compare PK and BA at 2 SC injection sites and assess intra-subject variability	Open-label, randomized, 3-way crossover, 5-day washout	B Disetronic pen for SC injection	100 SC (abdomen [2 injections] and thigh [1 injection])	18 healthy postmenopausal women
A Phase I, Open-label, Randomized, Two-way Crossover Bioequivalence Study Comparing Two Formulations of ALX1-11, with and without $ZnCl_2$, in Healthy Postmenopausal Women` (CL1-11-012) NPS Allelix Corp.	Determine BE of a formulation without (Formulation B) and with (Formulation ZC) 30 mM zinc chloride stabilizer after single injections	Open-label, randomized, 2-way crossover, 7-day washout	B, ZC Disetronic pen for SC injection	100 SC (abdomen)	64 healthy postmenopausal women
A Single-dose Bioequivalence Study Comparing Two Different Formulations of Subcutaneous rhPTH (1-84) in Healthy Male Subjects (SH-PTH-0001) Astra Hässle AB, Sweden	Assess BE and PK of new formulation of rhPTH(1- 84) (Formulation B) compared with Phase II formulation (Formulation A)	Single-dose, open-label, randomized, 2-way crossover, 1-to-28-day washout	A IV infusion B Disetronic pen for SC injection	100 SC (abdomen)	43 healthy men
A 3-way Crossover Study of ALX1-11 (rhPTH[1-84]) Administered to Healthy Postmenopausal Women by Intradermal or Subcutaneous Injection (CL1-11-017) NPS Allelix Corp.	Compare PK (including relative BA) and PD of PTH administered intradermally (1.5-mm and 2.0-mm needle lengths) versus SC injection (8-mm needle length)	Single-center, open-label, randomized, 3-way crossover, 1-week washout	B Disetronic pen for SC injection	100 intradermal (1.5 and 2 mm deep, abdomen) SC (8 mm deep, abdomen)	22 healthy postmenopausal women

BA = bioavailability; BE = bioequivalence; IV = intravenous; PD = pharmacodynamics; PK = pharmacokinetics; SC = subcutaneous; IV = intravenous
[a]Formulation A: lyophilized powder to be reconstituted for injection; Formulation B: lyophilized powder to be reconstituted for injection using a multi-dose injection pen; Formulation ZC: same as B with the addition of 30 mM zinc chloride stabilizer (not developed further).
[b]Syringes for IV infusion: 1 mL, 26-G, 3/8 in needle, 0.5 mL injection volume; Disetronic pen: 14-dose cartridge, 31-G, 8 mm needle, 71.4 µL injection volume; Ypsomed pen: 14-dose cartridge, 31-G, 8 mm needle, 71.4 µL injection volume; Haselmeier pen: 14-dose cartridge, 31-G, 8 mm needle ,71.4 µL injection volume.

An overview of all clinical pharmacology studies in the rhPTH(1-84) development program is provided in the tables below:

Table 3: healthy subject and patient PK and initial tolerability studies

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects[1] Sex (M/F) Mean Age (Range)	Treatment Details (Study Drug/ Dose/Form/Route/Frequency/ Duration)	Study Status	Study Report Location
PBR-930812	Multiple dose safety and PK	Safety and tolerability, maximum tolerated dose, and PK profile	Double-blind, placebo-controlled, multiple dose safety and tolerability study	Healthy postmenopausal women	48 (0/48), Mean age 55 (47-64)	rhPTH(1-84): 0.5, 1, 1.5, 2, 2.5, and 3 µg/kg SC in the thigh, 7-day repeat dose	Complete	CTD Module 5.3.3.1
PBR-930811	Single dose safety and PK	Safety and tolerability, no effect dose, maximum tolerated dose, and PK profile	Double-blind, placebo-controlled, ascending single dose safety and tolerability study	Healthy postmenopausal women	32 (0/32), Mean age 56 (48-60)	rhPTH(1-84): 0.02, 0.05, 0.1, 0.2, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 µg/kg SC in the thigh, 3 single doses	Complete	CTD Module 5.3.3.1

C09-002	Single dose PK and PD	Assess the PK and PD of rhPTH(1-84) administered as single SC doses of 50 µg and 100 µg	Open-label, escalating single-dose	Subjects with Hypopara-thyroidism	7 (1/6), median age 51.0 (39-69)	rhPTH(1-84) 50 µg SC in the thigh, single dose; washout ≥ 7 days, rhPTH(1-84) 100 µg SC in the thigh, single dose.	Complete	CTD Module 5.3.3.2
Mosekilde IIT PK/PD Substudy [EudraCT #2008-000606-36]	PK and PD	Determine diurnal variations in biochemical indices following SC administration of rhPTH(1-84)	Randomized, double-blind, placebo-controlled, parallel-group IIT.	Subjects with Hypopara-thyroidism	39 (6/33), Mean age rhPTH(1-84) group 53.8 (SD 11.9), Mean age placebo group 49.6 (SD 10.6)	rhPTH(1-84) 100 µg SC in the thigh, QD for 24 weeks, PK/PD measures were performed on the last day of treatment.	Complete	CTD Module 5.3.3.2

Table 4: renal and hepatic impairment studies in the Natpara development program

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects[1] Sex (M/F) Mean Age (Range)	Treatment Details (Study Drug/ Dose/Form/Route/Frequency/ Duration)	Study Status	Study Report Location
Intrinsic Factor PK Study Reports (CTD Module 5.3.3.3)								
CL1-11-009 (Hepatic Impairment)	PK, disease state	PK, effect of hepatic impairment on BA	Disease-state comparison, open-label	Men and women ≥45 years old (healthy or with moderate hepatic impairment)	24 (12 hepatic impaired and 12 healthy), (12/12), Mean age 57.5 (45-71)	rhPTH(1-84): 100 µg SC in the abdomen, single dose	Complete	CTD Module 5.3.3.3
CL1-11-010 (Renal Impairment)	PK, disease state	PK, effect of renal impairment on BA	Disease-state comparison, open-label	Men and women ≥45 years old (healthy or with mild-to-moderate renal impairment)	32 (16 renal impaired and 16 healthy), (16/16), Mean age 61.0 (45-82)	rhPTH(1-84): 100 µg SC in the abdomen, single dose	Complete	CTD Module 5.3.3.3

Table 5: population PK/PD analysis

Protocol No.	Type of Study	Study Objective(s)	Study Design	Key Inclusion Criteria of Subjects	No. of Subjects[1] Sex (M/F) Mean Age (Range)	Treatment Details (Study Drug/ Dose/Form/Route/Frequency/ Duration)	Study Status	Study Report Location
NPSP-PCS-101 Overall Pop PK and PK/PD Report and Addendum	Population PK and PK/PD	Develop a population PK model of rhPTH(1-84)	PK modeling, PK/PD correlation analysis and Specific Antibody effects on PK	16 studies combined	Hypoparathyroidism: 136 (30/106), age 46.7 (19-74) years. Non-hypoparathyroidism: 1410 (99/1311), age 61.1 (18-88) years.	rhPTH(1-84) SC in the thigh or abdomen QD, single dose or multiple doses up to 18 months.	Complete	CTD Module 5.3.3.5
ALX1-11-93001 [Pop PK substudy of TOP ALX1-11-93001]	Population PK performed in a subset of subjects in an Efficacy and Safety study.	Estimate the PK parameters of PTH(1-84) in the TOP population, and investigate possible covariate-parameter relationships within the population	Randomized, double-blind, placebo-controlled, parallel-group	Postmenopausal women with osteoporosis	In Pop PK substudy: 621 (320 rhPTH(1-84), 301 placebo), (0/621), Mean age 65.0 (47-88)	rhPTH(1-84): 100 µg SC in the abdomen or thigh, QD for 18 months	Complete	CTD Module 5.3.3.5

Table 6: overview of all pharmacodynamic, efficacy and safety studies

CL1-11-007	1	Single dose, 3-way crossover study	rhPTH(1-84) 100µg SC in thigh or abdomen	PK - BA - PD	18	3 single dose	0/18 60.5 (mean)	Healthy Postmenopausal women	the effect of SC injection into the thigh versus the abdomen
CL1-11-012	1	open-label, randomized, two-way crossover study	100µg ALX1-11(ZnCl2 formulation); 100µg ALX1-11 abdomen	PK - PD	64	single dose	0/64 58.2 (mean)	Healthy Postmenopausal women	systemic PTH exposure after SC administration of 2 different formulations
CL1-11-013	1	open-label, randomized, 2-way crossover study	100 µg dose of rhPTH(1-84) IV (15 min) or SC in abdomen	PK - BA - PD	12	single dose	0/12 60.2 (mean)	Healthy Postmenopausal women	systemic PTH exposure after IV or SC administration
CL1-11-017	1	randomized, 3 way crossover study	100 µg rhPTH(1-84) injection at 3 depths in the abdomen	PK - PD	22	single dose	0/22 56.0 (mean)	Healthy Postmenopausal women	PK/PD at different depths of administration
CL1-11-006	35 centers in 8 countries: 4 Argentina, 5 Brazil, 2 Bulgaria, 2 Canada, 5 Israel, 6 Mexico, 3 Russia, and 8 United States	ACR substudy of randomized, double-blind, placebo-controlled study	100 µg rhPTH(1-84) or placebo in thigh/abdomen SC	PD substudy	rhPTH(1-84), 131; placebo, 238	single dose	0/369	osteoporosis patients enrolled in TOP	acute calcemic response (ACR) study
CL1-11-008	26 clinical centers in the United States, Argentina, and Mexico	double-blind, multicenter, randomized, placebo-controlled, parallel-group study	100 µg rhPTH(1-84) + placebo Ca-supplement; placebo + 700 mg Ca-supplement or 100 µg rhPTH(1-84) + 700 mg Ca-supplement	PD substudy	24; 30; 25	1 day substudy	0/79	postmenopausal women with osteoporosis	acute calcemic response (ACR) study
N01-AR-9-2245 NIAMS-045	4 centers in the U.S.	ACR substudy of randomized, double-blind, study	ALX1-11 (100 µg) + ALN-Placebo; ALX1-11 (100 µg) + ALN (10 mg); ALX1-11-Placebo + ALN (10 mg); ALX1-11-Placebo + ALN (10 mg)	PD substudy	119; 60; 59	1 day substudy	0/238	postmenopausal women with low BMD	calcemic response (ACR) during 8 hours
CL1-11-040 (REPLACE)	32 (28 with randomized subjects) sites in 8 countries (USA 19, Canada 3, Denmark 3, Hungary 3, Belgium 1, France 1, Italy 1, UK1)	Randomized, double-blind, placebo-controlled	50, 75, and 100 µg (flexible doses) or placebo	Efficacy and Safety	rhPTH(1-84), 84; placebo, 40	24 weeks	26/98 48.5	hypoparathyroidism for ⩾ 18 months	% subjects with 50% reduction oral Ca dose, 50% reduction calcitriol/alphacalcidol, serum ACSC between 1.875 mmol/L and ULN (vs. Baseline)

PAR-C10-007 (RELAY)	11 centers in the U.S.	Randomized, dose-blinded	25 or 50 µg (fixed doses)	Efficacy and Tolerability	25 µg, 19; 50 µg, 23	8 weeks	7/35 50.7 (25 µg group) and 46.5 (50 µg group)	hypoparathyroidism for ⩾ 18 months + new to program, or from C09-002 or CL1-11-040	% subjects with reduction to ≤500 mg/day oral Ca dose, and ≤0.25 µg/day calcitriol, and serum ACSC between 1.875 mmol/L and ULN (vs. baseline)
PAR-C10-008 (RACE)	12 investigative sites in the US	Open label	25, 50, 75, and 100 µg (flexible doses)	Safety and Tolerability	49	52 weeks + extension ONGOING	9/40 48.1	previously completed Study PAR-C10-007 and/or Study CL1-11-040	% subjects with 50% reduction OR reduction to ≤500 mg/day oral Ca dose, 50% reduction calcitriol/alphacalcidol OR ≤0.25 µg/day calcitriol, serum ACSC between 1.875 mmol/L and ULN (vs. Baseline)
PAR-C10-009 (REPEAT)	3 study centers located in Hungary	Open label	50, 75, and 100 µg (flexible doses)	Safety and Tolerability PK/PD	24	24 weeks	3/21 52.7	previously completed Study CL1-11-040 or enrolled in study but discontinued during optimization	% subjects with 50% reduction OR reduction to ≤500 mg/day oral Ca dose, 50% reduction calcitriol/alphacalcidol OR ≤0.25 µg/day calcitriol OR ≤0.50 µg/day alphacalcidol, serum ACSC between 1.875 mmol/L and ULN (vs. baseline)
C09-002 CSR	1	Open label, Escalating, Single-Dose Study	50. 100 µg	PK/PD	7	2 doses	6/1 52.0 (mean)	hypoparathyroidism for ≥ 12 months	(PK) of NPSP558 administered as single subcutaneous (SC) doses of 50 µg and 100 µg in subjects with hypoparathyroidism, secondary: PD
Mosekilde IIT	1 in Denmark	PK/PD substudy	rhPTH(1-84) 100 µg SC or placebo	PK/PD	22; 17	1 day substudy, last day of 24 weeks administration	6/33 53.8 (mean, active group) and 49.6 (mean, placebo)	hypoparathyroidism for ≥ 12 months	diurnal variations biochemical indices following rhPTH(1-84) after 24 weeks of daily treatment

2.4.2. Pharmacokinetics

Absorption, distribution, metabolism and elimination

In single- and multiple-dose studies in subjects with normal parathyroid function and in subjects with hypoparathyroidism, the plasma PTH(1-84) concentration-time profile seen after SC injection of rhPTH(1-84) into either thigh or abdomen was typically characterized by 2 peaks. An initial peak was achieved by roughly 5 to 15 minutes after dosing. A second peak, representing a slower rate of uptake from the injection site, occurred between 1 and 2 hours after dosing. PTH(1-84) levels declined gradually from the second peak and returned to predose levels at 12 to 24 hours. The mechanism(s) responsible for this double-peak plasma PTH(1-84) profile are poorly understood. Schwietert et al. believed that this double-peak profile in the serum PTH (1-84) concentrations probably indicates that the exogenously administered rhPTH (1-84) is released from the subcutaneous injection site into the systemic circulation at different rates. The PK of PTH(1-84) following SC administration of rhPTH(1-84) in the thigh was similar in normal subjects, in postmenopausal women with or without osteoporosis and in subjects with hypoparathyroidism.

The mean absolute bioavailability of PTH after subcutaneous administration of 100 µg PTH in the abdomen of healthy postmenopausal women was determined to be 55% (range 36% to 92%). Since PTH is known to be rapidly hydrolysed by non-specific peptidases in the liver the possibility exists that pre-systemic metabolism may also occur at the injection site.

The bioavailability of PTH is dependent of the site of injection. Injection into the thigh of subjects with normal parathyroid function results in a slower rate of absorption and a slower rate of decrease from the peak with a delayed return to pre-dose levels compared to injection in the abdomen. Similar overall exposure are obtained in both situations. The Cmax after administration in the abdomen is 2-fold the Cmax observed after administration in the thigh. Since the response is dependent on a threshold in PTH concentration and the duration of PTH levels above this threshold and not direct proportional to the PTH concentration, the choice of the subcutaneous injection in the thigh (once a day in alternating thighs) is supported. These results are in accordance with the POP PK results where PTH(1-84) clearance is associated with injection site.

Overall bioavailability of PTH(1-84) was higher with SC injection compared to intra-dermal injections, increasing with increasing depth of injection. There was an inverse relationship between the depth of injection and the calcaemic response, with the highest change in calcium occurring with SC injection. Thus, SC injection is the preferred route in the treatment of hypoparathyroidism with rhPTH(1-84).

Five different pens have been used throughout the clinical development for PTH. It is recognized that a different bioavailability can be observed depending on the type of pen used for administration. The Applicant provided the results of two bioequivalence studies: one between the Ypsomed pen and the Haselmeier pen and one between the Ypsomed pen and the SHL pen. Whereas the first study successfully demonstrated bioequivalence, the second one failed to show this. According to the Applicant this was due to two outliers, demonstrating an AUC value of 1.74 and 1.58% of the reference medicinal products geometric mean AUC. As per bioequivalence guideline, reassessment of bioequivalence was performed after removal of these subjects. This resulted in point estimates (90% CI) of 112.94 (98.83-129.06) and 110.97 (97.02-126.92) for AUC and Cmax, respectively. This means that the exposure to PTH(1-84) with the SHL pen is not ~30%, but rather ~13% higher than the Ypsomed pen used during the clinical development program. In a subsequent step, the Applicant proposed to take into account the actual administered dose during the BE study. These doses have been recorded in accordance with the protocol of Study PAR-C13-004, where the following has been written: ‘Based on pen and cartridge weight changes from before to after injection administration, the

study pharmacist or designee confirmed that the appropriate dose amount was given. Expected weight changes were provided by the sponsor.' Analysis of these results revealed that the in vivo administration of PTH(1-84) with the Ypsomed and SHL pens is characterized by an unacceptable high variability, presumably resulting even in an (almost) void injection. This has been demonstrated in different clinical studies with rhPTH(1-84) (studies CL1-11-007, CL1-11-009, CL1-11-010, PAR-C13-004, C09-002 and PAR-C10-007), in which no or only marginally increased plasma PTH(1-84) concentrations have been observed for some of the subjects. Further, the Applicant stated that 'lack of systemic absorption has not been observed with the use of Haselmeier or SHL pens'. Although it is agreed that none of the subjects did fulfil the criterion of a AUC < 5% of the reference medicinal product geometric mean AUC, it is noted that this is only borderline for one of the subjects after injection with the SHL pen (AUC = 5.6%) and that, overall, only 55 subjects have been treated with a single administrations. Therefore, data obtained with the SHL pen are too scarce to make a sufficiently substantiated conclusion. The Applicant subsequently decided not to use the SHL pen for commercialisation but instead to propose the Haselmeier pen. This pen (i.e. the Natpar pen; also referred to as Shire Q-Cliq pen is to be used in combination with the Duoject Mixing device (see also the Quality section of this report). Also for this pen, pen weights before and after administration have been recorded. These revealed that also for the Haselmeier pen a substantial variability in administered dose has been recorded, with administered doses ranging from 50.01 to 93.41 mg and with > 10% of subjects having a dose deviating > 20% from the target dose. However, if the same Haselmeier pen will be used during the studies that will be done as post authorisation measures, the same variability will also be introduced in the results of these studies and as such, it will be accounted for. In addition, it should be noted that US post-marketing data concerning this product delivered with the Haselmeier pen are available (see the Safety section of this report). Therefore, the issue associated with the variability observed with the Haselmeier pen (i.e. the Natpar pen proposed for commercialisation) was considered to be sufficiently considered for the benefit risk profile of this product.

The product being administered as subcutaneous injection, data on influence of food are not relevant.

The results of the data obtained after iv administration indicate that PTH is only marginally distributed outside of the plasma water. According to the Applicant, the pharmacokinetics after iv administration are described by a 2-compartment model characterized by a rapid distribution phase with a half-life of several minutes and an elimination phase with a longer half-life of approximately 0.5 hours, whereas the subcutaneous administration of PTH can be described by a one-compartment model with first order absorption and elimination.

No specific metabolism studies in humans have been performed with PTH. Literature data indicates that Kupffer cells in the liver take up and degrade about 70% of the circulating PTH into C-terminal fragments that are then released back into the systemic circulation. The proximal kidney metabolizes another 20% of circulating PTH arriving from the glomerular filtrate and by peritubular absorption and, like the liver, returns C-terminal fragments to the systemic circulation. Thus, both the parathyroid glands and peripheral metabolism contribute to circulating levels of C-terminal fragments. N-terminal PTH fragments, such as those being analogue to teriparatide (PTH(1-34)), are neither secreted by the parathyroid glands nor released into the circulation following peripheral metabolism of PTH. Because of this, the total quantity of C-terminal fragments in the circulation is often higher than that of full length PTH and can greatly exceed native hormone levels when renal function is impaired, as in severe chronic renal failure.

The C-terminal fragments have been untill recently regarded as inert byproducts of PTH metabolism, since they do not interact with the PTH/PTH-related peptide (PTHrP) receptor, which mediates the classical hormone actions. Current findings instead indicate that C-PTH would interact with a putative C-PTH receptor (Scillitani et al., J Endocrinol Invest 2011; 34: 23-26). This way, C-PTH seems to exert

specific effects on calcium homeostasis and bone metabolism, opposite to those of the synthetic agonist of PTH/PTHrP receptor (i.e. PTH 1-34). In vitro and in vivo data indicate that C-PTH, by interacting with specific receptors, could have an anti-calcaemic action, as well as a pro-apoptotic effect on both osteocytes and osteoclasts. This in turn could result in a reduced activity of the latter cells, with a consequent inhibition of bone resorption. It is, however, agreed with the Applicant that a C-PTH receptor has never been confirmed and that the potency and/or concentration of these fragments appears not to be sufficiently high to affect calcium and bone metabolism in patients with hypoparathyroidism who are treated with rhPTH(1-84). In addition, since PTH(1-84) levels return to baseline levels by approximately 12 hours post injection, it is unlikely that the C-terminal PTH fragments derived from the exogenously administered would remain in the circulation at 24 hours after the injection. Therefore, no chronic accumulation of C-terminal PTH fragments is anticipated.

The question did arise whether data could be provided in hypoparathyroidism subjects to ascertain serum calcium and C-terminal PTH fragments over 24 hours post administration of rhPTH(1-84) Lack of such data added to concerns on the short-term and long-term clinical safety consequences of wide fluctuations in serum [Ca++] over 24 hours after each administration of study drug (see Safety section of this report).

Concerning dose-linearity over the exposure range, it is considered that the results of studies PBR-930811,PBR-930812 and C09-002 do not support a claim for linear dose proportionality across the full range of doses studied. The observed curvilinear relationship between dose and both AUC and Cmax, suggests that the bioequivalence studies should be performed using a low dose of study drug as this represents the most sensitive-to-difference region of the graphical relationships. The applicant proposed that the apparent non-linearity is due to a higher contribution of endogenous PTH at the lower doses and with a calculation to subtract endogenous concentrations the adjusted AUC's are with the linearity requirements for 25- 100 µg. This explanation appears reasonable. Data for lower doses shows some non-linearity below 1 µg/ml however this may be due to poor definition of the PK profile, in addition it is highlighted that an alternative assay methodology was used.

Population PK

Population PK and PK/PD analysis results were submitted. However, additional data, analyses and discussion are expected to ensure that the optimal dose is eventually used in patients. The applicant acknowledged the value of a more mechanistic PK/PD model to characterise the exposure-response relationship over the empirical approach used in their original modelling. Given the complex interrelationship between PTH, serum calcium and 24 hour urinary calcium excretion, the empirical model utilised was viewed initially as inadequate to guide appropriate drug dosing (particularly schedule dependence of drug effect).

In answer to the last round of questions, the applicant committed to use this approach to characterize PK and PK/PD data to be generated post-marketing. A clinical pharmacology trial to assess the pharmacokinetics (PK) and pharmacokinetic/pharmacodynamic effects (PK/PD) of Natpar (parathyroid hormone) and the impact of dose and dosing regimen on the control of serum calcium and normalization of calcium excretion in urine using mechanism-based approach will be performed by the applicant as a post authorisation measure to further address remaining deficiencies of the previously developed model. Modelling and simulation with mechanistic model-based assessment of prior PK/PD data is expected to be used to inform the design of this trial. Simulations should be used to explore whether data collection as currently planned would allow appropriately characterising this mechanism based model so that there will be a suitable tool for prediction and simulation of unexplored scenarios (e.g. tid dosing).

Special populations

Mild-to-moderate renal impairment does not seem to alter the pharmacokinetics of 100 microgram PTH administrated subcutaneously in the abdomen after single dose. Section 4.2 of the SmPC reflects these observations mentioning that no adjustment to the administered dose is required in subjects with mild-to-moderate renal impairment and that no data are available in patients with severe renal impairment. In addition to the patients on renal dialysis, the lack of data in patients with severe renal impairment has been adequately added in section 5.2 of the SmPC. In section 4.4., it is stated that patients with severe renal disease have not been evaluated in clinical trials.

Patients with severe renal impairment were excluded in the clinical trials to reduce variability in the populations. Overall hypoparathyroidism (no baseline PTH secretion) patient population is essentially middle aged, and the concomitant treatments with oral calcium and active vitamin D are very different from osteoporosis (normal PTH secretion) in the elderly population. Therefore, contraindications for Natpar can be expected to be different with some aspects between Natpar and the previously approved product Preotact. For preotact, since other drug treatments for osteoporosis were available, it was concluded that patients with these impairments could use other drug classes for treating osteoporosis and a contraindication was accepted. In hypoparathyroidism, and in the context of a “not well controlled” patient with either severe renal or hepatic impairment, there is no other class of drug that can be used to treat hypoparathyroidism. Moreover, treatment with Natpar is titrated to effect i.e., to achieve a defined serum calcium range and Natpar offers 4 different dosages that allow to adjust the serum calcium level together with variable doses of oral calcium and active vitamin D. Therefore, CHMP did not require a contraindication in patients with severe renal impairment for this product.

Mild-to-moderate hepatic impairment (total score of 7 to 9 on the Child-Pugh scale) does not seem to alter the pharmacokinetics of 100 microgram PTH administrated subcutaneously in the abdomen after single dose. Section 4.2 of the SmPC reflects these observations mentioning that no adjustment to the administered dose is required in subjects with mild-to-moderate hepatic impairment and that no data are available in patients with severe hepatic impairment. The lack of data in patients with severe hepatic impairment has been adequately added in section 5.2. In section 4.4., it is stated that patients with severe hepatic disease have not been evaluated in clinical trials.

There is no trial investigating especially the effect of ethnicity as primary endpoint. Since 253 of the 274 subjects included in the POP PK analysis are reported as Caucasian (2 as black, 8 as Asian and 9 as Hispanic) no effect of race on the clearance or volume of distribution of PTH could be established as the predominance of Caucasians precludes the identification of an effect even if one existed. However, based on the previous Preotact assessment, it seems that the results of the substudy CL1-11-006 supports the conclusion that the ethnicity factor is not suspected to influence the PK of PTH. However, earlier experience in patients from other ethnic origins in the osteoporosis indication of rhPTH(1-84) is not considered extrapolable since it concerned only female patients with a different background than patients with hypoparathyroidism. Important uncertainties remain regarding the PK, efficacy and safety of rhPTH(1-84) in hypoparathyroidism treatment in patients from other ethnic origins than White (see RMP).

According to the POP PK analysis, there is a clear effect of bodyweight on the apparent clearance and on the apparent volume of distribution. In this context, a detailed discussion on the potential influence of weight on the PK profile and the Pk variability of Natpar has been asked by CHMP, especially considering the route of administration and the potential impact of adipose tissue thickness. The applicant was asked to discuss the convenience of an individualised dosing regimen on the basis of body weight and discuss the dosing regimen in overweight patients. Based on the PK/PD relationship of PTH1-84 and calcium levels and the analysis of body weight and BMI, the clinical data indicate there was no difference in responder rates in the REPLACE or RACE studies (see efficacy/safety sections).

Taking into account that the previous authorised product of rhPTH (Preotact) was indicated for postmenopausal osteoporosis, several studies were carried out in post-menopausal women. Taking into account that rhPTH is indicated in adults with hypoparathyroidism including male subjects, that male subjects appeared to have greater PTH exposure in study CL1-11-010 and that there is an effect of gender factor on the apparent volume of distribution in POP PK, the applicant has been asked by CHMP to further summarize the influence of gender factor on the rhPTH PK characteristics and its clinical relevance. Based on the fact that there is no direct linear relationship between PTH1-84 and calcium levels and considering the responder rate provided by the applicant for the REPLACE study, CHMP agrees with the applicant that the influence of gender factor on the rhPTH PK characteristics cannot be considered as clinically relevant. However, human data on PK, efficacy and safety in male patients remain limited compared to females, which was not a major concern.

Although the data in elderly patients over 65 years age are limited, based on the Population Pharmacokinetic Analysis of Recombinant Human Parathyroid Hormone in Subjects with and without Hypoparathyroidism, NPSP-PCS-101, no difference in PK was detected with regard to age and therefore dosage adjustment based on age is not required. Section 5.2 of the SmPC informs that data with patients of 65 years and older are very limited.

The safety and efficacy of Natpar in children less than 18 years of age have not yet been established.

Drug-drug PK interactions

Since PTH(1-84) is an endogenous peptide in healthy people, the most likely predominant metabolism is hydrolytic degradation and not related to cytochrome P450-dependent oxidative enzyme activity. Therefore, rhPTH(1-84) is unlikely to be involved in any drug-drug interactions related to cytochrome activity. It is not expected to bind to plasma proteins, and has a low volume of distribution similar to extracellular fluid volume; therefore it is not expected to be involved in drug displacement interactions.

A specific drug interaction study with alendronate and rhPTH(1-84) (PaTH study) was performed, and no interaction was observed with alendronate. There was also no evidence of any influence on the PK of covariates based upon the classes of concomitant medications in the final population PK analysis. No evidence of drug interactions was identified during extensive clinical studies in subjects with either hypoparathyroidism or osteoporosis. No obvious effect of thiazide diuretics on PTH clearance is expected from a mechanistic perspective. During the previous submission for Preotact, the lack of effect of thiazide diuretics on PTH clearance was confirmed in a post hoc analysis of subjects participating in the PopPK (ALX1-11-93001) and ACR (CL1-11-006) sub-studies of TOP. In the same way, no PK interactions were observed with the related drug teriparatide (PTH 1-34) in formal drug-drug evaluations with hydrochlorothiazide or furosemide.

2.4.3. Pharmacodynamics

A clear understanding of the pharmacodynamics of the compound provides guidance for designing studies, by means of physiological parameters within the serum and urine of the patient. Primary pharmacology is important for this kind of working mechanism, since there are many physiological parameters available that can further substantiate the proposed working mechanism. Therefore, pharmacodynamic data is not only important to reveal the working mechanism, but also to demonstrate efficacy for this orphan medicinal product for which data is available on a limited number of patients. Data concerning serum and urinary concentrations or physiological parameters as an

indication of the PD response to changes in systemic PTH(1-84) concentrations is generated from studies in the clinical pharmacology program (including PK studies and efficacy studies).

Pharmacodynamic (sub)studies were performed in healthy subjects (or osteoporosis patients with normal PTH levels), others in hypoparathyroidism patients, some after single dosing but several also after long term treatment with rhPTH(1-84).

Study PBR-930811 and PBR-930812 were studies performed in healthy subjects, in a search for dose response properties. Study PBR-930811 was a single dose study demonstrating that serum total (/ionized) calcium concentration and dose appear to follow sigmoidal functions, with little or no effect at doses below 1.0 µg/kg and a maximum plateau effect at doses above 2.0 µg/kg, with urine calcium/creatinine ratio (risk for hypercalciuria) only increasing with doses greater than 2.0 µg/kg). Study PBR-930812 was an ascending multiple dose study in which the chosen dose for each subject was administered during a week. Mean serum total calcium returned to baseline (without risk of hypercalcaemia) each day for all doses less than 2.5 µg/kg.

Studies CL-1-11-007, CL1-11-012 and CL1-11-13 are also performed in healthy subjects and show that there is no direct linear relationship between PTH concentration in serum and calcium response. There is a delay in the response, and the magnitude and duration of the calcium response seem to be more dependent on the duration of the elevated PTH(1-84) levels rather than on the absolute magnitude of the increase. This is very clear when comparing the IV versus SC administration (CL1-11-013) in which the AUC0-24 after IV administration is nearly 2-fold greater than after SC dosing in the abdomen, and the peak PTH(1-84) concentration 23-fold greater, but in contrast the calcium response was less after IV administration. CL1-11-012 shows an exploratory formulation (not retained) that has a lower Cmax but also with a greater calcium response. Study CL1-11-007 resulted in the conclusion that although injection in the abdomen results in a higher Cmax than injection in the thigh, the magnitude and duration of calcium response is higher after injection in the thigh. Therefore it was decided that this was the preferred injection site.

CL1-11-017 investigated the depth of injection. There were no major differences but there was a tendency towards higher calcium response after SC administration.

Study C09-002 was the ‘pivotal PD study’ with PD response measured in hypoparathyroidism patients. It was an open-label, escalating, single-dose study in 7 subjects with a diagnosis of hypoparathyroidism for ≥ 12 months. Calcitriol (usual dose) + calcium supplement was given the first day, followed by 50 µgor alternatively 100 µg rhPTH(1-84) + calcium supplement the day after, with a washout of 7 days between the two dosages. PD responses of serum total calcium, albumin, albumin-corrected total calcium, magnesium, phosphate, 1,25-dihydroxyvitamin D [1,25(OH)2D], and creatinine were measured in blood samples collected for 24 hours after dosing of usual daily calcitriol or after a single SC injection of rhPTH(1-84). Timed urine collections were also made during 24 hours after dosing to see renal responses. As summarized in the table below, each measured physiological parameter is an indication of parts of the working mechanism of PTH and can therefore highlight the working mechanism of exogenous rhPTH(1-84), making the study highly relevant for PD response, but also for efficacy.

Table 7: overview physiological parameters

physiological parameter	indicator of
serum total calcium	tubular reabsorption, release from bone, intestinal absorption
urinary calcium	PTH(1,84)-induced increased reabsorption in kidney, increased serum calcium levels cleared
urinary cyclic AMP	PTH(1-84)-induced renal excretion cAMP
serum phosphate	phosphaturic action, bone resorption, intestinal absorption, other factors
urinary phosphate	PTH(1-84)-induced inhibition reabsorption in kidney
serum creatinine (exploratory)	GFR
urinary creatinine (exploratory)	GFR
osteocalcin	bone formation marker
serum $1,25(OH)_2D$	stimulatory effect of PTH(1-84) on the 1-hydroxylase enzyme, increased production
serum magnesium	decrease in urinary excretion
urinary magnesium	PTH(1,84)- induced increasing influx of magnesium into the distal convoluted cell
serum BSAP	bone formation marker
serum TRAP	bone resorption marker
urinary deoxypyridinoline	bone resorption marker
urinary hydroxyproline	bone resorption marker

Administration of rhPTH(1-84) results in increases in serum calcium (see Figure 5) and magnesium. Initial lowering of urinary calcium and magnesium was followed by a return to baseline due to increasing serum levels, which was in contrast with calcitriol administration. The difference between the two treatments was most evident in their effects on phosphate homeostasis because calcitriol administration had little effect on urinary phosphate and there was a small increase in serum phosphate. rhPTH(1-84) administration resulted however in a substantial decrease in serum phosphate by markedly increasing urinary phosphate excretion. The serum calcium x phosphate product was therefore decreased, being an important determinant of soft-tissue calcification, while calcitriol treatment on the other hand raised the concentration of this product. From this study it can be concluded that in contrast to the standard therapy calcitriol, mimicking all the physiological effects of the missing hormone helps normalizing calcium, magnesium, phosphate and vitamin D metabolism in subjects with hypoparathyroidism, explaining the reduction in requirements of calcium and active vitamin D, observed in the placebo-controlled trial.

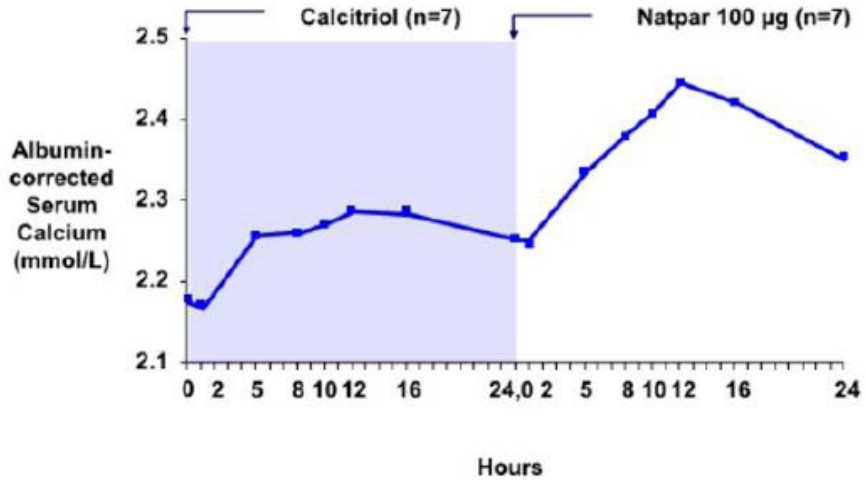


Figure 2: mean albumin-corrected serum total calcium levels following calitriol and Natpar 100 µg administration - study C09-002

The Mosekilde ITT study was a 1 day PK/PD substudy after a 24 week treatment of hypoparathyroidism patients with either 100 µg rhPTH(1-84) or placebo. The results were largely in agreement with results obtained by company-own data, although the peak serum calcium value differs from the study C09-002 (see Figure 7) The company stated that the peak serum calcium value of 10-12 hours which is based on the single-dose PK/PD study (C09-002), likely is not reflective of conditions at steady state, and that the multiple sampling from Sikjaer, et al provides a better estimation of the peak serum calcium levels. In the REPLACE study protocol, the interval for collecting samples for serum calcium measurements was established at 6-10 hours, based on the results of the investigator initiated trial.

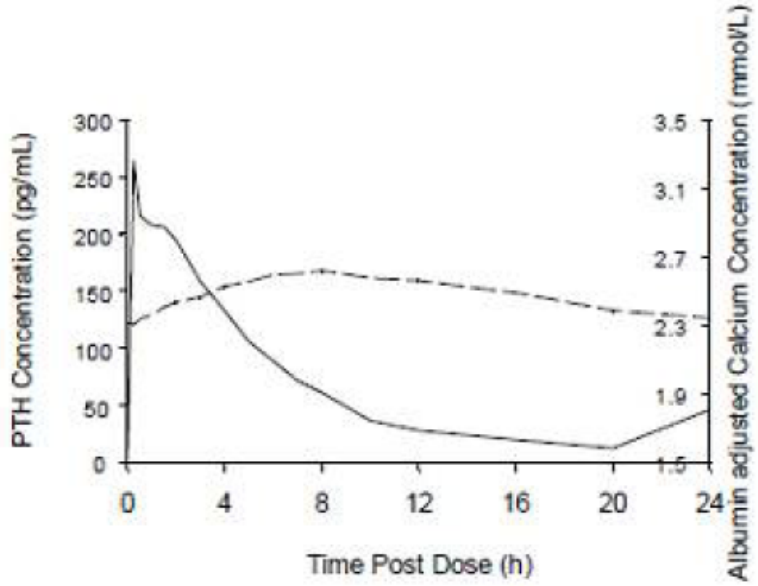


Figure 3: mean time profiles of rhPTH(1-84) plasma concentrations and ACSC in hypoparathyroidism subjects receiving Natpar 100µg – Mosekilde trial

Finally, three PK/PD studies were performed in osteoporosis patients. Similar to the Mosekilde substudy, CL1-11-006 was a substudy after administration of rhPTH(1-84) during 15 months. The magnitude of the change in serum calcium results are similar to the results after a single dose. Serum phosphate concentrations show an initial decrease in serum phosphate concentrations caused by the phosphaturic action of rhPTH(1-84). After the 4 hours post dose, factors other than rhPTH(1-84) are primarily responsible for the changes in serum phosphate. Study CL1-11-008 was a substudy of CAP which showed that calcium supplements (700 mg) in addition to rhPTH(1-84) administration had minimal effects on the acute serum total calcium or phosphate. Study N01-AR-9-2245 NIAMS-045 (ACR substudy of PaTH) demonstrated that the co-administration of alendronate does not affect the PK of rhPTH(1-84) and the plasma PTH(1-84) concentration-time profiles for 100 µg rhPTH(1-84) SC injections after 12 months of daily treatment, but does suppress systemic calcium levels, leading to an increase in the baseline PTH(1-84) concentrations and lowering the rhPTH(1-84)-initiated increase in calcium levels by 50%.

2.4.4. Discussion on clinical pharmacology

Many physiological parameters were measured throughout the studies summarized here. Some in healthy subjects (or osteoporosis patients with normal PTH levels), others in hypoparathyroidism patients, some after single dosing but several also after long term treatment with rhPTH(1-84).

In study C09-002 the magnitude and duration of the calcium response seems to be more dependent on the duration of the elevated PTH(1-84) levels rather than on the absolute magnitude of the increase and although there is an initial lowering of urinary calcium, this was followed after 6 hours by a return to baseline due to increasing serum levels. The question therefore was raised whether a twice/three times daily administration, a continuous administration via a pump device or a slow release formulation could be envisaged, decreasing the risk for hypercalciuria while maintaining the calcium levels in the normal, elevated range. The current profile (quick release, once daily) does not at all mimic the diurnal variation seen with endogenous parathyroid hormone in healthy subjects. It is considered that the ZnCl formulation (abandoned by the company at an early stage in the development plan for the indication of osteoporosis) which was associated with a flat peak in plasma parathyroid hormone concentration over 10hrs post administration would have been more suited to mimic the diurnal pattern found in plasma with endogenous parathyroid hormone, avoiding the observed gross swings in serum Ca++.

Additional modeling of a QD versus BID dosing conducted suggests that BID regimens of Narpara may give advantages over the proposed dosing. A PK/PD study to evaluate BID dosing regimens to control hypercalciuria will be part of the studies the applicant is conducting as post authorization measures. Primary objective of the study is 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 25 μg administered twice-daily, 50 μg administered twice-daily, and 100 μg administered once-daily, as well as the effect of supplemental oral calcium intake, in subjects with hypoparathyroidism. Further mechanistic PK/PD analysis allowing for conclusion on an optimal dose and dosing regimen are foreseen for this product. Preferably, continuous dosing using a pump device should be envisaged or a device that allows for individual dosing.

The interaction with drugs that may act on calcium/phosphate metabolism such as complexing anions, inhibitors of bone resorption, medication for parathyroid related disorders, drug causing hypercalcaemia, thiazide diuretics, digoxin, estrogens, calcitonin, systemic corticosteroids, anticonvulsants, fluoride, lithium were considered by the Applicant and relevant pharmacodynamic interactions for digoxin and for drugs that affect serum calcium levels are added in the SmPC.

From a PK perspective, a different bioavailability can be observed depending on the type of pen used for administration. The Applicant provided the results of two bioequivalence studies: one between the Ypsomed pen and the Haselmeier pen and one between the Ypsomed pen and the SHL pen. Bioequivalence has been demonstrated between the Ypsomed and Haselmeier pen. For the second bioequivalence study (Ypsomed vs SHL), 90% CI for Cmax and AUC after baseline-correction were slightly outside the 80.00-125.00% margins after removal of two outliers showing only marginal increases in PTH(1-84) concentrations after injection with the Ypsomed pen. Systemic exposure to the SHL pen was app. 13% higher in comparison with the Ypsomed pen. This is most probably due to the fact that with the SHL pen, in average, 11.3 mg more product is administered in comparison with the Ypsomed pen. Indeed, during this bioequivalence study, the weights of the pens have been recorded before and after administration to confirm that an appropriate dose was administered. Somewhat unexpectedly, these data showed that there is a high variability o the dose of product delivered, ranging from app. 40 to 80 mg for the Ypsomed pen and from app. 40 to 113 mg for the SHL pen (target weight is 72.1 mg). This study was the only one providing in vivo data for the SHL pen that was initially the pen intended for commercialisation. Therefore, the Applicant decided during the procedure to use the Haselmeier pen (also referred to as Shire Q-cliq pen in this report) instead of the SHL pen for marketing purposes. Although also for the Haselmeier pen a substantial variability could be observed in the delivered dose, it should be noted that, for this pen, bioequivalence was proven with the Ypsomed pen and long-term clinical data are available from the RACE study. No new unexpected safety signals have been observed in this study and the complaints were less as compared to the Ypsomed pen. In addition, US post-marketing data are available for this product that is

marketed in the US using the Haselmeier pen (see section on safety of this report). In addition, the variability will also be part of the post authorisation studies that will be undertaken provided that during these studies the Haselmeier pen will be used for dose administration. This is highly recommended as this will be the only way to also take into account this additional variability introduced by the pen.

The applicant acknowledged the value of a more mechanistic PK/PD model to characterise the exposure-response relationship,. Given the complex interrelationship between PTH, serum calcium and 24 hour urinary calcium excretion, the empirical model utilised was viewed as inadequate to guide appropriate drug dosing. The applicant will carry out further PK analysis in one PK study with a model-based approach for study design and data analysis.

2.4.5. Conclusions on clinical pharmacology

A high variability has been observed during Study PAR-C13-004, questioning the overall suitability of the pens to deliver an accurate and appropriate dose and, as such, impacting the efficacy and safety of the product. However, this additional variability will be taken into account in the post-authorisation studies provided the same pen (Haselmeier) will be used during these studies.

Acute changes in the systemic concentration of PTH(1-84) have short- (minutes to hours) and long-term (hours to days) effects on several physiological parameters related to calcium and phosphate homeostasis. An increase in plasma PTH(1-84) increases the renal excretion of cyclic AMP, increases and decreases the tubular reabsorption of calcium and phosphate, respectively, and increases release of calcium from the bone. Elevated PTH(1-84) increases 1,25(OH)2D production by the kidney, leading to an increase in intestinal absorption of calcium and phosphate.

Measurement of these physiological parameters was included in a number of the short-term studies as an indication of the PD response to changes in systemic PTH(1-84) concentrations. Although a peak ACSC level was observed after 10-12 hrs in the applicant's PD study, the applicant argues that the Mosekilde study, measuring post-dose [Ca++] after multiple dosing, is more reflective of the actual peak serum [Ca++] level. It is not agreed that this is the case.

Furthermore, results do not necessarily support a QD dosing regimen. The possibility of a beneficial effect on the urine calcium excretion after dosing twice/three times daily or a slow release formulation should be considered. A PK/PD study to evaluate BID dosing regimens is foreseen by the applicant. This is considered sufficient, if the company can conclude by means of further analysis of this study on the optimal dose and dosing regimen.

The above mentioned aspects are considered to be major deficiencies in the development programme which contribute to the requirement of a post-authorisation safety/efficacy study and the recommendation for a PK/PD study for further confirmation of the appropriateness of the QD dosing regimen.

2.5. Clinical efficacy

2.5.1. Dose response studies and main studies

A possible added value of hormone replacement therapy over the current standard therapy is recognised, and the working mechanism is plausible. It is agreed that current therapy does not resolve

the hormone deficiency in itself, while hormone replacement possibly can resolve the short- and long-term consequences of the deficiency and its current treatment. Some patients may have difficulties to maintain a stable serum calcium level when treated with calcium (carbonate/citrate) and vitamin D (calcitriol/alphacalcidol). In addition, it is noted that reports suggest that hypoparathyroid patients' quality of life is affected by the disease even when adequately treated with vitamin D and calcium.

Dose-response studies and main clinical studies

rhPTH doses of 50 to 100 µg per day were established as the expected therapeutic range, based on the phase I studies and in consideration of the safety margins established in the long-term toxicology studies. Among the efficacy and safety studies in hypoparathyroidism, 3 studies used a dose titration methodology and 1 study used fixed doses.

The applicant has presented as pivotal study a 24-week randomized, double-blind, placebo-controlled, phase 3 study in 124 subjects to investigate the use (efficacy and safety) of rhPTH[1-84] for the treatment of adults with hypoparathyroidism : REPLACE.

Methods

A randomized, double-blind, placebo-controlled phase III study using a replacement design in which the standard of care, oral calcium and active vitamin D, was decreased or eliminated while the investigational treatment was being up-titrated.

Study Participants

Hypoparathyroidism was defined by biochemical evidence from serum calcium and parathyroid hormone (PTH) levels, specifically hypocalcaemia at any time in the past and documented PTH levels below the lower limit of the laboratory normal range twice with the last 12 months. Exclusion criteria included a known history of hypoparathyroidism resulting from an activating mutation in the CaSR gene or impaired responsiveness to PTH (pseudohypoparathyroidism).

Adult subjects with hypoparathyroidism consisted of a screening and stabilization period of 2 to 16 weeks duration (as necessary to achieve stabilization (stable baseline oral calcium and active vitamin D metabolite/analog doses) prior to the first dose of study drug. The screening and stabilization periods were collectively known as the optimization period. During the optimization period (Visit 1 to Visit 5), the oral calcium and active vitamin D metabolite/analogue doses were adjusted towards a goal of an albumin-corrected total serum calcium concentration within the target range of 2.00 to 2.25 mmol/L. Subjects were optimized on calcium citrate (or in some cases, carbonate) and either calcitriol or alphacalcidol (study supplements). Subjects who were taking other forms of calcium prior to the study were converted to sponsor-provided supplements.

Treatments

Single doses (50, 75, or 100 µg) of NPSP558 or matching placebo were administered subcutaneously, once daily in the morning.

The comparator in this study was the matching placebo (sterile lyophilized powder consisting of sodium chloride, mannitol, and citric acid monohydrate for reconstitution with sterile diluent).

In addition, study-directed oral supplements were provided to subjects for use throughout the study (ie, from optimization through end of treatment) in the predefined strengths and lot numbers.

Objectives

The objectives of this clinical study were to evaluate the efficacy, safety, and tolerability of NPSP558 compared with placebo in adult subjects with hypoparathyroidism.

Outcomes/endpoints

Primary efficacy was demonstrated by a combined reduction in the need for oral supplementation with calcium and active vitamin D metabolites/analogs, and an albumin-corrected total serum calcium concentration that was normalized or maintained compared with the baseline value and did not exceed the upper limit of the laboratory normal range.

The primary efficacy variable was the percentage of subjects who met the triple efficacy endpoint at Week 24, based on investigator-prescribed data. A subject met the triple efficacy endpoint if he/she achieved:

- At least a 50% reduction from the baseline oral calcium supplementation dose
  and
- At least a 50% reduction from the baseline active vitamin D metabolite/analog dose
  and
- An albumin-corrected total serum calcium concentration that was maintained or normalized compared to the baseline value ($\geqslant$ 1.875 mmol/L) and did not exceed the upper limit of the laboratory normal range.

(The albumin-corrected total serum calcium goal was defined for protocol Amendment 7. Prior to Amendment 7, this parameter was defined as a clinically stable serum calcium level established at baseline and normalized by Week 24.)

The secondary efficacy endpoints of the study included a comparison of NPSP558 vs the placebo group on percentage reduction in calcium supplementation dose at week 24, proportion of subjects independent of supplemental active vitamin D metabolite/analog usage and a calcium supplementation dose of $\leq$ 500 mg/day or less by Week 24, frequency of clinical symptoms of hypocalcemia reported as AEs (including paresthesia, muscle cramping, tetany, seizures) during Week 16 to Week 24.

The exploratory endpoints of the study included comparisons between NPSP558 and placebo on the proportion of subjects that demonstrated at least a 50% reduction from baseline amounts of oral calcium supplementation and at least a 50% reduction from baseline amounts of active vitamin D metabolite/analog therapy by Week 24 of the study and stabilised ACSC (maintained or normalized compared to the baseline value), change from baseline in 24-hour urine calcium excretion, proportion of subjects that maintained a calcium-phosphate product in the normal range of less than or equal to 4.4 mmol2/L2 at week 24, change in BMD by dual energy x-ray absorptiometry of the lumbar vertebra (L1-L4), hip (total, trochanter, intertrochanter, Ward's triangle, and femoral neck) and distal one-third radius at Week 24 compared to baseline, change from baseline in bone turnover markers BSAP, s-CTx, P1NP, and osteocalcin at Week 24, change in QoL score as measured using the Short Form-36 (SF-36) Questionnaire from baseline to Week 24, percentage of subjects who met and maintained the 3 criteria of the triple efficacy endpoint from Study Week 16 through Study Week 24.

The safety endpoints included incidence of clinical episodes of hypocalcaemia (eg, adverse event [AEs] of hypocalcaemia and decreased blood calcium) at all visits, incidence of AEs related to hypercalcemia and hypercalciuria at all visits, incidence of all other adverse events, change in laboratory values, physical examination (including vital signs [blood pressure, pulse, and body temperature], body

weight, and body mass index [BMI] [derived]), and electrocardiogram (ECG) parameters (atrial and ventricular rates and PR, QRS, and QTc intervals).

Sample size

It was planned that approximately 110 adult male and female subjects with hypoparathyroidism would be randomized (2:1) to NPSP558 or placebo at approximately 30 multinational investigative sites. Approximately 84 (56 active and 28 placebo) subjects were expected to complete the study. With expected rates at which subjects would meet the triple efficacy endpoint of 40% and 10% for the active and placebo groups, respectively, 80% power was expected based on a 2-tailed test and an alpha of 0.05.

Randomisation

A randomization list was used via interactive voice response (IVR) or interactive web response (IWR) systems in a 2:1 ratio (NPSP558:placebo), centrally administered. Simple block randomization was applied without use of stratification factors. Forced randomization was not permitted for this study. Clinical study team members involved in the conduct of the study were not granted access to the randomization schedule or unblinded treatment codes until after database lock.

Blinding (masking)

Study drug was administered in a double-blind fashion during the 24 weeks that constituted the dosing period. Regardless of treatment arm or assigned dose, each cartridge contained a clear, colorless solution with 14 doses. Blinding was maintained at each titration interval and throughout the study by use of the IVR system. The medical monitor or his/her designee was to be notified by telephone within 24 hours following the unblinding of any subject for any reason. A record was to be kept of the reason for breaking the blind, the time of breaking and the name of the person who broke the blind.

Blinded laboratory results, including bone marker and PTH levels, were not accessible to the medical monitors, sponsor personnel or their designees, or study site personnel. No blind was broken in this study.

Statistical methods

Since this study included one primary and multiple secondary efficacy endpoints, a fixed sequence test procedure was used to control the study level type I error. The order of test sequence started with the primary efficacy endpoint and proceeded to the 3 secondary efficacy endpoints, in the order in which the secondary efficacy endpoints were defined.

Each of the tests was conducted using the Statistical Analysis Plan (SAP) documented statistical procedures with a type I error of 0.05. Any subsequent hypothesis tests were not executed unless all precedent tests in the sequence resulted in statistically significant results, ie, p-value < 0.05.

Three analysis populations were defined in this study. The ITT population, modified from the definition for the International Conference on Harmonisation (ICH), included all randomized subjects who received at least one dose of study drug and had at least one post baseline efficacy measurement. All efficacy analyses were conducted on the ITT population. The PP population was a subset of the ITT population, in which subjects had no significant protocol violations. Efficacy analyses based on PP population provided additional support for the study efficacy argument. The Safety population included

all randomized subjects who received at least one dose of study drug with any follow-up information. The Safety population was used for all safety-related statistical analyses.

A critical time point in the primary efficacy endpoint definition was Week 24, which coincided with the scheduled end of treatment (EOT). If a subject completed Week 24 efficacy assessments, the EOT would use the Week 24 data. If an ITT subject dropped out early or didn't have assessments at Week 24, then the last efficacy assessments would be carried forward to EOT. The EOT data was used for all efficacy analyses using the ITT population. Details of handling drop-out and missing data were documented in the study SAP.

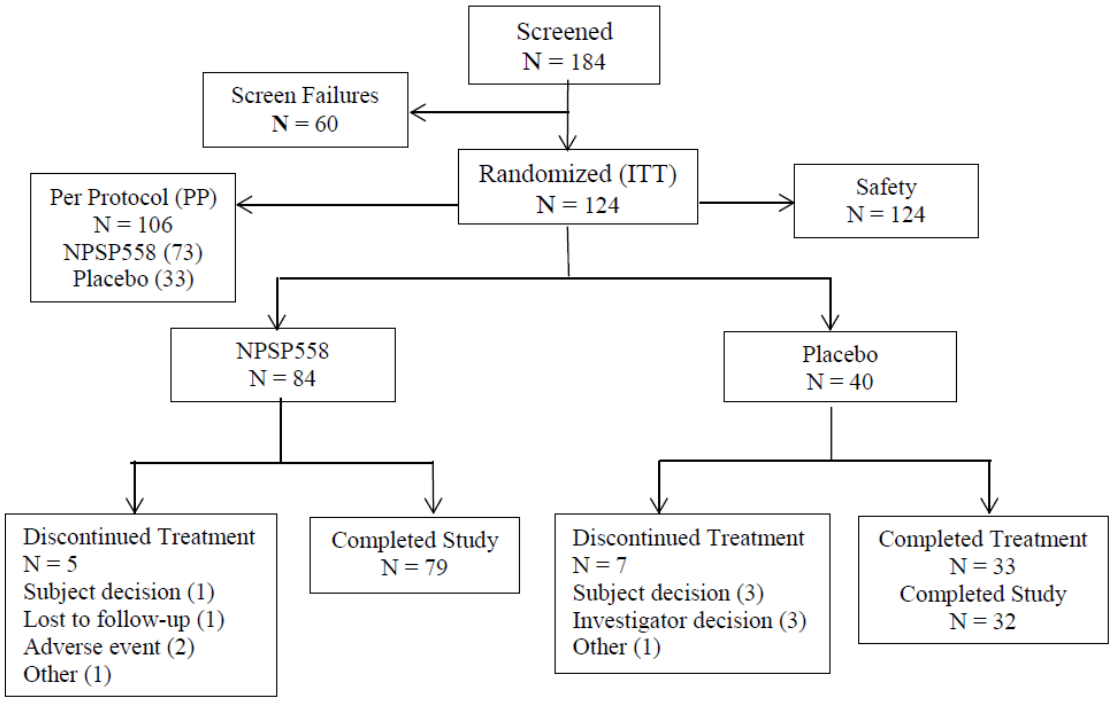
The number and percentage of subjects who met the triple efficacy endpoint were presented by treatment group. The 2-sided Fisher's Exact test was utilized to test for the difference in the rate at which subjects met the triple efficacy endpoint between NPSP558 and the placebo treatment groups. The rate difference and its 2-sided asymptotic 95% confidence interval (CI) were presented. Various supportive analyses for the primary endpoint were conducted to provide supportive information for the efficacy argument. Additional sensitivity analyses, including, Cochran-Mantel-Haenszel method, mixed-effect model repeated measures approach (MMRM), and using various percentages of reduction in daily doses of calcium and active vitamin D metabolite/analog as primary endpoint definition were utilized to determine the robustness of the primary efficacy analysis results. Prospectively defined subgroup analyses were also conducted, including age, gender, and prescribed active vitamin D at baseline subgroups. All the above analyses were also conducted using subject diary data.

Results

The triple efficacy endpoint (primary analysis) at week 24 was achieved with statistical significance, but the frequency of clinical symptoms of hypocalcaemia during week 16 to week 24 was not statistically different between treatment group and placebo group. rhPTH(1-84) treatment resulted in increased serum calcium, but no significantly reduced urinary calcium excretion. Mean calcium-phosphate product significantly decreased, BMD readings showed statistically significant improvement in the most hip locations and all bone turnover markers (BSAP, s-CTx, P1NP, and osteocalcin) increased from baseline during treatment with rhPTH(-184). Quality of life (SF-36) showed no consistently higher scores in the rhPTH(1-84) group over placebo.

For more details about the results see section "Summary of main efficacy results: REPLACE"

Participant flow



ITT = intent-to-treat population; N = total number of subjects; PP = per protocol population

Figure 4: subject disposition

Twelve (9.7%) of the 124 subjects did not complete study treatment (ie, discontinued prior to Visit 16), 5 (6.0%) in the NPSP558 group and 7 (17.5%) in the placebo group. In the NPSP558 treatment group, 2 subjects discontinued due to AEs: Subject 1010-0006, who had a current history of hypertension and a previous 24-year history of smoking half a pack of cigarettes a day, discontinued on Day 122 after experiencing a CVA; and Subject 4002–0003 (Day 58) withdrew due to multiple non serious AEs. The additional 3 discontinuations were unrelated to safety issues: subject decision (unspecified, Subject 0002-0002, Day 66), lost to follow-up (Subject 1021-0001, Day 68), and subject and investigator decision (Subject 2001-0009, Day 85).

In the placebo group, 3 subjects discontinued participation in the study due to the investigator's decision after it was determined that the subjects (1003–0002, 1005–0006, and 1014-0003) were noncompliant with study procedures. Three subjects ended treatment due to personal decisions. Subject 0001–0001 chose to leave the study due to increased calcium in urine and her concern that it might lead to problems with kidney stones (this subject had a history of recurrent kidney stones and urinary tract infections).

Subject 1008-0001 moved and could no longer make trips to the clinic and Subject 4002-0004 was unable to cope with the rigors of the study design. One additional subject (1010-0003) was discontinued due to unspecified noncompliance.

Recruitment

A total of 32 sites in 8 countries (USA 19, Canada 3, Denmark 3, Hungary 3, Belgium 1, France 1, Italy 1, UK 1) screened 184 subjects in order to randomize 124 subjects. Sixty subjects failed screening. Twenty-eight sites randomized subjects. Eighty-four subjects were randomized to the NPSP558 treatment group and 40 subjects were randomized to the placebo group.

Conduct of the study

24-week treatment period initiated with randomization (2:1) to once daily (QD) subcutaneous (SC) treatment with either NPSP558 or placebo. The initial NPSP558 dosage was 50 µg QD SC and the dosage could be up-titrated, first to 75 µg QD SC and subsequently to 100 µg QD SC, following a pre-defined sequence of dose escalation / down-titration. The titration period for purposes of analysis included the 5-week period of up-titration of study drug through the end of Week 12, since most up- or down-titration of study drug and oral calcium/active vitamin D supplementation occurred during this time period. Subjects were to undergo staged reductions in calcium and active vitamin D metabolite/analog supplementation while maintaining or normalizing their ACSC, and while up-titrating/downtitrating the study drug. 12 weeks maintenance phase was next, with a constant dosage of study drug maintained.

Baseline data

The mean duration of hypoparathyroidism was 11.6 (± 8.12) years in the placebo group and 14.6 (± 11.16) years in the NPSP558 group and the 2 treatment groups were well balanced for duration, with similar proportions of subjects with disease durations of ≤ 5 years (NPSP558, 15/84 [17.9%]; placebo 10/40 [25.0%]), > 5 to 10 years (NPSP558, 27/84 [32.1%]; placebo 13/40 [32.5%]), and > 10 years (NPSP558, 42/84 [50.0%]; placebo 17/40 [42.5%]). At baseline, most subjects were receiving a prescribed calcium dose of ≤ 2000 mg/day in the NPSP558 group (57/84 [67.9%]) and placebo group (29/40 [72.5%]), while high dose (> 0.5 µg/day of calcitriol or > 1.0 µg/day alphacalcidol) active vitamin D metabolite/analog dosing was prescribed at baseline in 56/84 (66.7%) NPSP558 subjects and 25/40 (62.5%) placebo subjects.

Differences between screening (ie, prior to the optimization period) and baseline characteristics were observed by review of selected laboratory parameters and oral supplement doses at these 2 time points, for subjects who were eventually randomized. Mean (± standard deviation) values for these parameters for subjects who had data at both time points show that optimization led to a more homogenous study population by decreasing the variability of the effects of hypoparathyroidism.

Numbers analysed

Table 8: summary of study analysis populations: all randomized subjects

Analysis Population	Placebo n (%)	NPSP558 n (%)	Total n (%)
Number of subjects randomized	40	84	124
Intent-to-Treat	40 (100.0)	84 (100.0)	124 (100.0)
Per Protocol	33 (82.5)	73 (86.9)	106 (85.5)
Safety	40 (100.0)	84 (100.0)	124 (100.0)
Completed Treatment[a]	33 (82.5)	79 (94.0)	112 (90.3)
Completed Study/Follow-up[b]	32 (80.0)	79 (94.0)	111 (89.5)

CRF = case report form; EOS = end of study

Note: Percentages are based on the number of randomized subjects in each treatment arm.

[a] Number (%) of subjects who completed the study based on the study exit case report form (CRF) at Visit 16/EOS

[b] Number (%) of subjects who completed the study based on the study exit CRF at Visit 16/EOS and finished the follow-up Visit 18 (Week 28)

Summary of main efficacy results: REPLACE

The following table summarizes the efficacy results from the main study REPLACE supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9: efficacy results REPLACE study

Title: REPLACE			
Study identifier	REPLACE		
Design	Randomized, double-blind, placebo-controlled		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 2-16 weeks 4 weeks
Hypothesis	Replacement design		
Treatments groups	Active treatment group		50, 75, or 100 µg of NPSP558 administered subcutaneously, once daily in the morning into alternating thighs in the morning via a reusable injection pen device (Ypsomed)
	Placebo group		placebo cartridges were provided to match the 3 dose titration steps of NPSP558
Endpoints and definitions	Primary endpoint	triple endpoint	• At least a 50% reduction from the baseline oral calcium supplementation dose + • At least a 50% reduction from the baseline active vitamin D metabolite/analog dose + • An albumin-corrected total serum calcium concentration that was maintained or normalized compared to the baseline value (≥ 1.875 mmol/L) and did not exceed the upper limit of the laboratory normal range
	Secondary endpoint	Ca^{2+} suppl	Percentage change from baseline in calcium supplementation dose at Week 24
		Vit D suppl independent	Proportion of subjects that achieved independence from supplemental active vitamin D metabolite/analog usage and a calcium supplementation dose of 500 mg/day, or less by Week 24
		hypocalcaemia events	frequency of clinical symptoms of hypocalcaemia reported as adverse events (including paresthesia, muscle cramping, tetany, seizures) during Week 16 to Week 24

	Exploratory endpoints	Triple endpoint + normalized ACSC	subjects meeting triple endpoint + ACSC level normalized at week 16, 20, 24 assessments that was maintained or normalized compared to the baseline value
		Urine calcium	Change from baseline in 24-hour urine calcium excretion at Week 24
		Calcium-phosphate	calcium-phosphate product at Week 24
		BMD	BMD in Z-scores by dual-energy x-ray absorptiometry of the lumbar vertebra (L1-L4), hip (total, trochanter, intertrochanter, Ward's triangle and femoral neck) and distal one-third radius at Week 24
		BTM	bone turnover markers BSAP, s-CTx, P1NP and osteocalcin at Week 24
		QoL	Change in quality of life score as measured using the Short Form-36 (SF-36) questionnaire from baseline to Week 24
		Early triple endpoint + maintenance	subjects who met and maintained the 3 criteria of the triple efficacy endpoint from Study Week 16 through Study Week 24.
Database lock	1/11/2011		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	"Modified" Intent to treat: included all randomized subjects who received at least one dose of study drug and had at least one post-baseline efficacy measurement. For a subject whose study treatment was still ongoing after Visit 14 (Week 16), all 3 criteria had to be met for the subject to have met the triple efficacy endpoint. For the end-of-treatment time point, subjects were considered to not have met the triple efficacy endpoint (ie, failures) if they did not have sufficient drug exposure (discontinued treatment before Visit 14 [Week 16]) Week 24 (EOT)		
Descriptive statistics and estimate variability	Treatment group	rhPTH (1-84) 50-75-100 µg	placebo
	Number of subjects	84	40
	Triple endpoint absolute number responders (%)	46 (54.8)	1 (2.5)
	95 % C.I.	43.5-65.7	0.1-13.2
Effect estimate per comparison	Primary endpoint	Comparison groups	Active treatment vs placebo

		Treatment difference (%)	52.3
		95% C.I.	40.6 - 64.0
		P-value	p<0.001
Notes	Based on investigator described data		
Analysis description	**Secondary analysis**		
Descriptive statistics and estimate variability	Treatment group	rhPTH (1-84) 50-75-100 µg	placebo
	Number of subjects	84	40
	Ca^{2+} suppl mean decrease from baseline (%)	-51.81	+2.40
	95 % C.I.	± 45.71	± 38.37
	Vit D suppl independent absolute number (%)	35 (41.7)	1 (2.5)
	95 % C.I.	31.0 – 52.9	0.1 – 13.2
	hypocalcaemia events absolute number (%)	29 (34.5)	15 (37.5)
	95 % C.I.	24.5 – 45.7	22.7 – 54.2
Notes	Based on investigator described data		
Analysis description	**Exploratory analysis**		
Descriptive statistics and estimate variability	Treatment group	rhPTH (1-84) 50-75-100 µg	placebo
	Number of subjects	84	40
	Triple endpoint + normalized ACSC absolute numbers (%)	37 (44)	1 (2.5)
	95 % C.I.	33.2 - 55.3	0.1 - 13.2
	Urine calcium Mean (mmol/24hr)	-1.99	-2.28
	95 % C.I.	± 4.85	± 4.27
	Calcium-phosphate (mean change from baseline)	-0.406	-0.073
	95 % C.I.	-0.516, -0.332	-0.170, 0.097

	BMD mean changes from baseline	Total hip -0.160 Hip trochanter -0.201 Hip femoral neck -0.193 Intertrochanter -0.104 Ward's triangle -0.162 Lumbar spine -0.046 Distal one-third radius -0.015	Total hip 0.012 Hip trochanter 0.040 Hip femoral neck 0.017 Intertrochanter 0.014 Ward's triangle 0.038 Lumbar spine 0.047 Distal one-third radius 0.049
	95% C.I.	Total hip ±0.218 Hip trochanter ± .289 Hip femoral neck ±0.305 Intertrochanter ±0.205 Ward's triangle ±0.407 Lumbar spine ±0.479 Distal one-third radius ±0.342	Total hip ± 0.112 Hip trochanter ± 0.162 Hip femoral neck ±0.218 Intertrochanter ±0.154 Ward's triangle ±0.449 Lumbar spine ±0.275 Distal one-third radius ±0.318
	BTM	BSAP 21.31 s-CTx 809.5 P1NP 308.2 Osteocalcin 26.45	BSAP 0.20 s-CTx 8.4 P1NP 2.7 Osteocalcin -0.49
	95 % C.I.	BSAP ±18.333 s-CTx ±658.94 P1NP ±238.63 Osteocalcin ±28.372	BSAP ±1.760 s-CTx ±127.18 P1NP ±13.55 Osteocalcin ±1.595
	QoL between group comparison mean difference	Physical Functioning 1.11 Role-physical 5.05 Bodily pain 6.83 General health 4.26 Vitality 4.16 Social functioning 2.35 Role-emotional -1.2 Mental health 2.48 Physical component scores 2.09 Mental component scores 0.35	
	95 % C.I. (p-value)	Physical Functioning [-5.93, 8.14] (0.756) Role-physical [-2.87, 12.98] (0.209) Bodily pain [-1.45, 15.11] (0.105) General health [-1.07, 9.59] (0.116) Vitality [-2.17, 10.49] (0.195) Social functioning [-5.43, 10.14] (0.550) Role-emotional [-8.07, 5.63] (0.725) Mental health [-2.68, 7.64] (0.343) Physical component scores [-0.38, 4.56] (0.096) Mental component scores [-2.50, 3.20] (0.806)	
	Early triple endpoint + maintenance in absolute numbers (%)	37 (44.0)	1 (2.5)
	95 % C.I. (%)	33.2 - 55.3	0.1 - 13.2
Notes	Based on investigator described data		

Long-term study: RACE

RACE was a long-term, open-label study using rhPTH(1-84) for the treatment of adult male and female subjects with hypoparathyroidism. Efficacy data were available for 41 subjects at Month 24. The subjects must have previously completed Study PAR-C10-007 (8 weeks of active therapy) and/or

Study CL1-11-040 (Visit 18). rhPTH(1-84) at doses of 25 µg, 50 µg, 75 µg, or 100 µg were administered SC QD in the morning into alternating thighs based on a subject's TSC level at baseline via a multidose pen injector. The starting dose of rhPTH(1-84) for this study was 25 or 50 µg SC QD, and there was a fixed protocol for adjusting supplements and dosage according to measured TSC levels. The primary objective of this study was to demonstrate the long-term safety and tolerability of SC rhPTH(1-84) as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.

Based on investigator-described data, 34/45 (75.6%) subjects met the triple efficacy endpoint at Week 52 (95% CI: 60.5, 87.1), 21/41 (51.2%) subjects met the triple efficacy endpoint at Month 24 (95% CI: 35.1, 67.1), and 24/48 (50.0%) subjects met the triple efficacy endpoint at EOT (95% CI: 35.2, 64.8). Furthermore, the study indicated that serum calcium levels could be maintained within the target range of 2.0 to 2.25 mmol/L, urine calcium excretion was maintained, serum phosphate levels were decreased and an increase in the calcium-phosphate product of greater than 4.4 $mmol^2/L^2$ was not obtained. Increasing serum BTMs were observed which reflects possible effects of rhPTH(1-84) on bone remodeling.

This was an open label study that had the advantage that the mean exposure was 119 weeks (approximately 24 months), with the majority of subjects (n = 44) on study for at least 24 months. The primary efficacy endpoint was met with a high statistical significance. One of the goals was to demonstrate persistence of efficacy. The number of subjects meeting the primary triple efficacy endpoint at 24 months was however 21/41 (51.2%), while the number of subjects meeting this endpoint at week 52 is 34/45 (75.6 %).

The following table summarizes the efficacy results from the main study RACE supporting the present application, a long-term open-label study investigating the safety and tolerability of NPSP558 for the treatment of adults with hypoparathyroidism.

Table 10: efficacy results RACE study

Title: RACE		
Study identifier	PAR-C10-008	
Design	An Open-label Study, Phase 3 Study	
	Subjects must have previously completed the double-blind randomized NPSP558 RELAY study (8 weeks of active therapy) and/or previously completed the double-blind, placebo-controlled NPSP558 REPLACE study (24 weeks of treatment and 4 weeks of follow-up after discontinuation of treatment – Visit 18).	
	Duration of study:	1 year (with option to extend by 1 additional year)
Aim of study	To optimize NPSP558 dosing while reducing calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible while maintaining total serum calcium levels according to the NPSP558 and Supplement Titration Guideline.	
Treatment group	49 subjects (one group only, no comparator) The starting dose of NPSP558 for this study was 25 or 50µg SC once daily Subjects' NPSP558 dose could be increased in increments of 25µg to a maximum of 100 µg SC QD by the investigator at any time during the study, with the goal of achieving or maintaining total serum calcium levels (pre-dose) in the range of 2.0 to 2.25mmol/L. Adjustment of supplemental calcium and calcitriol regimens was based on total serum calcium levels, with the goal to be a reduction or removal of calcitriol treatment to the maximum degree clinically possible and to decrease the prescribed oral calcium supplementation to ⩽ 500 mg daily. Once a subject achieved a stable serum calcium (target: between 2.0 to 2.25mmol/L) with the minimum doses of supplements possible, they were maintained at that dose of NPSP558.	
Endpoints and definitions	Safety evaluation (primary objective)	To demonstrate the long-term safety and tolerability of subcutaneous (SC) NPSP558 (recombinant human parathyroid hormone [1-84]) as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.
	Efficacy evaluation (secondary objectives)	A responder is a subject in whom the following three conditions were fulfilled at Week 52 (Visit 9), Month 24, and at end-of-treatment: ≥50% reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of ≤500 mg AND ≥50% reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of ≤0.25 µg AND An albumin-corrected serum calcium concentration that is normalized or maintained compared to the baseline value (≥1.875 mmol/L) and does not exceed the ULN of the central laboratory
		Additional efficacy evaluations are described
Database lock	Study is on-going, an interim report is submitted. Date of database soft lock: 03 January 2013 (Interim) & 20 June 2014 (SAEs and Markedly Abnormal Labs)	
Results and Analysis		
Analysis description	**Primary Analysis**	

Analysis population and time point description	Safety population The mean duration of exposure was 833.0 (± 205.09) days.
Outcomes	NPSP558 administered at the doses of 25, 50, 75, and 100µg SC daily was generally well-tolerated. There were no deaths during the study. No new unexpected safety signals were found in the TEAE analysis.
	Secondary analysis
Outcomes	34/45 (75.6%) subjects were responders at Week 52 (95% CI of 60.35 to 87.1) 21/41 (51.2%) subjects were responders at Month 24 (95% CI of 35.1 to 67.1). 24/48 (50.0%) subjects were responders fulfilling the 3 criteria of response at the time of their last study visit (95% CI of 35.2 to 64.8). [End-of-treatment was defined as the last determination of response or last available measurement during the treatment period up to the interim data cut-off date].

Supportive studies

The RELAY study was a NPS sponsored 8-week study. It was a randomized, dose-blinded study with 25 µg or 50 µg rhPTH(1-84) SC QD administered. The results suggest that rhPTH(1-84) at fixed dosages of 25 µg and 50 µg/day are not sufficient for the treatment of the majority of subjects with hypoparathyroidism, but that it is recognised that for very few patients, the additional dosage of 25 µg can be considered. A starting dose of 50 µg is an appropriate starting dosage for the majority of patients with hypoparathyroidism.

The open-label REPEAT study was primarily a safety and tolerability study, performed in the Hungarian sites. This study extended exposure of rhPTH(1-84) for 16 subjects and introduced study drug exposure to an additional 8 subjects for 24 weeks. The study was designed to demonstrate continued safety while extending efficacy results realized during Study CL1-11-040. In order to better mimic usual clinical practice in this patient population, the frequency and the intensity of the medical investigations was reduced after completing rhPTH(1-84) titration. 75.0% of the subjects became independent of active vitamin D, while maintaining an oral calcium dose of ≤ 500 mg/day. Fifteen of 24 (62.5%) subjects completed the end of treatment visit on a dose of 100 µg SC QD, 5/24 (20.8%) completed on 75 µg SC QD, and 4/24 (16.7%) completed on 50 µg SC QD, with 1 of the 4 subjects on every other day dosing.

Table 11: efficacy results REPEAT study

Title: : A 6-Month Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH[1-84]), for the Treatment of Adults with Hypoparathyroidism – A Clinical Extension Study (REPEAT)			
Study identifier	PAR-C10-009		
Design	A 6-Month Open-label Study, Phase 3 Study		
	This study enrolled subjects who had completed Study CL1-11-040 (REPLACE) or who were enrolled in REPLACE but were not randomized due to the closure of randomization.		
	Duration of main phase: Follow-up phase	24 weeks 4 weeks	
Aim of study	To optimize NPSP558 dosing while reducing calcitriol or alphacalcidol and oral calcium citrate supplementation to as low as safely possible while maintaining total serum calcium levels. A study drug and supplement titration guideline was provided as part of the protocol.		
Treatment group	All subjects enrolled in this study received NPSP558; there was no control group. Subjects received daily doses of 50, 75, and 100µg SC study drug administered subcutaneously in the thigh. All subjects were started on 50µg SC study drug daily The starting dose of NPSP558 50µg could be titrated up in increments of 25µg at every visit up to Week 16 (i.e. Weeks 2, 4, and 8) to a maximum dose of 100µg SC daily. Adjustment of supplemental calcium and calcitriol or alphacalcidol regimens were to be based on total serum calcium levels, with the goal being a reduction or removal of calcitriol/alphacalcidol treatment to the maximum degree clinically possible and a decrease in the prescribed oral calcium supplementation to ≤500 mg daily. Once a subject achieved a stable serum calcium (target: between 2.0 and 2.25mmol/L) with the minimum doses of supplements possible, they were to be maintained at that dose of NPSP558.		
Endpoints and definitions	Safety evaluation (primary objective)	To demonstrate the safety and tolerability of subcutaneous (SC) NPSP558 as hormone replacement therapy administered for 6 months for the treatment of hypoparathyroidism in adult subjects.	

	Efficacy evaluation (secondary objectives)	A responder was a subject in whom the following three conditions were fulfilled at Week 24 (Visit 6) ≥50% reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of ≤500 mg/day AND ≥50% reduction from baseline in dose of oral calcitriol/alphacalcidol supplementation or an oral calcitriol dose of ≤0.25µg/day or alphacalcidol dose of ≤0.50µg/day AND A total serum calcium concentration that was normalized or maintained compared to the baseline value and did not exceed the ULN of the central laboratory Secondary efficacy endpoints were: • Mean percentage changes from baseline in supplemental oral calcium and supplemental calcitriol/alphacalcidol dosages at each visit • Proportion of subjects achieving the primary endpoint at each visit • Mean change from baseline in 24-hour urine calcium excretion Exploratory endpoints are also described.
Database lock	22 May 2012	
Results and Analysis		
Analysis description	**Primary Analysis**	
Analysis population and time point description	The Safety population consisted of 24 subjects who received at least one dose of study drug. Mean exposure to study drug, based on the current study, without regard to previous exposure in the REPLACE study, was 169.4 (± 1.81) days.	
Outcomes	There were no deaths during the study and no discontinuations due to AEs. No SAEs were reported for any subject. The most frequently reported TEAEs by preferred term were: hypoaesthesia (12/24 [50%]); muscle spasms and vitamin D decreased (both 6/24 [25%]); hypercalcaemia (5/24 [20.8%]), fatigue, headache, and hypocalcaemia (all 4/24 [16.7%]); arthralgia, hypoesthesia oral and tetany (all 3/24 [12.5%]).	
	Secondary analysis	
Outcomes	18/24 subjects were responders at week 24 6/24 subjects were non-responders at week 24.	

The Mosekilde IIT was performed independently and included 62 patients (32 in the rhPTH(1-84) 100 µg group and 30 in the placebo group). Dosage adjustment of active vitamin D metabolites and calcium supplementation was only allowed upon hypercalcaemia or hypercalciuria, hence the higher incidence of hypercalcaemia. The rhPTH(1-84) injections were therefore regarded as add-on therapy. The number of patients showing hypercalcaemia was important with serum calcium levels ranging up to 3.8 mmol/L. This was accommodated by reducing oral active vitamin D and calcium or decreasing the frequency of PTH injections to less than daily (occurred in 5/29). Although the number of patients

with hypoparathyroidism treated with rhPTH(1-84) is increased by this study, the design is different and the added knowledge relevant for the application is limited.

Clinical studies in special populations

There are no efficacy studies in special populations. 4 patients ≥65 years received rhPTH(1-84) in the REPLACE study, 4 patients received placebo. 2 patients ≥65 years were entered into the non-controlled trial (RACE).

Analysis performed across trials (pooled analyses AND meta-analysis)

Baseline characteristics groups in the efficacy and safety studies in hypoparathyroidism were similar besides: the population consists of a largely female and white population (greater than 75% of subjects in each study were female, more than 90% of all subjects were white).

Efficacy results were not pooled among studies. However, the primary (triple) efficacy endpoints in Studies PAR-C10-007, PAR-C10-008, and PAR-C10-009 were very similar to the primary efficacy endpoint in Study CL1-11-040. In all 4 studies, the triple efficacy endpoint was a composite that required a responder to have a predefined reduction in oral calcium and a predefined reduction in active vitamin D dose, while maintaining serum calcium concentration at a predefined level.

Changes in active vitamin D metabolite and calcium supplementation were measured in each of the 4 efficacy and safety studies in hypoparathyroidism (CL1-11-040, PAR-C10-007, PAR-C10-008, PAR-C10-009), and Mosekilde IITs. Whereas in the NPS-sponsored studies the protocol enforced reductions in active vitamin D first and then in oral calcium with initiation or up-titration of rhPTH(1-84), in case of the Mosekilde study, alterations in active vitamin D and oral calcium only occurred when hypercalcaemia or hypercalciuria was already manifested. Active vitamin D and calcium dose decreased significantly in the rhPTH(1-84) arms in all studies.

Serum phosphate levels were significantly decreased in serum and plasma in the rhPTH(1-84) treatment groups as compared with placebo/baseline in all studies. Reductions in 24-hour-urinary calcium excretion in the rhPTH(1-84) group were not significant and not conclusive, and must be seen in the context of concurrent serum calcium levels.

Across the studies, baseline BTMs were generally below normal or in the lower end of the normal range. Treatment with rhPTH(1-84) increased all BTMs ($p < 0.001$ for all markers). During continued treatment, change in serum bone markers either plateaued (BSAP and osteocalcin), decreased after Week 40 (s CTx), or decreased after Week 52 (P1NP).

Treatment with rhPTH(1-84) tended to normalize Z-scores and decrease BMD. As compared with the corresponding placebo groups in Study CL1-11-040 and the Mosekilde IIT, the changes in several locations seen with rhPTH(1-84) were statistically significant.

Sufficient information regarding fracture prevalence in this condition is lacking, but a modest reduction in BMD following administration of rhPTH(1-84) might result in improvement of the material properties of bone in these patients

It can be concluded that rhPTH(1-84) has some effect on decreasing the hyperdense bones seen at baseline in subjects with hypoparathyroidism while the current standard of treatment for hypoparathyroidism (calcium and active vitamin D) has no effect on bone metabolic parameters.

2.5.2. Discussion on clinical efficacy

Design and conduct of clinical studies

This is the case for all applicant's studies, including the investigator initiated Mosekilde trial. Even for the small sample size, the treatment effect is adequate to arrive at statistical significant effects for the efficacy primary endpoint of the REPLACE, RACE, RELAY and REPEAT studies.

The primary registration study, REPLACE, was randomized, double-blind and placebo-controlled. It employed a pre-randomization optimization period during which subjects' oral calcium and active vitamin D doses were adjusted towards a goal of an albumin-corrected total serum calcium (ACSC) concentration within the target range (2.0 to 2.25 mmol/L), in order to protect them against the mandatory withdrawal of oral calcium and active vitamin D called for in the protocol. Thereafter, subjects were randomly assigned to receive 24 weeks of treatment with either rhPTH(1-84) or placebo. The rhPTH(1-84) group started on 50 µg subcutaneous (SC) once daily (QD) and could be up-titrated to 75 µg SC QD and then to 100 µg SC QD. Down-titration in 25 µg QD increments was also allowed, but not to dosages less than 50 µg SC QD. Upon discontinuation of study drug, all subjects entered a 4-week post-treatment follow-up period. The study had well-defined and reliable methods for assessment of subjects' response, and included pre-specified methods for analysis of the results.

The primary endpoint in this study was a composite consisting of 3 components (triple efficacy endpoint) consisting of achievement of eucalcaemia while targeting a clinically significant reduction in the requirement for oral calcium and vitamin D. This does not allow to assess any direct effect on one of the main target organs: i.e the kidney (calciuria, phosphaturia). These effects are assessed as secondary endpoint, but a clear treatment effect has not been demonstrated. Furthermore, due to the optimization phase, patients were at a higher serum calcium level than before, which makes it by design, due to safety reasons, harder to demonstrate that the number of hypocalcaemia symptoms is lowered. Also by design, in the context of one advancing drug and adjusting other medications according to protocol during the titration phase, it is normal that episodes of hypercalcaemia occur more frequently. Furthermore, the long-term effects on clinical hard endpoints such as benefit of rhPTH(1-84) vs standard treatment on e.g. nephrocalcinosis/nephrolithiasis, renal impairment can only be demonstrated in a study that is longer term. With this respect, a placebo controlled study lasting 24 weeks is very short for an indication for a permanent administration.

Although the REPLACE study was described as blinded, physicians were required to review serum [Ca++] results in order to titrate study drug. It would have been very easy, then, for physicians to work out who was in receipt of active study drug because rhPTH(1-84) will raise serum [Ca++] (in most cases) whilst placebo will not.
It is considered that, on this occasion, a more informative and clinically relevant study would have been one that was open-label and without a placebo control. Subjects would have established a serum [Ca++] within the reference interval at baseline and be titrated with rhPTH(1-84) to maintain serum [Ca++] within the reference interval post-dose and throughout a 24hr period. In order to achieve this, a slow release version of the current product would be advantageous, to be administered either 2 or 3 times per day (with a view to re-create the diurnal variation of parathyroid hormone in serum but mainly to maintain serum [Ca++] within the reference interval).

It is anticipated that a different dosing regimen would better control serum calcium and phosphate and urinary calcium in the patient. Such a different dosing regimen will be included in one arm of a clinical trial in the hypoparathyroid population, which will be conducted as a post approval commitment (specific obligation) for Natpar to confirm the positive benefit/risk of the product by investigating a number of relevant outcome parameters.

In the D120 responses, the company details the breakdown of subjects who took part in the REPLACE study regarding the cause of hypoparathyroidism. There were 71% subjects with post-surgical hypoparathyroidism, 26 % subjects had idiopathic hypoparathyroidism, 1% autoimmune and 1% genetic syndrome. It would have been preferred for the studied population to be homogeneous, and this is regarded as a deficiency of the study design. 27 adult subjects with a variety of causes of hypoparathyroidism other than neck surgery represent a mixed population in themselves, with differing prognosis and consequences to clinical safety (especially immunogenicity response). It is noted that the Expert Meeting on Natpar (see below)has recommended not to differentiate between surgical and non-surgical cases of hypoparathyroidism regarding the potential to develop antibodies to Natpar.

Study RELAY was an 8-week, randomized, dose-blinded, dose comparison study which evaluated the efficacy and tolerability of 2 low, fixed dosage regimens of rhPTH(1-84), 25 µg QD and 50 µg QD as replacement therapy for the treatment of adult patients with hypoparathyroidism.

Studies RACE and REPEAT were each open-label extension studies. Although they were designed primarily to evaluate long-term safety and tolerability of rhPTH(1-84), efficacy was also assessed in these studies. Study RACE is an ongoing, 12-month study with an additional extension and closed to further enrollment, with a narrative description until the data cutoff date of 03 January 2014. The rhPTH(1-84) dosing regimen in Study RACE started at 25 or 50 µg SC QD and the dosage could be adjusted in 25 µg increments to as high as 100 µg SC QD or to as low as 25 µg SC QD as needed to maintain appropriate serum calcium levels or due to any safety concerns. It was an open label study that had the advantage that the mean exposure was 119 weeks (approximately 24 months), with the majority of subjects (n = 44) on study for at least 24 months. Study REPEAT was 24 weeks in duration and is completed. The rhPTH(1-84) dosing regimen in Study REPEAT started at 50 µg SC QD and dosage could be adjusted upwards to as high as 100 µg SC QD or downwards to 50 µg SC QD as needed to maintain appropriate serum calcium levels or due to any safety concerns.

The Mosekilde IIT study was a 6-month, double-blind, randomized, placebo-controlled parallel-group study comparing the effect of adding rhPTH(1-84) 100 µg SC or similar placebo to conventional treatment with calcium and active vitamin D (alphacalcidol/calcitriol). It included and 62 patients (32 in the rhPTH(1-84) 100 µg group and 30 in the placebo group).Efficacy endpoints included indices of calcium-phosphate homeostasis, effects on plasma 1,25-dihydroxyvitamin D (1,25[OH]2 vitamin D) levels, bone mineral density (BMD), and biochemical markers of bone turnover. The Mosekilde IIT is supportive of the efficacy, and has another design in that respect that the primary endpoint was different, and that dosage adjustment of active vitamin D metabolites and calcium supplementation was only allowed hypercalcaemia or hypercalciuria, hence the higher incidence of hypercalcaemia. The rhPTH(1-84) injections were therefore regarded as add-on therapy.

Efficacy data and additional analyses

RhPTH(1-84) achieves adequate calcium levels while significantly decreasing the requirement for oral calcium citrate and active vitamin D. The primary efficacy endpoint was met with a high statistical significance, and this is consistent throughout all studies.

However, in the REPLACE study, 11 rhPTH(1-84) subjects who met the triple efficacy criteria at Week 12 no longer met the 3 criteria at Week 24. Furthermore, after 24 weeks of treatment in the REPLACE study, there is still no stable mean calcium serum level obtained in the patients in the active treatment group. However, there is a small increase in mean calcium supplementation dose. In the RACE study, the number of subjects meeting the primary triple efficacy endpoint at 24 months was 21/41 (51.2%), while the number of subjects meeting this endpoint at week 52 is 34/45 (75.6 %). These results raise

questions about the persistence of efficacy, and this concern is to be addressed in the registry and in the open label RACE trial. A warning for tachyphylaxis is included in SmPC section 4.4 and RMP. Concerning neutralizing antibodies, it is demonstrated that these subjects responded to treatment in similar proportions to those without antibodies, suggesting that the antibodies do not neutralize the activity of the drug product. Long-term effects on efficacy is however also unknown. Long-term bone effects are missing also.

Concerning the secondary endpoints in the REPLACE, there was a statistically significant percent change from baseline in oral calcium doses with a 52 % reduction in the calcium dose for patients on rhPTH(1-84) compared with a 2 % increase for patients on placebo. A higher percentage of patients in the active treatment group achieved independence from active vitamin D at week 24, and took a calcium dose of 500 milligrams or less (43 % vs 6 % in placebo group). However, the change in hypocalcaemic symptoms reported as adverse events was about the same for the active and placebo-treated patients.

An important exploratory endpoint looks at the impact of decreased serum phosphate on calcium phosphate product, and the active treatment group has a decrease in mean serum calcium phosphate product, maintained until rhPTH(1-84) is stopped. At week 24, the decrease in calcium phosphate product in the active arm is greater than in the placebo arm. The mean 24-hour urinary calcium excretion in REPLACE was similar in the placebo and treatment groups, this was attributed to increases in total serum calcium in the rhPTH(1-84) group, while total serum calcium decreased in the placebo group. Although there might be a meaningful reduction of urinary calcium (reduction in contrast to increase in serum calcium), this reduction is not demonstrated by this study. Therefore a clear immediate treatment effect has not been demonstrated. However, improvement is claimed indirectly by the applicant (and supported by the expert consultation, see below) since hypercalciuric patients are retained in the criteria for patients eligible for treatment with Natpar. Due to the design and duration of the study, long-term assessment of clinical hard endpoints such as benefit of hormone replacement therapy vs standard treatment on e.g. nephrocalcinosis/lithiasis, renal impairment were not possible.

Serum [Ca++] was measured pre-dose of study drug. Only at visit 13 of the REPLACE study was serum [Ca++] measured pre-dose, at 1 hour post dose and then at 6-10 hours post dose. These results show that many subjects display hypercalcaemia (and since the peak [Ca++] occurs at 10-12hrs post dose then the extent of hypercalcaemia is not adequately shown by these results).

About 16% of subjects did not respond to Natpar at visit 13 by an increase in serum [Ca++] by 6hrs (plasma parathyroid hormone concentration was shown to rise as expected): it is considered that these subjects display either tachyphylaxis or desensitisation, perhaps as a consequence of the time-profile of Natpar in comparison to endogenous parathyroid hormone. Natpar is administered in quick-release form, achieving a peak concentration by 1-2 hours that is (about) 4 times the upper limit of the reference interval of endogenous parathyroid hormone and then decays with a half-life of about 3 hours. The parathyroid hormone receptor on cell surfaces belongs to the family of G-coupled protein receptors and is known to exhibit desensitization. In the D120 responses, these cases were confirmed by the company, but not adequately described or evaluated withPD data provided but not in terms of the primary endpoint. The possibility of tachyphylaxis is included in the SmPC.

About 5% of subjects do not show either an increase in serum [Ca++] or an increase in plasma parathyroid hormone concentration following administration of Natpar at visit 13. This had previously been found by the company in studies CL1-11-007, CL1-11-009 and CL1-11-010 but does not seem to have been pursued. Possible explanations are non-compliance (it is understood that subjects would have been monitored at visit 13, making this seem unlikely. Also, the company reports a high rate of compliance), device failure (the event seems to occur whatever device has been used) or the presence

of neutralising antibodies (the company reports that these are not found in recipients). Although the PK failure of study drug in 4 subjects was confirmed by the company, these cases were not adequately described or evaluated by the company.

Of the 2 NPS sponsored studies that are considered supportive, the RELAY study was probably performed to introduce an additional minimum dose of 25 µg. Efficacy results are indeed consistent with other studies, but it is recognised that for very few patients, the additional dosage of 25 µg can be considered. The REPEAT study on the other hand was primarily a safety and tolerability study. Both study results are consistent with the study result from the REPLACE study.

The RELAY, RACE and REPEAT studies were extension studies of the REPLACE study and so subject to selection bias. These studies had the primary objective of collecting data on clinical safety.

Very few patients ≥ 65 years were involved in the trials. The population consists of a largely female and white population (more than 75% of subjects in each study were female, more than 90% of all subjects were white).

Additional expert consultation

CHMP had requested an ad hoc expert meeting to obtain the opinion of experts in the field on a possible niche indication for patients where conventional treatment is inadequate to control symptoms of hypocalcaemia or for patients where conventional treatment is difficult, and in particular to explore whether they find that PTH replacement might have an added value in these cases. Questions were addressed to the ad hoc expert group. The corresponding answers are presented below:

1. **Please discuss how well patients with hypoparathyroidism can be controlled by current standard treatment and whether there is a need for other treatment options for all patients with hypoparathyroidism, for a specific subgroup or for specific aspects of the disease.**

All experts attending the ad hoc expert meeting (SAG) saw a need for other treatment options beyond standard treatment, which is currently based on active vitamin D analogues and calcium supplements. While current standard treatment in many cases controls serum calcium levels reasonably well (targeting a serum calcium in the low-normal range or slightly below the lower limit of the normal range), many other aspects of the disease can remain unsatisfactory: Long-term consequences, which are felt to occur more frequently even under standard treatment, include: the risk of ectopic calcifications, in particular of the kidney (nephrocalcinosis) with deterioration of renal function, for which elevated serum phosphate levels and a deranged serum calcium-phosphate product may be indicators; CNS manifestations such as impaired cognitive function, anxiety, psychiatric manifestations. Current standard treatment replaces only incompletely the physiological actions of parathyroid hormone (PTH). Supraphysiological doses of oral calcium supplements and active vitamin D metabolites (or high doses of cholecalciferol in some cases) may cause problems of their own, such as gastrointestinal side effects of ingestion of large quantities of calcium salts or vitamin D intoxication. The patient representatives pointed out in particular the symptoms which can occur still under standard treatment, such as difficult-to-control episodes of cramps, body stiffness with considerable impact on daily activities, or the feeling of “brain fog”; also they raised concerns about long-terms consequences from current standard of care.

Concluding this question, the expert group saw a need for other treatment options beyond standard treatment for the above reasons.

2. **Please discuss the relevance of the results of the pivotal study. In particular discuss:**

- **The clinical relevance of the statistically significant results in favour of Natpar for the primary endpoint (responders were defined as having a ≥50% reduction in oral calcium and vitamin D intake and a target pre-dose serum [Ca++] between 1.87 mmol/L and the upper limit of the reference interval for [Ca++]) i.e. the importance of reducing supplements in relation to the use of standard treatment.**
- **The clinical relevance of data (including possible limitations of the data set) with respect to fluctuations in serum [Ca++] also in the context of the proposed dosing schedule? Has the company shown that Natpar achieves the calcium status that you seek for the patient?**

The expert group was of the view that substitution of the missing hormone, PTH, would in principle be expected of value. Based on the available data for Natpar in the pivotal trial (REPLACE) and supportive trial (RACE), the views on the possible benefit were as follows:

a) Serum calcium: The expert group considered the serum calcium values 24 hours post injections as reasonably well achieved but would not see this as a particular clinical benefit. The expert group was, however, highly critical of the short term calcium fluctuations after each injection. This was highlighted in an analysis presented by the co-rapporteur of the serum calcium values 6 hours post injection, which were collected at one point during the REPLACE trial, at visit 13; here, serum calcium values varied widely in the Natpar-treated group 6 hours post injection; a number of patients (ca. 40%) experienced outright hypercalcaemia (whereas on the other hand ca. 20% did not show any increase in serum calcium). It was criticized that at no point maximal and minimal serum calcium values over 24 hours post injection had been measured; serum calcium levels physiologically are tightly regulated, although it was pointed out that in hypoparathyroidism there are also broader fluctuations linked to calcium ingestions than physiological, therefore the wide fluctuations observed were of concern to the expert group.

With regard to the fluctuations in serum calcium (and to some extent serum phosphate, see below) delivery by pump or as slow release form, or as twice daily application, would be expected to address better the problem. The experts noted the applicant's intention to study further dose regimens (25 and 50 microgram BID use), which was welcomed. The patient representatives pointed out that some patients, using the approved product in the US, or another PTH preparation off label in the EU, split the daily dose by using a syringe, because of the time-limited action of Natpar and symptom relief perceived.

b) Serum phosphate: The reduction of hyperphosphataemia was seen as significant and beneficial, as long-term elevated serum phosphate levels are likely linked to ectopic calcifications. However it was noted critically that the effect of Natpar lasted only for ca. 8-12 hours out of 24 hours.

c) Parameters of renal calcium excretion: With regard to hypercalciuria, 24 hour calcium excretion did not show an improvement with Natpar vs. control at the end of the REPLACE study. A limitation of the available data is that renal handling of calcium has not been properly measured in the REPLACE study, e.g. with measurement of the fractional excretion of calcium (which might be lowered under Natpar treatment).

d) Markers of bone turnover: There is an indication of increase (i.e. towards normalisation) of markers of bone turnover. This is consistent with findings from other studies in patients with hypoparathyroidism, who tend to have low bone turnover, showing an improvement towards normal bone turnover with PTH injections. However, whether this might translate into a clinical benefit is not known, as this may improve trabecular bone density (which is already increased in hypoparathyroidism) but may increase porosity of cortical bone.

e) Clinical improvement, Quality of life (QoL): The expert group found it disappointing that the applicant could not demonstrate any improvement of these parameters in their studies, as most expert group members felt this was the outcome in most need of improvement and could have been expected from such a hormone replacement treatment (see also section 5). However, it was acknowledged that instruments such as a general SF36 questionnaire might not be very sensitive and appropriate for

hypoparathyroidism; further research in this field is encouraged. The patient representatives pointed out that there were many patients anecdotally reporting a significant improvement in quality of life, cognitive symptoms as well as cramps and tetanic equivalents, and that this was also very much their personal experience. Several experts added that published uncontrolled studies, circumstantial evidence and individual patients' narratives suggest improvements under such therapy.

When asked what was felt missing in the studies, the experts mentioned cognitive testing, more specific QoL testing, and, at selected time points, measurements of serum phosphate (2-3 times per day), a calcium serum profile measurement over 24 hours and a proper calcium clearance measurement.

Concluding this question, the experts voiced some criticism and concern with the proposed dosing schedule and the serum calcium fluctuations post injections (which could be expected to be of lower extent if Natpar would be administered in divided doses) but acknowledged the potential value of PTH treatment with Natpar (short and long term) with the existing posology for some patients.

3. **Currently, it is suggested to use Natpar in patients not well controlled/refractory to standard treatment. Could it be acceptable to extrapolate data achieved in the pivotal clinical trial for Natpar in patients that were optimized on stable calcium levels to those patients not well controlled/refractory to standard treatment?**

It was pointed out and acknowledged that responses in all subgroups of the REPLACE study were similar. Overall, the expert group was of the view that the benefits seen in the study population might also translate into benefits for patients refractory to existing standard therapy.
However, it was felt that criteria to define such patients as proposed by the applicant may be too far-reaching; these were based on therapeutic goals in a recently published EU guidance paper (European Society of Endocrinology Clinical Guideline: Treatment of chronic hypoparathyroidism in adults. Eur J Endocrinol. 2015 Aug; 173:G1-G20). However, therapeutic goals defined in this guideline were intended to provide guidance for optimisation of treatment, and not necessarily to define those patients considered to be "refractory" to treatment.
The experts were asked to consider possible criteria to define such patients. Factors suggested to be of likely relevance were severe and persistent symptoms related to hypoparathyroidism and, as laboratory parameters, hyperphosphataemia (with serum phosphate > 1.6 mmol/L), hypercalciuria (with 24-hour urinary calcium > 8 or 10 mmol/24 hours) and serum calcium outside the optimal range despite use of supraphysiological doses of active vitamin D (≥ 3 microgram of 1-α-hydroxycholecalciferol or equivalent) or fluctuating wildly without apparent cause.
In any case, the experts suggested treatment with Natpar should be in the hands of specialist care.

4. **By including both patients after neck surgery and others with a variety of conditions leading to hypoparathyroidism, the studied patient population is quite diverse. The development of antibodies should be taken into account for the patient group that has never been exposed to endogenous hormone. Do you think this is a risk in terms of responding differently, considering immunogenicity, tachyphylaxis?**

The experts considered that there is only a very low number of patients without circulating PTH from birth. Moreover, any potential problem with neutralising antibodies should become apparent during treatment.
However, development of tachyphylaxis on therapy with Natpar was considered to be a possibility which could not be excluded, but may become apparent as an increase of doses of calcium and active vitamin D needed.

5. In case of a registry, which efficacy and safety aspects should be followed in order to gather more long term data?

The expert group pointed out limitations with the proposal of a registry, due to the lack of a control group, in particular in the light of the many questions to be resolved and e.g. that certain evaluations are deemed not possible in that context such as cognitive testing. A drug product-based registry was considered to have disadvantages vs. a disease-based registry, the latter however being doubtful to be available. Overall, the expert group did see a need for post authorisation studies and expressed a strong view that the applicant should be required to initiate and maintain such data generation if the product were to be approved. Post-authorisation follow up may include safety aspects as well as efficacy parameters, with a focus on long-term outcome (in particular kidney stone formation, nephrocalcinosis, deterioration of renal function, brain calcifications), QoL (in particular reduction of specific clinical symptoms such as episodes of tetanic equivalent but also impairment of daily activities), cognitive testing and more detailed measurements of calcium post injections. Additionally, long-term impact on bone metabolism should be considered (both potentially beneficial due to improved remodelling or adverse due to increased porosity of cortical bone). Further exploration of other posologies, such as twice daily injections or a slow release formulation should also be encouraged. This was also emphasized by the apparent ongoing off label use with dose splitting to optimise response to symptoms, as reported by the patient representatives (see above).

2.5.3. Conclusions on clinical efficacy

The primary endpoint in the pivotal efficacy study was focused on maintaining serum calcium within the target plasma level range, titrating active vitamin D metabolites and calcium supplementation. Primary efficacy was demonstrated by a combined reduction in the need for oral supplementation with calcium and active vitamin D metabolites/analogues, and an albumin-corrected total serum calcium concentration that was normalized or maintained compared with the baseline value and did not exceed the upper limit of the laboratory normal range.

Use of Natpar exposes most subjects to marked diurnal swings in serum [Ca++] outside the reference interval. Some subjects did not respond to Natpar by an increase in serum [Ca++].

Furthermore, direct effects on one of the main target organs, i.e. the kidney, cannot be concluded by the primary endpoint that was used. The primary endpoint and the duration of the study does not allow to demonstrate clinical benefit versus standard treatment for those who do well with active vitamin D metabolites and calcium supplements, e.g. the avoidance of long-term consequences such as nephrocalcinosis/nephrolithiasis and renal impairment.

Although it is recognized that many measures were taken for safety reasons, and that also the design is influenced by this, the primary endpoint used does not allow to assess any direct effect on one of the main target organ: i.e the kidney (calciuria, phosphaturia). The treatment with Natpar should therefore be limited to a very restricted patient population, in which treatment with calcium and vitamin D metabolites is insufficient to obtain stable levels of calcium. During the procedure the applicant provided the results from two subgroups defined by different criteria as not adequately controlled by standard treatment:

The first set of criteria identified patients who need larger doses of oral calcium and active vitamin D to raise serum calcium and/or to control the symptoms of hypocalcaemia. By applying these criteria, 20 subjects (5 on placebo, 15 on Natpar) were identified in REPLACE. It is acceptable that the difference in primary endpoint is not statistically significant and it is acknowledged that there is a similar difference compared to the entire REPLACE population. Graphic time-profiles that summarize the main

biological parameters (albumin-corrected serum calcium, serum phosphate, calcium-phosphate product and serum creatinine), the symptoms of hypocalcaemia and the daily dose of oral calcium, active vitamin D and Natpar were provided.

A different subgroup of patients that are not well controlled was defined by the applicant, based on recent guidelines of the European Society of Endocrinology, although therapeutic goals defined in this guideline were intended to provide guidance for optimisation of treatment, and not necessarily to define those patients considered to be “refractory” to treatment. Furthermore, this subgroup does not reflect the subgroup of hypoparathyroidism patients that do currently have a demonstrated benefit for the treatment if responding to the primary endpoint. This resulted in 100 unique subjects (33 on placebo; 67 on Natpar) out of 124 subjects that meet one of the criteria in the REPLACE trial.

The design of the pivotal trial shows a clear and substantial effect of rhPTH(1-84) to decrease daily calcium and active vitamin D metabolite requirements in hypoparathyroidism patients. The significant decrease of the serum calcium-phosphate product suggests potential further benefits. However, in the absence of a demonstrated more definite long term benefit (see below), the CHMP concluded that this treatment should be limited to a restricted patient population in which treatment with calcium and vitamin D metabolites is insufficient to obtain stable and acceptable levels of calcium and phosphate, or for which standard therapy results in intolerable adverse events or persistent, severe hypoparathyroidism symptoms (now reflected in the indication wording of section 4.1 of the SmPC), which CHMP identified as a currently unmet need (see also section 3.2.3, Additional considerations on the benefit-risk balance, of this report).

Therefore, there remains a need to establish a clear, more definite, benefit of treatment with Natpar in such a restricted population, i.e. in the approved indication in patients with chronic hypoparathyroidism that are not adequately controlled with standard therapy alone. As concluded also during the ad hoc expert meeting, cognitive testing (more specific QoL testing) and, at selected time points, measurements of serum phosphate (2-3 times per day), a calcium serum profile measurement over 24 hours and a proper calcium clearance measurement are lacking in the studies. These will be collected as additional and more definite, relevant clinical outcomes to confirm the positive benefit/risk of the product as part of the conditional marketing authorisation and constitute a specific obligation of the applicant under Art. 5 of Commission Regulation 507/2006. Therefore the applicant has the obligation to conduct a randomised controlled trial comparing Natpar to Standard of Care and to alternative dosing (optimal dosing resulting from a PK/PD study), investigating the appropriateness of the dose, cognitive data and QOL, as well as other parameters of calcium-phosphate metabolism, including calcium serum profile, serum phosphate and renal calcium clearance (see also section 2.7 risk management and section 4 recommendation).

2.6. Clinical safety

Patient exposure

The rhPTH(1-84) clinical development program (primary data source) includes 13 Clinical Pharmacology Studies, 4 efficacy and safety studies in hypoparathyroidism, of which one ongoing, and a supporting development program consisting of 7 osteoporosis studies (3 placebo-controlled, 2 active controlled and 2 long-term extensions).

This small number of patients with hypoparathyroidism is supplemented with safety data from osteoporosis studies. This population is, however, different with respect to sufficiency of parathyroid hormone (PTH), its implications on calcium and phosphate metabolism and the affected organs and

body systems and background morbidity. Therefore, the contribution of the data from the osteoporosis studies to the safety analysis in patients with hypoparathyroidism is very limited.

The first cut-off of the ongoing study PAR-C10-008 (RACE) was 03 January 2014 with the exception of serious adverse events (SAEs) and markedly abnormal laboratory values for which a data cut-off of 20 June 2014 was used.

The updated cut-off for the ongoing RACE trial was 30 September 2014.

Table 12: Patient exposure in primary safety data source

	Comparator		rhPTH(1-84)			
	Placebo n	Active Control n	Alone n (m)	In combination[#] n	rhPTH(1-84) Dose	Duration of treatment
Clinical Pharmacology studies (13 Studies)						
Hypoparathyroidism Open-label			7		50 and 100 microg	2 single doses
All (incl. osteoporosis)	49	0	361			
Studies in Hypoparathyroidism						
Placebo-controlled CL1-11-040 REPLACE	40	0	84	0	50, 75 and 100 microg (flexible)	24 weeks
Dose comparison concurrent controlled PAR-C10-007 RELAY	0	0	42(19)	0	25 (n=19) or 50 (n=23) microg (fixed)	8 weeks
Uncontrolled PAR-C10-008 RACE*	0	0	49(46)	0	25, 50, 75 and 100 microg (flexible)	52 weeks + extension ongoing
Uncontrolled PAR-C10-009 REPEAT	0	0	24(16)	0	50, 75 and 100 microg (flexible)	24 weeks
Total	40	0	**121(3)**	0		
Studies in Osteoporosis						
Total	1425	150	2715	149		
Grand Total Unique subjects	1514	150	3194	149		

n = number of subjects in the treatment group
m = number of subjects who have already been counted in the previous study among the primary data source in the treatment group.
* Study PAR-C10-008 – RACE is currently ongoing with a data cutoff of January 3, 2014.
[#] In combination with alendronate or eostrogen-progestin hormone replacement therapy

Table 13: Exposure to rhPTH(1-84) in studies in hypoparathyroidism

	Clinical Pharmacology Studies[a]	Efficacy and Safety Studies in Hypoparathyroidism[b]
Parameter	rhPTH(1-84) (Any dose) (N=359)	rhPTH(1-84) (Any dose) (N=121)
Cumulative Exposure, n (%)		
Any exposure	359 (100)	121 (100)
≥ 1 week	35 (9.7)	121 (100)
≥ 12 weeks	0	116 (95.9)
≥ 24 weeks	0	108 (89.3)
≥ 52 weeks	0	47 (38.8)
≥ 104 weeks	0	45 (37.2)
≥ 156 weeks	0	14 (11.6)
Exposure Duration (weeks)		
n	359	121
Mean	0.33	72.54
SD	0.243	58.270
Median	0.29	48.00
Min, Max	0.1, 1.0	5.3, 176.1
Number of Person Years of Exposure	2.24	168.22

The number of person years exposure in the NPS-sponsored hypoparathyroidism studies was 168.22. The median duration of exposure to rhPTH(1-84) was 48.00 weeks.

Among the 121 subjects treated with rhPTH(1-84) in the efficacy and safety studies in hypoparathyroidism, 108 subjects received at least 24 weeks of treatment, and therefore, the short-term exposure is acceptable.

At the cut-off date of 30 September 2014 for the ongoing RACE trial 41 patients were exposed for ≥ 36 months.

For a product that is intended for chronic use, and for which no significant reduction in urinary calcium has been demonstrated, the number of patients receiving long term treatment is limited to draw conclusions on the long term (efficacy and) safety aspects.

The placebo treated population with only 40 patients is very small to allow comparison with the PTH-treated group. 37 subjects received at least 12 weeks of treatment and 31 subjects received at least 24 weeks of treatment. The median duration of exposure to placebo was 24.12 weeks and the total person years of exposure 17.22.

Demographic and other characteristics of the study population

The reader is referred to the clinical part for a detailed description of the characteristics of the study population.

In the studies in hypoparathyroidism, the majority of the subjects were female (79.3%) and most patients were white, non-hispanic. The elderly population in the efficacy and safety studies hypoparathyroidism, is limited: only 6 patients were 65 years of age or older and no subjects were 75 years of age or older. No patients with severe renal and hepatic impairment have been included.

Pen

During the procedure the Applicant decided against the use of the SHL pen for commercialization and switched to the Haselmeier pen (also referred to as Shire Q-cliq pen in this report) as the pen to be used for commercialisation for Natpar. The Haselmeier pen has only been used in the RACE trial as of 30 September 2014, i.e. after cut-off date. Bio-equivalence with the Ypsomed pen was assessed in trial PAR-C10-005.

Adverse events

Common adverse events

The most frequent treatment emergent adverse events, reported in more than 10% of rhPTH(1-84)-treated subjects in the clinical hypoparathyroidism studies were paresthesia (43.0%), tetany (34.7%), hypocalcaemia (33.9%), headaches (28.1%), upper respiratory tract infection (25.6%), nausea (24.8%), hypercalcaemia (24.0%), arthralgia (17.4%), abdominal pain (15.7%), diarrhea (15.7%), fatigue (14.0%), cognition and attention disorders and disturbances (13.2%), vomiting (13.2%), back pain (12.4%), pain in extremity (12.4%), vitamin D decreased (11.6%), anxiety symptoms (10.7%), hypercalciuria (10.7%), injection site reactions(10.7%).

The on-treatment TEAEs were analyzed for time of any occurrence. During the first year of exposure which represented the greatest number of subjects on treatment, with the exception of hypocalcaemia, pain in extremity, lower respiratory tract infection, influenza, vitamin D deficiency, urolithiasis, and gastroenteritis viral, the incidence rates of the analyzed TEAEs which occurred by the ≥ 1 to < 12 week interval, tended to peak in that interval and decline thereafter. The incidence rates for paresthesia, diarrhea, pain in extremity, lower respiratory tract infection, urolithiasis, and gastroenteritis viral remained approximately the same in the ≥ 1 to < 12 week and ≥ 12 to < 24 week intervals. The highest incidences of hypocalcaemia and pain in extremity was during the ≥ 52 to < 104 week and ≥ 12 to < 24 week intervals, respectively.

The higher incidence of adverse events during the first 12 weeks of management (that appear to reflect metabolic disturbance) is understood because attempts are being made to establish the appropriate dose of study drug.

Table 14: On-treatment TEAEs reported in ≥5% rhPTH(1-84) in any time interval

	Time to Onset						
Adverse Event Grouping[a] or MedDRA Preferred Term	<1 week (N=121) n (%)	≥1-<12 weeks (N=121) n (%)	≥12-<24 weeks (N=116) n (%)	≥24-<52 weeks (N=108) n (%)	≥52-<104 weeks (N=47) n (%)	≥104-<156 weeks (N=45) n (%)	≥156 weeks (N=14) n (%)
Paraesthesia[a]	5 (4.1)	33 (27.3)	31 (26.7)	6 (5.6)	6 (12.8)	0	0
Tetany[a]	4 (3.3)	28 (23.1)	17 (14.7)	11 (10.2)	11 (23.4)	4 (8.9)	0
Hypocalcaemia[a]	1 (0.8)	11 (9.1)	17 (14.7)	15 (13.9)	9 (19.1)	2 (4.4)	0
Headaches[a]	8 (6.6)	25 (20.7)	9 (7.8)	5 (4.6)	3 (6.4)	1 (2.2)	0
Upper respiratory tract infection[a]	1 (0.8)	18 (14.9)	11 (9.5)	7 (6.5)	9 (19.1)	1 (2.2)	0
Nausea	11 (9.1)	15 (12.4)	5 (4.3)	5 (4.6)	7 (14.9)	2 (4.4)	0
Hypercalcaemia[a]	2 (1.7)	16 (13.2)	11 (9.5)	1 (0.9)	2 (4.3)	3 (6.7)	0
Abdominal pain[a]	3 (2.5)	10 (8.3)	7 (6.0)	5 (4.6)	3 (6.4)	0	0
Arthralgia	1 (0.8)	11 (9.1)	7 (6.0)	4 (3.7)	3 (6.4)	0	0
Fatigue	1 (0.8)	12 (9.9)	5 (4.3)	3 (2.8)	3 (6.4)	0	0
Diarrhoea	0	7 (5.8)	5 (4.3)	5 (4.6)	2 (4.3)	2 (4.4)	0
Cognition and attention disorders and disturbances[a]	2 (1.7)	9 (7.4)	2 (1.7)	4 (3.7)	2 (4.3)	0	0
Pain in extremity	0	6 (5.0)	7 (6.0)	3 (2.8)	2 (4.3)	1 (2.2)	0
Hypercalciuria[a]	2 (1.7)	6 (5.0)	1 (0.9)	5 (4.6)	3 (6.4)	1 (2.2)	0
Vomiting	1 (0.8)	7 (5.8)	3 (2.6)	4 (3.7)	2 (4.3)	0	0
Back pain	0	7 (5.8)	2 (1.7)	1 (0.9)	4 (8.5)	1 (2.2)	0
Lower respiratory tract infection[a]	0	1 (0.8)	2 (1.7)	5 (4.6)	5 (10.6)	1 (2.2)	0
Anxiety symptoms[a]	1 (0.8)	6 (5.0)	3 (2.6)	0	3 (6.4)	0	0
Influenza[a]	0	1 (0.8)	3 (2.6)	0	7 (14.9)	1 (2.2)	0
Palpitations	0	7 (5.8)	0	2 (1.9)	1 (2.1)	0	0
Vitamin D deficiency	0	2 (1.7)	0	4 (3.7)	3 (6.4)	0	0

The most frequent post-treatment TEAEs in these PTH subjects were paresthesia (20.7%), hypocalcaemia (19.8%) and tetany (11.6%).

Adverse drug reactions

At day 120 and 180, the company was requested to carry out a relatedness exercise for all reported adverse events, not only those that occurred in >5% of patients. In the day 180 responses, all events reported in pivotal study CL1-11-040 were reviewed and all MedDRA PTs reported in at least 3 subjects exposed to Natpara were assessed for relationship to treatment according the classification 1) Hypercalcaemia symptom, 2) Hypocalcaemia symptom, 3) Drug administration event, and 4) Other events that may be related to treatment. Events reported in fewer than 3 subjects were also assessed for inclusion in category 3) and 4) above. Biologic plausibility was assessed. Other considerations included known mechanism, and if reported dechallenge-rechallenge. Resulting in the ADR table below (very common ≥ 1/10, common ≥1/100 to < 1/10).

Table 15: Adverse drug reactions

SOC	Very Common	Common	Overdose
Cardiac		Palpitations	ECG changes
Gastrointestinal	Diarrhoea Nausea Vomiting	Abdominal pain upper	
General		Asthenia Chest pain Fatigue Injection site reaction (erythema, hematoma) Thirst	
Investigations		antiPTH antibody positive Bl-25-hydroxycholecalciferol decreased Vitamin D Decreased	
Metabolism	Hypercalcaemia Hypocalcaemia	Hypomagnesemia Tetany	
Musculoskeletal	Arthralgia Muscle spasms	Muscle twitching Musculoskeletal pain Myalgia Neck Pain Pain in Extremity	
Neurological	Headache Hypoesthesia (including facial, oral) Paraesthesia (including oral)	Somnolence	Dizziness
Psychiatric		Anxiety Insomnia	
Renal		Hypercalciuria Pollakiuria	
Respiratory		Cough	
Vascular		Hypertension	Hypotension

Adverse events of special interest

Hypocalcaemia, hypercalcaemia, and hypercalciuria

Hypocalcaemia, hypercalcaemia, and hypercalciuria were considered adverse events of special interest (AESI) in the clinical development program of rhPTH(1-84) in subjects with hypoparathyroidism due to

the underlying physiology of hypoparathyroidism and the mechanism of action of rhPTH(1-84), the dose titration and oral calcium and active vitamin D modification in the hypoparathyroidism studies.

Individual PTs were combined with the associated laboratory PT. Hypocalcemia includes the AEs with the preferred terms of "hypocalcemia" and "blood calcium decreased", hypercalcemia includes the AEs with the preferred terms of "hypercalcemia" and "blood calcium increased", and hypercalciuria includes the AEs with the preferred terms of "hypercalciuria" and "urine calcium increased".

Individual calcium laboratory parameters alone were reviewed, which may or may not have been reported as an AE.

Clinical symptoms were reviewed as a secondary efficacy endpoint.

Table 16: Summary of hypocalcaemia, hypercalcaemia and hypercalciuria by study period in the Replace study

	Placebo		rhPTH(1-84)	
Study Period Adverse Event of Interest	Subjects (N=40) n (%)	Events	Subjects (N=84) n (%)	Events
Optimization (before the first dose date)				
Hypocalcaemia	3(7.5)	4	7 (8.3)	15
Hypercalcaemia	0	0	3 (3.6)	3
Hypercalciuria	2 (5.0)	2	6 (7.1)	6
Treatment (the first dose date to the last dose date)				
Hypocalcaemia	9 (22.5)	9	23 (27.4)	43
Hypercalcaemia	1 (2.5)	1	16 (19.0)	19
Hypercalciuria	3 (7.5)	4	9 (10.7)	10
Titration period (the first dose date to before the date of CRF Visit 13)				
Hypocalcaemia	7 (17.5)	7	9 (10.7)	16
Hypercalcaemia	1 (2.5)	1	12 (14.3)	13
Hypercalciuria	3 (7.5)	4	8 (9.5)	8
Stable period (the date of CRF Visit 13 to the last dose date)				
Hypocalcaemia	4 (10.0)	4	19 (22.6)	29
Hypercalcaemia	0	0	8 (9.5)	8
Hypercalciuria	2 (5.0)	2	8 (9.5)	9

AE = adverse event; CRF = case report form; n= number of subjects with the event of interest during the active titration period; N = total number of subjects in the treatment group

Hypercalcaemia

Double-blind, placebo-controlled Study CL1-11-040

Optimization period (before the first dose date)

In the placebo-controlled Study CL1-11-040, during the optimization period, 3/84 (3.6%) subjects (3 events) who were eventually randomized to rhPTH(1-84) and no subjects who were eventually randomized to placebo experienced an AE of hypercalcaemia. These subjects all had on-treatment TEAEs of hypercalcaemia and/or hypocalcaemia.

Titration period (through week 12)

During the titration period of the placebo controlled Study CL1-11-040, hypercalcemic events occurred more frequently in the rhPTH(1 84)-treated subjects than in the placebo treated subjects. Both the treatment emergent adverse events and the ACSC laboratory values support this trend: 12/84

(14.3%) rhPTH(1-84) subjects (13 events) and 1/40 (2.5%) placebo subjects (1 event) reported hypercalcaemia; ACSC values between > 2.65 mmol/L and ≤ 2.98 mmol/L hypercalcaemia occurred in 8/81 (9.9%) rhPTH(1-84) subjects and not in placebo-treated subjects. One PTH-treated patient (1.2%) and no placebo treated patient had an ACSC value > 2.98 mmol/L.

Two of the events occurred 2 and 3 days after the initiation of 50 µg of rhPTH(1-84), however all others occurred well into the titration period ranging between Study Day 25 and Study Day 57, following up-titration to 75 or 100 µg of rhPTH(1-84).

In the PTH group, one event was serious, resulting in an interruption of the study drug.

All events resolved. Four subjects in the PTH group had hypercalcaemia with a duration of more than 7 days (range 15 to 58 days), 2 of these subjects interrupted their study drug regimen.

This larger number of hypercalcaemia in the PTH-treated group can be explained because both PTH and supplements have an effect on mineral homeostasis and need to be adapted. Placebo treated patients only had short-term reductions in their oral calcium and vitamin D supplements and quickly returned to their baseline supplements, by study design. Concomitantly, mean ACSC levels increased over baseline in rhPTH(1-84) subjects during this titration period, while there was an expected decrease in serum calcium in the placebo group.

As the number of patients with hypercalcaemia in the titration period is high (14%), very close monitoring of the patients is required.

Stable period (following week 12 to week 24)

In rhPTH(1-84)-treated subjects during the stable period, less hypercalcaemia was reported either as an AE or assessed by central laboratory values as compared to the titration period, but still, 8/84 (9.5%) of rhPTH(1-84)-treated subjects had 8 AEs of hypercalcaemia, no AE were reported in the placebo group. In the PTH group one event was severe, which resulted in an interruption of the PTH dose and a subsequent reduction from 100 µg to 75 µg daily.

Hypercalcaemia, defined as ACSC > 2.98 mmol/L, occurred in no rhPTH(1-84) subjects and in 1/33 (3.0%) placebo subjects. Based on ACSC values between > 2.65 mmol/L and ≤ 2.98 mmol/L, hypercalcaemia occurred in 4/79 (5.1%) rhPTH(1-84) subjects and not in placebo subjects.

Concomitantly, mean ACSC values returned to baseline in rhPTH(1 84) subjects during the stable period.

Also during the stable period of the placebo controlled REPLACE study, the incidence of hypercalcaemia was higher in the rhPTH(1-84)-treated subjects than in the placebo-treated subjects. This requires regular monitoring of serum calcium during treatment.

Post-treatment period (after the last dose of drug)

In the post-treatment period, 3 placebo subjects and 2 rhPTH-treated subjects experienced a post-treatment AE of hypercalcaemia. Among the rhPTH-treated subjects, 1 subject had a post-treatment TESAE of hypercalcaemia and 1 subject had a post-treatment AE of hypercalcaemia that led to discontinuation (ie, the event of hypercalcaemia was recorded 1 day after the date of the last dose of rhPTH[1-84]). In addition, although one of the placebo-treated subjects did not have an AE of hypercalcaemia per se, this subject had an ACSC level at Visit 16 of 3.17 mmol/L that was secondary to the post-treatment TESAE of dehydration and unrelated to study drug.

Overall

Across all of the efficacy and safety studies in hypoparathyroidism there were 29/121 (24%) hypercalcaemia cases. There were no placebo-treated subjects and there was one rhPTH(1-84)-treated subject with an on-treatment serious adverse event of hypercalcaemia.

Of the 8 subjects (2 placebo- and 6 PTH-treated subjects) who participated in additional studies, one had further episodes of hypercalcaemia.

Long-term

Table 18 shows that also in the 52 week period from week 52 to week 104 hypercalcaemia was reported as a TEAE in 4.3% (2 patients) of the population and from week 104 to week 156 in 7.1% (3 patients) of the population.

In the open label RACE study, in total, seven subjects experienced 11 treatment-emergent adverse events of **hypercalcemia** or blood calcium increased since baseline. Seven events were considered related to study drug by the investigators, 2 events resulted in an interruption of study drug in addition to a reduction in study drug dosing, 2 events resulted in dose reduction and other medication change, and 3 events resulted in an interruption of study drug and a change in other medication. All events of hypercalcemia (11/11) were mild or moderate and eventually resolved.

Hypercalcaemia rarely occurs in the reference treatment (oral calcium and vit D derivatives) and can have serious clinical consequences. Also at the end of the stable period in the placebo controlled study and in the long-term open-label study TEAE of hypercalcaemia are reported.
Moreover, serum [Ca^{2+}] levels were measured pre-dose. Only in study CL1-11-040 at visit 13 serum [Ca^{2+}] levels were measured 6-10 hrs post dose, when serum [Ca^{2+}] levels are higher after rhPTH treatment. 35/75 subjects are shown to be hypercalcaemic at 6-10hrs post dose i.e. serum [Ca^{2+}] >2.55mmol/L. Two subjects in the rhPTH group had ACSC ≥ 3.00 mmol/L and 5 had ACSC ≥ 2.95 mmol/L. This illustrates the high incidence of hypercalcaemia in the rhPTH treated group, although only 5 hypercalcaemia related events were reported in 3 subjects in the following week. In the placebo group there was one patient with ACSC >2.55mmol/L 6-12 hours post dose (2.65 mmol/L). Post-dose hypercalcaemia, based on (post-dose) ACSC, has not been adequately investigated by the Applicant.

No TEAEs of nephrocalcinosis or nephrolithiasis were reported during the on-treatment phase for any subject who had hypercalcaemia. This should however be followed on the long-term.

Hypocalcaemia

Double-blind, placebo-controlled Study CL1-11-040

Optimization period

During the optimization period, 7/84 (8.3%) subjects (15 events) who were eventually randomized to rhPTH and 3/40 (7.5%) subjects (4 events) who were eventually randomized to placebo experienced an AE of hypocalcaemia. Of these 10 subjects, 6 subjects also had on-treatment AEs of hypocalcaemia.

Titration period

During the titration period, hypocalcemic events occurred more frequently in the placebo-treated subjects than in the rhPTH-treated subjects. Both the treatment emergent adverse events and the ACSC laboratory values support this trend: 9/84 (10.7%) rhPTH subjects and 7/40 (17.5%) placebo subjects experienced an event of hypocalcaemia; ACSC values < 1.88 mmol/L, occurred in 12/81 (14.8%) rhPTH subjects and 12/37 (32.4%) placebo subjects; ACSC values between 1.88 mmol/L and < 2.0 mmol/L occurred in 36/81 (44.4%) rhPTH subjects and 31/37 (83.8%) placebo subjects during this time period.

More subjects in the placebo arm had hypocalcaemia, which can be attributed to the protocol-mandated reduction in oral calcium and active vitamin D.

Stable period

In the stable period, only down-titration of rhPTH(1-84) was allowed and adjustments to oral calcium and active vitamin D were made as needed. 19/84 (22.5%) subjects in the rhPTH group experienced 29 AEs of hypocalcaemia compared to 4/40 (10.0%) subjects (4 events) in the placebo group; ACSC values < 1.88 mmol/L, occurred in 17/79 (21.5%) subjects in the rhPTH group and 5/33 (15.2%) subjects in the placebo group; values between 1.88 mmol/L and < 2.0 mmol/L occurred in 35/79 (44.3%) rhPTH subjects and 14/33 (42.4%) placebo subjects during this time period. The incidence rate per subject per visit of ACSC < 1.88 mmol/L is 10.8%, which means that 1 out of 10 subject visit of patients in the PTH group presented ACSC values < 1.88 mmol/L, compared to 6 out of 100 in the placebo group.

As explained by the Applicant, several factors might account for this. First, the rhPTH(1-84) subjects had experienced reductions or elimination of oral calcium and active vitamin D supplementation in the titration period whereas placebo subjects increased their calcium and active vitamin D supplementation back towards their baseline level in the later phase of the titration period. After Week 5, rhPTH(1-84) subjects were not allowed to increase their rhPTH(1-84) dose to compensate for their loss in oral calcium and active vitamin D supplementation. Indeed, 5 of the 19 subjects with ACSC-assessed hypocalcaemia had to remain at a dose less than 100 µg of rhPTH(1-84) despite ACSC-proven hypocalcaemia.
Another factor to consider is the decrease in 25-hydroxyvitamin D levels seen in the rhPTH(1-84) subject group. One of the actions of PTH is to convert 25-hydroxyvitamin-D into the active $1,25(OH)_2D$. In the presence of low levels of inactive vitamin D this conversion may have been less productive, thus, contributing to hypocalcaemia. Nine of the 17 subjects assessed with hypocalcaemia based on a central laboratory value of ACSC < 1.88 mmol/L had a 25-hydroxyvitamin D level of less than 75 nmol/L at the time of the event, a level assumed to be the lower range of normal 25-hydroxyvitamin D in blood.

Events occurring in this phase of the study were generally of short duration and were easily managed by adjustment of oral supplements. Four PTH-treated subjects experienced on-treatment hypocalcaemia that required treatment with intravenous calcium gluconate. The albumin-corrected total serum calcium levels for these subjects at or around the time of the event ranged from 1.75 to 1.92 mmol/L. All of the events were considered to be SAEs or significant events. All of the events were resolved by the end of study.

During the overall on-treatment period, there were 40 reports of ACSC < 1.88 mmol/L in rhPTH(1-84)-treated subjects. Of these, 6 (15.0%) were associated with hypoparathyroidism symptoms within ±7 days of the reported occurrence. During this time period, there were 36 reports of ACSC < 1.88 mmol/L in the placebo group. Six (16.7%) of these events were associated with hypoparathyroidism symptoms.

Post-treatment

After discontinuation of study drug, subjects were followed up for an additional 4 weeks in the post-treatment period. 27/84 (32.1%) rhPTH(1-84)-treated subjects (31 times) and 4/40 (10.0%) placebo-treated subjects (4 times) experienced hypocalcaemia. In 3 rhPTH(1-84)-treated subjects and in 1 placebo subject, the post-treatment hypocalcaemia was considered moderate or severe, and in each of these subjects the AE of hypocalcaemia required treatment with IV calcium gluconate. Albumin-corrected total serum calcium levels for these subjects ranged from 1.47 to 1.97 mmol/L at or around the time of the event. All of the events were considered to be SAEs or significant events. With the

exception of Subject 8002-0008, all of the events were resolved by the end of study. Two additional subjects in the PTH group had moderate post-treatment events of hypocalcaemia reported in the safety databases. All of the events were considered to be SAEs or significant adverse events. Serum calcium levels at the time of the events ranged from 1.40 to 1.90 mmol/L. All events resolved following administration of IV calcium gluconate.

This underlines that discontinuation or interruption of rhPTH(1-84) treatment in hypoparathyroidism subjects needs to be accompanied by reinstitution of supplements in sufficient doses and frequent monitoring of serum calcium.

The occurrence of hypocalcaemia is a major concern in non-compliant patients. Even upon drug discontinuation with reinstitution of supplements in sufficient doses and frequent monitoring of serum calcium, moderate or severe cases of hypocalcaemia requiring treatment with IV calcium occurred.

Overall

Across all of the efficacy and safety studies in hypoparathyroidism, 41/121 (39.9%) rhPTH-treated subjects experienced an on-treatment AE of hypocalcaemia. No subject had an on-treatment AE of hypocalcaemia which led to discontinuation.

According to the Applicant, there was no apparent subject demographic or clinical feature (including 25[OH] vitamin D levels) that distinguished subjects with hypocalcaemia AEs from the general study populations.

Long-term

Table 18 shows that also in the 52 week period from week 52 to week 104 hypocalcaemia was reported as a TEAE in 19.1% (9 patients) of the population and from week 104 to week 156 in 4.8% (2 patients) of the population.

In the ongoing open-label study PAR-C10-008, study drug titration in both directions was allowed throughout the study, as of the data cutoff date of 03 January 2014, 17/49 (34.7%) subjects reported 31 AEs of hypocalcaemia and/or blood calcium decreased. Most of the events were transient in nature ranging between 1 and 34 days duration, with the majority having a duration of 10 days or less. There were 8 subjects who had events that were of longer duration or still ongoing at the time of data cut-off (03 January 2014). Only 2 subjects had events occurring within the first 3 months of the study, the others occurred well after initiation of treatment in the study. Two additional subjects experienced hypocalcaemia between 03 January 2014 and 30 September 2014.

Looking at ACSC values in the on-treatment period of Study PAR-C10-008, there were 28 reports of ACSC < 1.88 mmol/L and 5 of these (17.9%) were associated with symptoms of hypoparathyroidism within ±7 days of the reported value.

In the stable period of the Replace study, hypocalcaemia rates in the stable phase for both the AE and ACSC criteria were higher in the rhPTH(1-84) subjects than in placebo subjects.

Hypercalciuria

For the entire titration period of the replace trial, 8/84 (9.5%) rhPTH(1-84) subjects and 3/40 (7.5%) placebo subjects reported 1 AE of hypercalciuria. Hypercalciuria defined as 24-hour urinary calcium ≥ 7.5 mmol/24 hr occurred in 56/81 (69.1%) rhPTH(1-84) subjects and 17/37 (45.9%) in placebo subjects.

In the titration period, hypercalciuria AEs and hypercalciura rates based on 24-hour urine calcium levels were lower in the placebo subjects paralleling the concomitant decrease in serum calcium and driven by the down titration of active vitamin D supplement.

During the stable period of the replace trial, more rhPTH(1-84)-treated subjects (8/84 (9.5%)) had an AE of hypercalciuria then placebo subjects (2/40 (5.0%)).

Also hypercalciuria defined as 24-hour urinary calcium ≥ 7.5 mmol/24 hr occurred more often in rhPTH(1-84) subjects (42/79 (53.2%)) than in placebo subjects (13/33 (39.4%)).

For both treatment groups there was an overall decrease in 24-hour urine calcium excretion. Levels were: -1.99 (±4.85) mmol/24 hr in the rhPTH(1-84) group and -2.28 (±4.27) mmol/24 hr in the placebo group (p=0.439).

At Week 24, a slightly lower percentage of subjects in the rhPTH(1-84) group (34%, 25/74) compared to the placebo group (39%, 13/33) had 24-hour urine calcium excretion > 7.5mmol/24 hours.

Persistence of the effect on urinary calcium excretion is seen in long-term study, PAR-C10-008.

Table 18 shows that also in the 52 week period from week 52 to week 104 hypercalciuria was reported as a TEAE in 6.4% (3 patients) of the population and from week 104 to week 156 in 2.4% (1 patient) of the population.

The long-term clinical effects of the lack of reduction of urine calcium concentrations by the treatment, the increased incidence of hypercalciuria AEs relative to placebo and 10% of patients having persistent hypercalciuria are not known.

Vital signs and cardiovascular safety

In general, across the efficacy and safety studies in hypoparathyroidism, the means, medians, and ranges for systolic and diastolic blood pressure, pulse and respiration rate, and temperature were similar at baseline and endpoint. Most of the instances of markedly abnormal values were associated with blood pressure or pulse rate, and were similarly distributed between the rhPTH(1-84) and placebo-treated subjects in the placebo-controlled studies.

Since elevations in serum calcium will cause a known shortening of the QTc interval and PTH is administered as a replacement therapy, no thorough QT study is requested. The extent of QTc shortening observed in subjects treated with rhPTH(1-84) is far less than the extent of shortening in the arrhythmogenic congenital short QT syndrome (SQTS). No subjects in clinical studies in hypoparathyroidism had QTcF values below the lower limit of normal (< 370 ms)and none had a short QT related arrhythmia, whereas one subject in the placebo group had a treatment emergent finding of atrial fibrillation. SQTS is caused by gain of function potassium channelopathies not related to cardiac calcium channels. It is unlikely that the on treatment QTcF values, which are in the normal range, would incur an increased risk of arrhythmia. There is no evidence for such an acquired or drug-induced short QT syndrome. Furthermore, rhPTH(1-84) had no effects on PR and QRS.

There is concern that the company has not investigated the immediate effect of hypercalcaemia (for instance by recording continuous ECG) but the risk of post-dose hypercalcaemia is currently mitigated by close monitoring as described in the SmPC (see clinical section of the report).

Renal and urinary disorders

Hypercalciuria is discussed above.

In the Replace study, pollakiuria occurred in 3 PTH-treated subjects (3.6%) and in one placebo-treated subject. In PAR-C10-007 it was reported in 3 subjects, it was not reported in PAR-C10-008 or PAR-C10-009. Given that rhPTH(1-84) increases serum calcium in hypoparathyroidism subjects just initiating treatment, transient pollakiuria could be an expected occurrence in some subjects.

Nephrolithiasis was reported in 2 subjects in Study PAR-C10-008 in the efficacy and safety studies in hypoparathyroidism.

Apart from effects expected from the mechanism of action of rhPTH(1-84), no renal-related AEs in rhPTH(1-84)-treated subjects have been indicated.

The currently provided data are, however, insufficient to assess the long-term effects of this treatment on renal damage.

Injection site reactions

Injection site reactions occurred in 0 to 13% of the PTH-treated subjects, were mild to moderate in severity and none was considered serious or lead to discontinuation of the treatment. Mild injection site hematoma, injection site swelling, and injection site erythema were reported.

Overdosage

Cases of overdose or accidental overdose were usually the consequence of misunderstanding that resulted in misuse or misoperation of the Ypsomed injection pen. There were no cases of overdose with the Q-Cliq currently in use in the ongoing long-term study. Hypercalcaemia and/or hypercalciuria were reported for the majority of subjects who had a TEAE of overdose or accidental overdose of rhPTH(1-84). In most cases, the serum calcium did not exceed 3.3 mmol/L, study drug was temporarily interrupted, additional education provided, and the adverse event resolved.

Withdrawal

The post-treatment phase of the placebo-controlled study CL1-11-040 and Study PAR-C10-009 in hypoparathyroidism which included a protocol-specified post-treatment phase, provides the most accurate assessment of withdrawal effects.

In Study CL1-11-040, there were more rhPTH(1-84)-treated subjects than placebo-treated subjects who reported post-treatment TEAEs of paresthesia (21.4% rhPTH[1-84], 5.0% placebo), hypocalcaemia (26.2% rhPTH[1-84], 7.5% placebo), and tetany (11.9% rhPTH[1-84], 0 placebo). All other post-treatment TEAEs reported among the 84 rhPTH(1-84)-treated subjects in Study CL1-11-040 were reported in 3 (3.6%) or fewer subjects.

The post-treatment cases of hypocalcaemia upon treatment discontinuation are discussed above, under the hypocalcaemia section.

Pen complaints

The pen ultimately proposed for marketing is the Haselmeier pen. The delivery systems used for the hypoparathyroidism program were the Ypsomed pen injector and the Haselmeier pen injector (also referred to as Shire Q-cliq pen in this report)). The Ypsomed pen was used in the studies in hypoparathyroidism (Studies CL1-11-040, PAR-C10-007, PAR-C10-008, and PAR-C10-009). The Q-Cliq system is currently being used in the ongoing study, PAR-C10-008.

Across all Efficacy and Safety Studies, there were 0.286 complaints per 100 injections associated with use of the Ypsomed pen and 0.069 complaints per 100 injections associated with the Q-Cliq system. The majority of complaints were dose counter problems, dose activator problems, leaking medication, cartridge problems and dose knob problems. With the Ypsomed pen there were 28.4 TEAEs that were possibly related to pen complaints per 100 patient years exposure, for Q-Cliq this was 1.2 per 100 patient years.

The simulated use validation study PAR-C12-003 shows there is a risk for underdosing with the Haselmeier pen following incorrect use of the pen. Underdosing can be corrected by intake of oral Calcium and active vitamin D supplements following the appearance of symptoms.

Serious adverse events and deaths

No deaths occurred in the clinical pharmacology studies or the efficacy and safety studies in hypoparathyroidism.

There were 12 rhPTH(1-84)-treated subjects (9.9%) who experienced a total of 20 on-treatment TESAEs through 20 June 2014.

In the placebo-controlled study REPLACE CL 1-11-40, 5/84 (6.0%) rhPTH(1-84)-treated subjects experienced 7 on-treatment treatment-emergent serious adverse events, including back pain, cellulitis, cerebrovascular accident, diarrhea, diverticulitis, hypercalcaemia, and vomiting. None of these on-treatment TESAEs were reported in more than 1 subject. The single on-treatment TESAE that first occurred during the titration period (ie, the initial 12 weeks of treatment) was hypercalcaemia. All on-treatment TESAEs except for 1 episode of hypercalcaemia were considered not related to study drug by the investigator.

Two of 40 subjects (5.0%) treated with placebo experienced on-treatment TESAEs ('bronchospasm and obstruction' in one subject and epididymal tenderness in another).

Seven of 49 (14.3%) subjects in the open-label extension Study PAR-C10-008, experienced on-treatment TESAEs. These events included lung adenocarcinoma metastatic, rectal cancer, fracture (x2), and viral infection in 1 subject each, syncope, dyspnea, chest discomfort, and throat tightness in the same subject, gastroenteritis and hypocalcaemia both in the same subject, and cholelithiasis and cholecystitis both in the same subject. None of these events was considered by the investigator to be related to study drug.

Studies CL1-11-040 and PAR-C10-009 both included a protocol-specified post-treatment phase. During the post-treatment phase of Study CL1-11-040, there were 4 rhPTH(1-84)-treated subjects and 2 placebo subjects who experienced a TESAE. Among the rhPTH(1-84)-treated subjects, the post-treatment TESAEs included hypocalcaemia (2 subjects), hypercalcaemia (1 subject), and pancreatic disorders not elsewhere classified (1 subject). The post-treatment TESAE of hypercalcaemia occurred 7 days after the last dose of study drug was administered and the investigator indicated that the event may have been caused by an adjustment in the dose of active vitamin D post study termination. The post-treatment TESAEs reported by placebo subjects included hypocalcaemia and dehydration.

Due to the low frequency of on-treatment TESAEs in the studies, there were no obvious trends with respect to the time of first occurrence.

Osteosarcoma

Osteosarcoma is a rare cancer with an estimated incidence of 1.7 to 4.4 per million, depending on age. The peak incidence occurs in male adolescents. There is a secondary peak incidence in the elderly. Among the elderly, osteosarcoma often represents a secondary neoplasm, such as that which occurs with the transformation of Paget's disease of bone. Irradiation has also noted to be a risk factor associated with osteosarcoma in the elderly.

A potential risk of osteosarcoma has been described for Forsteo (teriparatide; rhPTH(1-34). Use of teriparatide for more than 2 years is not recommended.

Two case reports of osteosarcoma in patients using teriparatide (rhPTH(1-34)) have been identified. One patient was a postmenopausal woman in her 70s with a complex past medical history. The history included osteoporosis with vertebral fractures, and she was treated with teriparatide in a manner

consistent with the label. Sometime after beginning her second year of teriparatide therapy, she was found to have metastatic cancer. The primary cancer site was never identified. The diagnosis included several tumor types, including an osteosarcoma.

Causality between teriparatide and the osteosarcoma in this patient cannot be established. This was a single case of >250,000 patients in the United States and >300,000 patients worldwide treated with teriparatide, the patient had a complex medical history, and the background incidence of osteosarcoma in the general population of men and women ≥ 60 years of age is 1 in 250,000 per year. (1.7 to 4.4 per million depending on age). Given the known incidence in the general population, very rare cases of osteosarcoma can be expected, irrespective of treatment with teriparatide. [Harper et al, 2007]

The second patient, a 67-year-old man, with potential teriparatide-induced osteosarcoma was complicated by a history of pelvic radiation. Given the location of the sarcoma within the field of radiation and the limited exposure to teriparatide before diagnosis (approximately 2 months), it is unlikely that teriparatide played the predominant role in the emergence of this patient's osteosarcoma. The investigators cannot, however, exclude the possibility that teriparatide magnified the carcinogenic effect of radiation therapy to induce the osteosarcoma. [Subbiah et al, 2010].

In the FDA adverse event reporting system, 8 cases of osteosarcoma were identified with a history of teriparatide use prior to the initial diagnosis of osteosarcoma. Pathology results consistent with a diagnosis of osteosarcoma were provided for 4 of the 8 cases. The history of previous radiation therapy was noted in two of eight cases. It is difficult to draw conclusions on the causality based on limited data, but there are at least 4 reported cases on a population estimated to be less than 1 million, i.e. more than the background incidence rate. Therefore an increased risk for osteosarcoma cannot be excluded in the osteoporosis population and given the non-clinical data, consequently neither in the hypoparathyroid population.

Based on experience with parathyroid hormone related products, there is concern that long-term exposure to Natpar may be associated with the development of osteosarcoma. Beyond routine pharmacovigilance, this concern is being addressed in the SmPC section 4.3 by contraindicating the use of the product for patient groups with a potentially higher risk to develop an osteosarcoma and by a warning in section 4.4 of the SmPC against the use of the product in young adults. Cases of osteosarcoma would also be captured in the registry, agreed with the applicant as a post authorization measure, however the extremely low incidence of osteosarcoma makes any conclusions to be likely very limited.

Laboratory findings

Consistent with the known pharmacologic effects of rhPTH(1-84) on mineral homeostasis, there were changes, sometimes marked, in calcium, magnesium, and phosphate levels in blood, serum, and/or urine.

In addition, a full range of haematology, clinical chemistry, and urinalysis testing was performed, and there were no clinically meaningful trends or observations suggestive of a safety concern with rhPTH(1-84) treatment.

There was no suggestion that rhPTH(1-84) causes drug-induced liver injury.
There were no cases that met the criteria for Hy's law (cases of drug-induced liver injury) across the entire development program.

In the placebo-controlled Efficacy and Safety Study in Hypoparathyroidism, no markedly abnormal treatment-emergent aminotransferase or bilirubin elevations or treatment-emergent liver-related AEs occurred in subjects treated with rhPTH(1-84). Likewise in Studies PAR-C10-007, PAR-C10-008, and

PAR-C10-009, the frequency of categorical aminotransferase elevations was relatively low and mild except for 1 subject with viral hepatitis.

There were no renal-related AEs or abnormalities in renal function tests or urinalysis tests apart from changes expected from the mechanism of action of rhPTH(1-84). In the placebo-controlled trial, CL1-11-040, creatinine clearance (estimated glomerular filtration rate) was relatively stable and no subjects had severe decreases or had results indicating end-stage renal disease.

The influence of PTH on bone mineral density and bone turnover markers is discussed in the efficacy section of this report.

Following a comment on PK data, the safety aspects of the accumulation of C-terminal PTH were discussed by the Applicant. C-terminal PTH fragments are not expected to accumulate chronically in most patients. Currently the possible safety consequences of such accumulation are not known. Any potential effect could be counterbalanced by PTH effect.

Safety in special populations

Gender

No clinically relevant gender differences in TEAE rates were observed in the efficacy and safety studies in hypoparathyroidism. However, the majority of the patient population were females.

Age

Since there were very few subjects ≥ 65 years of age (N=6 (5%)) and no subjects ≥ 75 years of age in the efficacy and safety studies in hypoparthyroidism, no conclusions can be made regarding differences in the incidence of on-treatment TEAEs by age.

Safety in elderly will remain a topic for further investigation in the RMP.

Race

There were very few Black subjects and subjects of other races in the efficacy and safety studies in hypoparathyroidism.

The lack of non-Caucasian subjects in the clinical safety database will remain a topic for further investigation in the RMP.

Pregnancy and lactation

The rhPTH(1-84) development program did not include pregnant women or lactating women.

Animal studies do not indicate harmful effects with respect to reproductive toxicity at clinically relevant exposures.

It is unknown whether rhPTH(1-84) is excreted in human milk. In rats, mean PTH(1-84) concentration in milk ranged from approximately 1.6 to 10.2 ng/mL at doses of 300 and 1000 mcg/kg/day. This resulted in plasma to milk concentration ratios of 2 to 42 with an overall mean ratio of 14.

Immunological events

Samples for assay of antibodies to parathyroid hormone and E. coli protein (host cell protein) were collected in:

- 1 pharmacokinetic/pharmacodynamic study:

Study C09-002

- 4 efficacy and safety studies sponsored by NPS:

  Study CL1-11-040 (REPLACE)

  Study PAR-C10-007 (RELAY)

  Study PAR-C10-008 (RACE)

  Study PAR-C10-009 (REPEAT)

- 1 investigator-initiated trial (Bilezikian IIT)

The 6 studies used to investigate immunogenicity are described below:

Study C09-002

This was an open-label, escalating, single-dose study to assess the PK and PD parameters of rhPTH(1-84) administered subcutaneously to 7 subjects with hypoparathyroidism. Subjects received single doses of rhPTH(1-84) 50 and 100 µg in Treatment Periods 1 and 2, respectively, with a 7-day washout period between treatment periods.

Serum samples were assayed for antibodies to rhPTH(1-84) using the Quest assay only once, predose in Treatment Period 1. One subject out of 7 subjects that completed the study had a positive screen for PTH antibodies prior to treatment administration. PK results for this subject were similar in periods 1 and 2.

Study C09-002 is not considered to be informative with regards to antibody development because this study employed the Quest assay for antibody detection.

Study CL1-11-040 (REPLACE) [main study for application]

This was a randomized, double-blind, placebo-controlled, Phase 3 study to investigate the use of rhPTH(1-84), for a 24-week treatment period for the treatment of adults with hypoparathyroidism.

- Antibodies to rhPTH(1-84) were measured by both Quest and Tandem.
- The blood samples taken at Visit 5 (baseline), prior to treatment with rhPTH(1-84), Visit 16 (post-treatment at 24 weeks) and follow-up Visit 18 (at Week 28, 4 weeks after stopping rhPTH[1-84] treatment) were analyzed by Quest Laboratories.
- A new method was developed to ensure that the assay technology used for PTH antibody testing conformed to FDA standards. A decision was made to use a new, validated MSD assay developed by Tandem Labs. This assay became available in January 2011 and was used to assay available samples for antibodies to PTH from 34 rhPTH(1-84) subjects and 17 placebo subjects at Visit 16 and/or Visit 18.
- Assays for antibodies with neutralizing activity (NAB) were not done as the method was not yet validated.
- Antibodies to ECP were not done as the ECP assay (TNJR11-019) required a baseline for each subject. A baseline was needed as the subjects may already have a high signal (being exposed to ECPs) prior to entering the trial. The signal is determined by the subtraction of the predose from the postdose values.
- It has been acknowledged (in the methods section of this assessment report) that the current product has had a long development programme, that regulatory standards and assays change

and improve and that the company has had to change assays to cater for changes in requirements over time. It is noted, however, that samples for analysis at a later date had not been retained (to test for neutralising antibodies, antibodies to ECP and to test all samples using the Tandem laboratory method).

Antibodies to PTH detected by the Tandem assay are presented in the following table:

Table 17 Number (%) of subjects in study CL1-11-040 with PTH Antibodies based on the Tandem MSD assay

Table 2-2 Number (%) of Subjects in Study CL1-11-040 with PTH Antibodies Based on the Tandem MSD Assay – Safety Population

Antibodies	Visit	Placebo (N=44) n (%) [a]	rhPTH(1-84) (N=90) n (%) [a]
PTH	Week 24 (Visit 16)	15	31
	Positive	2 (13.3)	8 (25.8)
	Specific	1 (6.7)	2 (6.5)
	Non-specific	1 (6.7)	6 (19.4)
	Negative	13 (86.7)	23 (74.2)
	Week 28 (Visit 18)	17	34
	Positive	2 (11.8)	8 (23.5)
	Specific	0	1 (2.9)
	Non-specific	2 (11.8)	7 (20.6)
	Negative	15 (88.2)	26 (76.5)

MSD = Meso-Scale Discovery; N = number of subjects; PTH = parathyroid hormone
Note: n is the number of subjects having antibodies to PTH at the analysis visit for those subjects who have a valid measurement at the visit
[a] The percentage is calculated based on the number of subjects having PTH antibody tests at the visit. Samples drawn outside analysis visit windows are not included in this number.
Source: Study CL1-11-040 CSR Table 14.3.7.2, Listing 16.2.9.6 and TNJR11-193

4 samples were classified as specific (positive for immune-depletion) to antibodies to PTH. Titres are reported as the log10 of the reciprocal dilution which is derived from the interpolation of the dilution at the assay specific cut point. All titres were <2.

Assays for neutralising antibodies and ECP antibodies were not done.

The incomplete nature of the testing strategy hinders full interpretation of results.

Study PAR-C10-007 (RELAY)

Study PAR-C10-007 (RELAY) was a randomized, double-blind study to investigate the safety and efficacy of rhPTH(1-84) at fixed doses of 25 µg and 50 µg SC daily for the treatment of 42 adults with hypoparathyroidism.

Serum samples were assayed for antibodies to rhPTH(1-84) and ECP at baseline and at Week 8. Samples were analyzed by both Quest (35 subjects at baseline and 31 subjects at Week 8) and Tandem (40 subjects were tested, 36 subjects at baseline and 29 subjects at Week 8).

Based on results obtained by the MSD method at Tandem Laboratories, 3 subjects previously treated with rhPTH(1-84) and 2 subjects previously not treated or treated with placebo had specific antibodies to PTH at baseline. Three of these subjects (2 previously drug, 1 previously not treated) remained positive at Week 8. All of the samples had very low titers. No subjects had antibodies with neutralizing activity. Similar to overall responder rate of about 22% in this study, 1 of the 5 (20%) subjects with specific antibodies to PTH was an efficacy responder.

8 samples in 6 subjects that tested positive for ECP: specificity for ECP antibodies was not collected in this study.

No subjects had a systemic hypersensitivity reaction or any immunogenicity-related event in this study. No subjects with specific antibodies to PTH had injection site reactions in this study.

The incomplete nature of the testing strategy hinders the overall assessment.

Study PAR-C10-008 (RACE)

Study PAR-C10-008 (RACE) is an ongoing long-term, open-label clinical extension study investigating the safety and tolerability of rhPTH(1-84), for the treatment of adults with hypoparathyroidism. The subjects who enrolled in this study must have previously completed Study PAR-C10-007 (8 weeks of active therapy) and/or previously completed the 24 weeks of treatment in Study CL1-11-040.

Samples for PTH and ECP antibody analysis are to be obtained at baseline (Visit 1, which used Week 8 results from Study PAR-C10-007, if available), Weeks 24, 40, 52, every 6 months during the long-term extension, and at the End of Treatment visit.

If any subject tests positive for PTH-specific antibodies at the final visit, they are to have follow-up blood draws for PTH antibodies at Months 2, 3, and 6 post-study. Antibodies to PTH, antibodies with neutralizing activity (NAB) and ECP were assayed by Tandem.

As of the cut-off date of 03 January 2014, in the Tandem MSD assay, 9 of 52 subjects tested positive for specific antibodies to PTH, including 2 subjects who had specific antibodies only at baseline. Baseline data for these subjects are the results from Week 8 of Study PAR-C10-007. One of these nine subjects had antibodies with neutralizing activity and was not a responder at that moment. As of 30 September 2014, in the Tandem Meso-Scale Discovery (MSD) assay, 10 of 49 subjects developed specific antibodies to PTH. The updated report describes four additional positive specific antibodies compared to the previous report.

11 subjects returned positive results for specific antibodies to E. Coli Protein.

Three of the subjects had specific antibodies to both ECP and to PTH in this study.

Only one subject tested specific for ECP in Study PAR-C10-008 had an injection site reaction. No subjects with specific antibodies to PTH had injection site reactions in this study. Out of the 9 subjects who were positive specific antibodies to PTH in the PAR-C10-008 study, 3 (33%) had hypersensitivity reactions. Out of the 40 subjects who were not positive/specific for antibodies to PTH, 2 (5%) had hypersensitivity reactions. No subjects with specific antibodies to PTH or ECP had hypersensitivity reactions related to rhPTH(1-84) in this study as of the cut-off date of 03 January 2014.

There does not seem to be an association between development of antibodies and clinical consequence such as hypersensitivity reaction in the RACE study.

Study PAR-C10-009 (REPEAT)

Study PAR-C10-009 (REPEAT) was a 6-month open-label clinical extension study investigating the safety and tolerability of rhPTH(1-84) for the treatment of 24 adults with hypoparathyroidism. All subjects enrolled in this study were from 3 study centres located in Hungary and had previously been enrolled in Study CL1-11-040.

Samples were obtained for testing for PTH antibodies at baseline and at EOT (Week 24). If any subject tested positive for PTH-specific antibodies at the final visit, they were to have follow-up blood draws for PTH antibodies at Months 2, 3, and 6 post-study.

All 24 subjects who enrolled in the study completed treatment and had antibody testing performed by the (Quest and) Tandem assay.

5 subjects returned positive results for antibodies to PTH; there were 2 subjects at baseline and 4 subjects at 24 weeks who tested positive and specific. One of these subjects tested positive for antibodies with neutralizing activity at Week 24, but not at baseline in this study and not in the previous study (CL1-11-040). At Week 24 this subject was a responder.

None of the subjects who tested specific to antibodies against PTH experienced injection site reactions, a systemic hypersensitivity reaction or any immunogenicity-related event in this study. No subjects in this study had injection site reactions. With the exception of one subject, who had received placebo in REPLACE (Study CL1-11-040) and did not respond in either study, all subjects who had specific antibodies to PTH were responders, including a subject with antibodies with neutralizing activity. Using the MSD method for the presence of antibodies to ECP (TNJR11-196), all subjects had negative results for antibodies to ECP.

There does not seem to be an association between development of antibodies and clinical consequence such as hypersensitivity reaction in the REPEAT study.

Bilezikian investigator-initiated trial

The ongoing Bilezikian IIT enrolled subjects who participated in a series of ongoing, prospective, open-label, investigator-initiated, sequential trials and extensions conducted under US IND 070449. The Principal Investigator of the study is John P. Bilezikian c/o Columbia University USA. The study was carried out to investigate the effects of rhPTH(1-84) replacement on bone structure in hypoparathyroidism. The study began on 16 August 2004 and consisted of a pilot study, an initial 2-year trial and subsequent extensions. 90 subjects have been enrolled by 3rd Jan 2014.

Antibody collection was started in July 2013 i.e. late addition to protocol. Therefore data on antibodies are only available for 11 of the 90 subjects. These subjects received the study drug prior to assay for 1 to 8.5 years. One of these 11 subjects had specific antibodies to PTH as of the cut-off date of 03 January 2014.

No subjects had hypersensitivity reactions associated with PTH as of the cut-off date.

Overall Results from Studies CL1-11-040, PAR-C10-007, PAR-C10-008 and PAR-C10-009

None of the subjects in the 4 NPS-sponsored safety and efficacy studies who tested specific to antibodies against PTH had a systemic hypersensitivity reaction related to rhPTH(1-84) or any immunogenicity-related event related to rhPTH(1-84) when antibodies specific to PTH were present.

1 subject in these 4 studies (in Study CL1-11-040) had an injection site reaction (haematoma/bruising) when specific antibodies to PTH were present. This subject had specific antibodies to PTH in Study PAR-C10-008 at Week 52 but not previously in this study and did not have injection site reactions in this study.

11/117 subjects (9.4%) in studies PAR-C10-007, PAR-C10-008 and PAR-C10-009 were found to have antibodies to ECP. (cut-off 03 January 2014)

Although antibodies to study drug and E. Coli Protein were detected only in low titre and although there does not seem to be any clinical consequence of antibody development, the number of results is small and the testing strategy incomplete over all 4 clinical studies. In addition, there is concern that the immunological response of those subjects who are hypoparathyroid for reasons other than post-neck surgery will be different in type and magnitude from those who had hypoparathyroidism post-

neck surgery. None of the recipients developed a systemic hypersensitivity reaction related to rhPTH(1-84).

Safety related to drug-drug interactions and other interactions

Among the Efficacy and Safety Studies in Hypoparathyroidism, there were few notable differences between the incidences of individual on-treatment adverse event preferred terms between rhPTH(1-84) or placebo-treated subjects who did and did not receive a concomitant medication in a particular class. None of the observed differences was considered to be of sufficient clinical importance to impact labelling.

The inotropic effects of digoxin are affected by serum calcium levels. Combined use of parathyroid hormone (rDNA) and cardiac glycosides (e.g., digoxin) may predispose patients to digitalis toxicity if hypercalcaemia develops.

For any drug that affects serum calcium levels (e.g., lithium, fluoride thiazides), influence on patients' serum calcium levels should be monitored.

Discontinuation due to AES

Clinical pharmacology studies

The TEAEs leading to discontinuation included vomiting, nausea, syncope, hyperhidrosis (all in 1 subject), and urticaria in another subject. One rhPTH(1-84)-treated subject, had elevated liver function tests that were not recorded as an AE, but led to study discontinuation.
There was 1 additional rhPTH(1-84)-treated subject who experienced a pruritic rash (judged by the investigator to be related to the study drug) the day after dosing in the first period of a crossover study and the subject did not receive study medication in the second dosing period.

Efficacy and safety studies in hyperparathyroidism

There were a total of 5 rhPTH-treated subjects who discontinued due to an on-treatment treatment-emergent adverse event.

Treatment-emergent AEs leading to discontinuation occurred in 3 subjects in the Replace study: rash (1 subject); cerebrovascular accident (1 subject); and arthralgia, anxiety symptoms, asthenia, cognition and attention disorders and disturbances, decreased appetite, depressive disorders, headaches, injection site reactions, nausea, pain in extremity, and tetany (all occurring in one subject). The only TEAE leading to discontinuation in the Relay study was arthralgia occurring in one subject. In the Race open-label extension study, one subject discontinued due to lung adenocarcinoma metastatic. No subjects discontinued in the Repeat Study.

No events except for arthralgia (2 subjects) were reported by more than 1 subject in either study group. No subjects discontinued due to an on-treatment event of hypercalcaemia, hypocalcaemia, or hypercalciuria. There was 1 rhPTH(1-84)-treated subjects in the Replace study who experienced a TEAE that led to drug discontinuation 1 day after the last dose of treatment (hypercalcaemia).

2.6.1. Discussion on clinical safety

Patient exposure

In general, the assessment of the different safety aspects is sufficient on the short term (108 subjects that received at least 24 weeks of treatment), given the product's orphan designation.

There are only 47 patients with hypoparathyroidism with at least 1 year exposure and 41 patients treated for 3 years. For a product that is intended for chronic use, for which no significant reduction in

urinary calcium has been demonstrated, for which there is a very high calcium fluctuation 24 hours post-dose and for which the mid-term effects of the QD drug administration are not known the number of patients receiving long term treatment is limited to draw conclusions on the long term (efficacy and) safety aspects.

Hypercalcaemia-induced nephrotoxicity, soft tissue calcifications and end-organ damage, immunogenic effects, cardiovascular effects, effects on bone and osteosarcoma should be followed on the long term.

The contribution of the data from the osteoporosis studies to the safety analysis in patients with hypoparathyroidism is very limited, given the differences between these populations with respect to sufficiency of parathyroid hormone, its implications on calcium and phosphate metabolism and the affected organs and body systems, the background morbidity and medications and the age.

Adverse drug reactions

The most common adverse drug reactions occurring with a frequency of more than 1 in 10 patients are signs and symptoms of hypercalcaemia and hypocalcaemia.

Hypercalcaemia

During the titration period of the placebo controlled Study CL1-11-040, hypercalcemic events occurred more frequently in the rhPTH(1 84)-treated subjects than in the placebo treated subjects. Both the treatment emergent adverse events and the ACSC laboratory values support this trend. In the PTH group, one event was serious, resulting in an interruption of the study drug. All events resolved. Four subjects in the PTH group had hypercalcaemia with a duration of more than 7 days (range 15 to 58 days), 2 of these subjects interrupted their study drug regimen.

This difference between placebo and rhPTH(1 84)-treated subjects can be partially explained based on the study protocol of the REPLACE study, there was an expected initial decrease in serum calcium in the placebo group and a trend toward higher serum calcium values in the PTH group. In the PTH group, both PTH and supplements have an effect on mineral homeostasis and need to be adapted, while placebo treated patients only had short-term reductions in their oral calcium and vitamin D supplements and quickly returned to their baseline supplements, by study design.

The number of patients with hypercalcaemia in the titration period is high (14%).

During the stable period of the placebo controlled Replace study, less hypercalcaemia was reported either as an AE or assessed by central laboratory values as compared to the titration period, but still, 8/84 (9.5%) of rhPTH(1-84)-treated subjects had 8 AEs of hypercalcaemia, no AE were reported in the placebo group. In the PTH group one event was severe, which resulted in an interruption of the PTH dose and a subsequent reduction from 100 µg to 75 µg daily.

Concomitantly, mean ACSC values returned to baseline in rhPTH(1 84) subjects during the stable period.

The incidence of hypercalcaemia during the stable period is also elevated (9.5%). The occurrence of this adverse event is worrisome, because it has been observed in optimal monitoring conditions and in ‘real live’ incidence could be higher and the outcome be more serious. This concern is therefore now addressed in a special warning in section 4.4 of the SmPC “Monitoring of patients during treatment” and in 2 detailed sections of the SmPC section 4.2 detailing needed measurements during as well as after initiation of treatment. Moreover, hypercalcaemia is rarely observed in the reference treatment (oral calcium and vit D derivative) and can have serious clinical consequences, making treatment with PTH less safe than the reference treatment in the currently proposed target population.

Moreover, serum [Ca^{2+}] levels were measured pre-dose. Only in study CL1-11-040 at visit 13 serum [Ca^{2+}] levels were measured 6-10 hrs after PTH dose administration, when serum [Ca^{2+}] levels were shown to be about 0.25 mmol/L (max 0.7 mmol/L) higher than pre-dose levels.

(Post-dose) hypercalcaemia, based on (post-dose) ACSC, has not been adequately investigated by the Applicant.

Also on the longer term, in the 52 week period from week 52 to week 104 hypercalcaemia was reported as a TEAE in 4.3% (2 patients) of the population and from week 104 to week 156 in 7.1% (3 patients) of the population.

High risk patients will probably be elderly patients with renal insufficiency, subjects with a disease predisposing to hypercalcaemia (active neoplasia, multiple myeloma, granulomatous disease), people taking thiazide diuretics and those taking digoxin.

No TEAEs of nephrocalcinosis or nephrolithiasis were reported during the on-treatment phase for any subject who had hypercalcaemia, however the number of patients on long-term treatment is limited.

There is also a concern that the company has not investigated the immediate effect of hypercalcaemia (for instance by recording continuous ECG) and that the long-term clinical safety issues of wide fluctuations in serum [Ca++] over 24 hours after each administration are unknown.

Hypocalcaemia

During the titration period of the placebo controlled Study CL1-11-040, hypocalcaemic events occurred more frequently in the placebo-treated subjects than in the rhPTH(1 84)-treated subjects. Both the treatment emergent adverse events and the ACSC laboratory values support this trend. More subjects in the placebo arm had hypocalcaemia, which can be attributed to the protocol-mandated reduction in oral calcium and active vitamin D.

In the stable period of the Replace study, hypocalcaemia rates for both the AE and ACSC criteria were higher in the rhPTH(1-84) subjects than in placebo subjects. (See MOs) Several factors might contribute to this increased incidence of hypocalcaemia in the PTH-treated group. After Week 5, rhPTH(1-84) subjects were not allowed to increase their rhPTH(1-84) dose to compensate for their loss in oral calcium and active vitamin D supplementation. (5 out of 19 patients) Another factor to consider is the decrease in 25-hydroxyvitamin D levels seen in the rhPTH(1-84) subject group. In the presence of low levels of inactive vitamin D its conversion to the active $1,25(OH)_2D$ may have been less productive, thus, contributing to hypocalcaemia.

Events occurring in this phase of the study were generally of short duration and were managed by adjustment of oral supplements. Four PTH-treated subjects experienced on-treatment hypocalcaemia that required treatment with intravenous calcium gluconate. All of the events were considered to be SAEs or significant events. All of the events were resolved by the end of study.

Hypocalcaemia events also occurred on the longer-term.

About 15% of the reports of < 1.88 mmol/L in rhPTH(1-84)-treated subjects were associated with hypoparathyroidism symptoms within ±7 days of the reported occurrence.

During the post-treatment period, i.e. after drug discontinuation, 27/84 (32.1%) rhPTH(1-84)-treated subjects and 4/40 (10.0%) placebo-treated subjects experienced a post-treatment AE of hypocalcaemia. In 3 rhPTH(1-84)-treated subjects and in 1 placebo subject, the post-treatment hypocalcaemia was considered moderate or severe. Two additional subjects in the PTH group had moderate post-treatment events of hypocalcaemia reported in the safety databases. In each of these subjects the AE of hypocalcaemia required treatment with IV calcium gluconate. This suggests that discontinuation or interruption of rhPTH(1-84) treatment in hypoparathyroidism subjects needs to be

accompanied by reinstitution of supplements in sufficient doses and frequent monitoring of serum calcium.

The occurrence of hypocalcaemia is a major concern in non-compliant patients. Even upon drug discontinuation with reinstitution of supplements in sufficient doses and frequent monitoring of serum calcium, moderate or severe cases of hypocalcaemia requiring treatment with IV calcium occurred.

Renal and urinary disorders

During the stable period of the replace trial, there were more AEs of hypercalciuria and events of hypercalciuria based on laboratory evaluations in the rh(PTH)(1-84)-treated subjects than in the placebo-treated subjects. The long-term clinical effects of the lack of reduction of urine calcium concentrations by the treatment, the increased incidence of hypercalciuria relative to placebo and 10% of patients having persistent hypercalciuria are not known.

Osteosarcoma

Two case reports of osteosarcoma in patients using teriparatide (rhPTH(1-34)) have been identified in literature. In the FDA adverse event reporting system, 8 cases of osteosarcoma were identified in patients with a history of teriparatide use. Pathology results consistent with a diagnosis of osteosarcoma were provided for 4 of the 8 cases.

Causality between teriparatide use and osteosarcoma cannot be established in these case reports. Teriparatide might magnify the effect of radiation therapy to induce osteosarcoma. There are at least 4 reported cases on a population estimated to be less than 1 million, i.e. more than the background incidence rate. Therefore an increased risk for osteosarcoma cannot be excluded in the osteoporosis population and given the non-clinical data, consequently neither in the hypoparathyroid population.

Based on experience with parathyroid hormone related products, there is concern that long-term exposure to Natpar may be associated with the development of osteosarcoma. Beyond routine pharmacovigilance, this concern is being addressed in the SmPC section 4.3 by contraindicating the use of the product for patient groups with a potentially higher risk to develop an osteosarcoma and by a warning in section 4.4 of the SmPC against the use of the product in young adults.

Pen (complaints) accordance

The pen proposed for marketing is the Haselmeier pen (Q-Cliq), which is used in the RACE trial. The Ypsomed pen was used in the majority of the efficacy and safety studies. There were less complaints with the Haselmeier pen than with the Ypsomed pen in these studies.

The simulated use validation study PAR-C12-003 shows there is a risk for underdosing with the Haselmeier pen following incorrect use of the pen. Underdosing can be corrected by intake of oral Calcium and active vitamin D supplements following the appearance of symptoms.

Safety in special populations

Elderly population

The elderly population is very limited, only 6 patients were 65 years of age or older, no subjects were 75 years of age or older. Therefore, no conclusions can be made regarding differences in the incidence of in-treatment TEAEs by age category.

Given the increased risk for adverse events and possible consequences e.g. of hypercalcaemia, the product should be used with even more caution in this population.

Renal insufficiency

Mild-to-moderate impairment of renal function had no clinically-relevant effects on the PK of PTH(1-84) or serum calcium concentrations after single SC administration of 100 µg rhPTH(1-84) in the abdomen of male or female subjects. No data are available on patients with severe renal impairment.

As creatinine clearance decreases, the peak plasma concentration of PTH(1-84) will increase.

There is an increased risk of hypercalcaemia and calciphylaxis in patients with severe renal insufficiency. The Applicant does not want to contra-indicate patients with severe renal impairment, based on lack of data, because the proposed therapeutic population has no alternative treatment.

Pregnancy and lactation

The development program did not include pregnant women or lactating women. There is however, no established therapeutic regimen for treatment of hypoparathyroidism during pregnancy. This is due particularly to uncertainty about the use of vitamin D or its analogues, as in animal experiments teratogenic side-effects have been reported. Nevertheless, vitamin D or its analogues are required to control tetany predisposing to abortion and preterm labour. However, management of maternal hypoparathyroidism with calcitriol and calcium is feasible, if the $1,25(OH)_2D3$ concentrations are adapted to the physiological needs during pregnancy and serum calcium levels are kept in the lower normal range.

Animal studies do not indicate harmful effects with respect to reproductive toxicity at clinically relevant exposures. It does not seem logic to deprive pregnant patients in which hypocalcaemia cannot be controlled by usual therapy from this treatment. Therefore, CHMP agreed with the proposed wording of the SmPC given that the indication is restricted.

Immunological events

As of the cut-off date of 03 January 2014, none of the subjects who tested positive to antibodies against PTH experienced injection site reactions, systemic hypersensitivity reactions related to PTH, or any immunogenicity-related event in this study, apart from one subject who developed a severe anaphylactic reaction to magnetic resonance imaging (MRI) dye (not related to rhPTH[1-84]) that resolved.

Although antibodies to study drug and *E. Coli* Protein were detected only in low titre and although there does not seem to be any clinical consequence of antibody development, the number of results is small and the testing strategy incomplete over all 4 clinical studies. In addition, there is concern that the immunological response of those subjects who are hypoparathyroid for reasons other than post-neck surgery will be different in type and magnitude from those who had hypoparathyroidism post-neck surgery. The applicant is committed to the continued monitoring of antibodies and their effect on safety and efficacy in RACE and future studies.

2.6.2. Conclusions on clinical safety

The most frequent ADRs are signs and symptoms of hypercalcaemia and hypocalcaemia.

The most important risks are the incidence of hypercalcaemia both during titration and the stable phase, and is potentially serious, and hypocalcaemia especially related with non-compliance. Post-dose hypercalcaemia has not been adequately documented, as well as ECG at trough and peak calcium concentrations.

There are major concerns over the long-term clinical safety consequences of wide fluctuations in serum [Ca2+] over 24 hours after each administration of study drug, either arising from the recurrent peak calcium concentration achieved or arising from the repeated rise and fall of serum calcium.

Additional long-term safety data will be obtained from the RACE trial, that is ongoing at time of this report. Also, additional long-term data on clinical safety and efficacy outcomes will be collected in the PARADIGHM registry study (see section 2.7 risk management of this report). Data collected in this study include bone-related outcomes, soft tissue calcifications and renal function, together with data on hypercalciuria and quality of life.

The number of results on antibody data is small and there is concern that the immunological response of those subjects who are hypoparathyroid for reasons other than post-neck surgery will be different in type and magnitude from those who had hypoparathyroidism post-neck surgery. The Company is committed to the continued monitoring of antibodies and their effect on safety and efficacy in RACE and future studies.

Osteosarcoma, effects on bone, hypercalcaemia-induced nephrotoxicity, soft tissue calcifications and end-organ damage, immunogenic effects, cardiovascular effects should be followed, as their incidence in larger populations and on the long term are not known. Long term effects will be followed post approval in a registry study.

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.5 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed the Risk Management Plan version 2.5 with the following content:

Safety concerns

Table 36: Summary of Safety Concerns

Important identified risks	Hypercalcaemia Hypocalcaemia
Important potential risks	Osteosarcoma and other bone tumours Medication errors Immunogenicity/neutralisation of rhPTH (1-84) biological activity Tachyphylaxis
Missing information	Use in patients < 18 years of age Use in pregnant or lactating women Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses Use in patients >65years of age Use in non-Caucasians Long-term safety and efficacy Use in patients with severe renal disease Use in patients with severe hepatic disease

rhPTH (1-84)=recombinant human parathyroid hormone (1-84) (Natpar)

Pharmacovigilance plan

Table 40: Overview of Ongoing and Planned Studies				
Study/Activity, Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
Clinical study SHP634-403: A Randomized, 3-Arm, Single-blind, Placebo-Controlled, Phase 4 Study to Evaluate Metabolic Control, Safety, and Symptoms Among Adult Subjects with Hypoparathyroidism Treated With Recombinant Human Parathyroid Hormone (rhPTH[1-84]) as a Single Daily Injection and <<Alternative Dosing Regimen TBD>> (Category 2)	**Primary:** To evaluate the effect of rhPTH (1-84) dosed as <<alternative dosing regimen TBD>> on overall metabolic control (as defined by pre-specified treatment targets) compared with active vitamin D and calcium supplements (conventional care) in subjects with hypoparathyroidism. **Secondary:** To evaluate the effect of rhPTH (1-84) dosed once daily on overall metabolic control (as defined by pre specified treatment targets) compared with conventional care. To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on cognitive status, hypoparathyroidism-related symptoms, and health-related quality of life compared with conventional care. To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on urine calcium	Hypercalcaemia Hypocalcaemia Immunogenicity/neutralisation of rhPTH (1-84) biological activity Tachyphylaxis	Planned	Final report: June 2023

Table 40: Overview of Ongoing and Planned Studies				
Study/Activity, Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
	excretion compared with conventional care. To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on the proportion of subjects achieving normal albumin-corrected serum calcium (2.20-2.55 mmol/L [8.8 10.2 mg/dL]) compared with conventional care. To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on the proportion of subjects achieving complete independence from active vitamin D and calcium supplements compared with conventional care. To evaluate the effect of rhPTH(1-84) dosed once daily and as <<alternative dosing regimen TBD>> on the proportion of subjects achieving the following: Free of active vitamin D supplement and on 500 mg of calcium per day or less Albumin-corrected serum calcium 2.0-2.55 mmol/L (8.0-10.2 mg/dL) Serum phosphate normal 0.81-1.45 mmol/L (2.5-4.5 mg/dL) 24 hour urine calcium excretion <7.5 mmol (300 mg)/24 hours in men and <6.25 mmol (250 mg)/24			

Table 40: Overview of Ongoing and Planned Studies				
Study/Activity, Type, Title and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
	hours in women compared with conventional therapy. To evaluate pre- and post-rhPTH (1-84) dosing serum albumin-corrected calcium levels in the once daily rhPTH (1-84) arm. To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on change from baseline in bone turnover markers compared with conventional care. To evaluate the effect of rhPTH (1-84) dosed once daily and as <<alternative dosing regimen TBD>> on change from baseline in bone mineral density compared with conventional care.			
PAR-R13-001, (PARADIGHM) Registry for Patients with Chronic Hypo-parathyroidism, (Category 1)	To characterize and describe the clinical course of chronic hypoparathyroidism under conditions of routine clinical practice. This includes, but is not limited to, treatments, symptoms, health-related quality of life (HRQoL), clinical outcomes, and comorbidity. To characterize and describe the long-term efficacy and safety profile of rhPTH (1-84) treatment in patients with chronic	Hypercalcaemia Hypocalcaemia Medication errors Tachyphylaxis Use in pregnant or lactating women Use in patients > 65 years of age Use in non-Caucasians Long-term safety and efficacy	Planned	Interim analyses with PBRERs Final study report 2035

Table 40: Overview of Ongoing and Planned Studies

Study/Activity, Type, Title and Category (1-3)	Objectives	Safety Concerns Addressed	Status (Planned, Started)	Date for Submission of Interim or Final Reports (Planned or Actual)
	hypoparathyroidism under conditions of routine clinical practice. This includes long-term effects of rhPTH (1-84) on renal, eye, bone, cardiovascular, and other outcomes relevant for patients with hypoparathyroidism.			
Clinical study PAR-C10-008 (RACE): A Long-term Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH [1-84]), for the Treatment of Adults with Hypoparathyroidism – A Clinical Extension Study (RACE) (Category 3)	**Primary objective:** The objective of this study is to demonstrate the long-term safety and tolerability of SC NPSP558 as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism. **Secondary objectives:** To evaluate the impact of different preparations of calcium and calcitriol on the response to NPSP558 replacement therapy. To demonstrate that dosing with NPSP558 across a dose range of 25 to 100 µg SC can be implemented in a safe and effective manner and can be maintained throughout long-term treatment. To evaluate the impact of calcium-sparing diuretics on serum and urinary calcium.	Hypercalcaemia Hypocalcaemia Immunogenicity/neutralisation of rhPTH (1-84) biological activity Tachyphylaxis Long-term safety and efficacy	Ongoing	May 2017

Q=quarter; rhPTH (1-84)=recombinant human parathyroid hormone (1-84) (Natpar); SC=subcutaneous

Risk minimisation measures

Table 44: Summary of Risk Minimisation Measures		
Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
Hypercalcaemia	Proposed text in SmPC: Dosing schedule (including initiation and titration) provided in Section 4.2. Special warnings and precaution in Section 4.4 to minimise hypercalcaemia by following recommended dosing, the monitoring information, and asking patients about symptoms. Treatment recommendation if severe hypercalcaemia occurs. Drug interactions with cardiac glycosides and drugs that affect serum calcium are discussed in Section 4.2. Hypercalcaemia is listed in Section 4.8. Overdose discussed in Section 4.9. Prescription only medicine.	None
Hypocalcaemia	Proposed text in SmPC: Dosing schedule (including initiation and titration) provided in Section 4.2. Special warnings and precaution in Section 4.4 regarding withdrawal of PTH (rDNA). Drug interactions with cardiac glycosides and drugs that affect serum calcium are discussed in Section 4.2. Hypocalcaemia is listed in Section 4.8. Prescription only medicine.	None
Osteosarcoma and other bone tumours	Proposed text in SmPC: Contraindications discussed in Section 4.3: Natpar is contraindicated in patients who are receiving or who have previously received radiation therapy to the skeleton; with skeletal malignancies or bone metastases; who are at increased baseline risk for osteosarcoma such as patients with Paget's disease of bone or hereditary disorders; with unexplained elevations of bone specific alkaline phosphatase. Special warnings and precautions in Section 4.4: Natpar should be used with caution in young adult patients with open epiphyses as these patients may be at increased risk for osteosarcoma Prescription only medicine	None
Medication errors	Proposed text in SmPC: Therapeutic indication in Section 4.1. Posology and method of administration described in	None

Table 44: Summary of Risk Minimisation Measures		
Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
	Section 4.2. Overdose discussed in Section 4.9. Updated IFU. Prescription only medicine.	
Immunogenicity/ neutralisation of rhPTH (1-84) biological activity	Proposed text in the SmPC: Anti-PTH antibody positive is listed as an ADR in Section 4.8. Prescription only medicine	None
Tachyphylaxis	Proposed text in the SmPC: Special warnings and precaution in Section 4.4 to monitor the response to serum calcium concentration to Natpar at intervals to detect tachyphylaxis.	None
Use in patients <18 of age	Proposed text in SmPC: Therapeutic indication in Section 4.1 Use in paediatric population discussed in Section 4.2. Prescription only medicine.	None
Use in pregnant or lactating women	Proposed text in SmPC. Fertility, pregnancy and lactation are discussed in Section 4.6. Prescription only medicine.	None
Long-term effects on bone structure and development in paediatric patients <18 years of age and young adults with open epiphyses	Proposed text in SmPC: Therapeutic indication in Section 4.1. Use in paediatric population discussed in Section 4.2. Prescription only medicine.	None
Use in patients >65 years of age	Proposed SmPC text: Warnings and precautions for use in subjects aged 65 and over discussed in Section 4.4. Prescription only medicine.	None
Use in non-Caucasians	Prescription only medicine	None
Long-term safety and efficacy	Prescription only medicine	None
Use in patients with severe renal disease	Proposed SmPC text: Description of requirements in cases of renal impairment provided in Section 4.2. Warnings and precautions for use in patients with severe renal disease discussed in Section 4.4. PK properties regarding renal impairment discussed in	None

Table 44: Summary of Risk Minimisation Measures		
Safety Concern	**Routine Risk Minimisation Measures**	**Additional Risk Minimisation Measures**
	Section 5.2. Prescription only medicine.	
Use in patients with severe hepatic disease	Proposed SmPC text: Description of requirements in cases of hepatic impairment provided in Section 4.2. Warnings and precautions for use in patients with severe hepatic disease discussed in Section 4.4. PK properties regarding hepatic impairment discussed in Section 5.2. Prescription only medicine.	None

ADR=adverse drug reaction; AUC=area under the curve; CrCl=creatinine clearance; C_{max}=maximum concentration; ECG=electrocardiogram; IFU= instructions for use; PK=pharmacokinetic; PTH=parathyroid hormone; PTH (rDNA)=recombinant human parathyroid hormone (Natpar); rhPTH (1-84)=recombinant human parathyroid hormone (1-84) (Natpar); SC=subcutaneous; SmPC=Summary of Product Characteristics

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EC) 726/2004, Natpar (parathyroid hormone) is included in the additional monitoring list as it is approved under a conditional marketing authorisation [Art 14(7) of Regulation (EC) No 726/2004].

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Hypoparathyroidism is a rare endocrine deficiency that is characterized by absent or inappropriately low circulating PTH levels, secreted normally by the parathyroid glands (mostly due to damage / removal of parathyroid glands or their blood supply during neck surgery, but also autoimmune conditions, congenital absence, genetic mutations, etc.).

Hypoparathyroidism results in hypocalcaemia and hyperphosphataemia, while in the urine there is increased calcium excretion and decreased phosphate excretion. Because calcium sensing receptors are widely distributed in the human body, a fluctuation in calcium may lead to multiple and very diverse symptoms, although these hypocalcaemia symptoms are generally reversible. The key symptoms involve the neuromuscular system: numbness, paraesthesia, twitching and tetany. Seizures, cardiac arrhythmias, cardiomyopathy, laryngeal spasm are more serious and potentially life-threatening effects, and difficulties in concentrating ("brain fog") and effects on mood and ideation are also described.

Current management of hypoparathyroidism consists of calcium (carbonate/citrate) and active vitamin D metabolites (calcitriol/alphacalcidol) in pharmacological doses sufficient to maintain the serum calcium just below or at the low end of the normal range, to protect the kidneys and to prevent long-term damage from a high calcium-phosphate product. Thiazide diuretics can be helpful, promoting renal calcium reabsorption. The required amounts of calcium and active vitamin D supplements vary widely across patients and there is a great intrapatient variability. Therefore, constant vigilance and monitoring is required. Some patients require magnesium supplementation and phosphate binders.

Although this treatment is able to achieve normal serum calcium levels, often hypercalciuria and hyperphosphataemia are present, due to the lack of PTH´s phosphaturic action on the kidney, putting patients at long-term risk of nephrocalcinosis and nephrolithiasis. With long-acting vitamin D and Vitamin D derivatives, vitamin D intoxication is not infrequent and is a serious risk. Additionally, well-being is not restored by this treatment. Current therapy does not address the root cause of hypoparathyroidism, namely lack of PTH. Providing a PTH hormone replacement can therefore expected to be beneficial.

3.2. Favourable effects

study C09-002 (PD) study demonstrates that single dose administration of rhPTH(1-84) has physiological effects of the missing hormone in hypoparathyroidism patients, after single dose administration rhPTH(1-84) vs calcitriol the following benefits were observed: increased mean albumin corrected serum calcium (ACSC) levels not returning to baseline levels, increased mean serum magnesium levels (AUC_{0-24} difference small), decreased mean serum phosphate levels, comparable mean serum $1,25(OH)_2D$ levels, increase mean urinary cAMP, initial decrease mean urinary calcium excretion, initial decrease mean urinary magnesium excretion, increase in phosphate excretion.

The REPLACE efficacy study is a 24-week double blind, placebo-controlled replacement study that clearly shows a benefit in terms of responders to the triple endpoint: 50 % reduction in calcium supplements, 50 % reduction in active vitamin D metabolites, maintaining patient within save range of serum calcium levels. The study met its primary triple endpoint with a p-value of <0.001: 1/40 responders (2.5%) in the placebo group (CI: 0.1-13.2) compared to 46/84 responders (54.8%) in the rhPTH(1-84) group (CI: 43.5-65.7).

Following secondary and exploratory endpoints show a statistically significant effect in the REPLACE study (besides those related to the efficacy endpoint, such as decrease in calcitriol and oral calcium dose): increase in serum BTMs ($p < 0.001$), higher BMD measured in many locations of the hip (all $p \leq 0.001$), decrease of phosphate serum levels (-0.16 ($\pm$ 0.25) mmol/L in rhPTH group vs -0.01 ($\pm$ 0.22) in placebo group)($p \leq 0.004$), decrease in calcium-phosphate product (2.808 ($\pm$0.4657) $mmol^2/L^2$ in rhPTH group vs 3.204 ($\pm$ 0.4429) $mmol^2/L^2$ in the placebo group) ($p < 0.001$). This demonstrates that treatment with rhPTH not only affects serum calcium, but also other aspects regulated by endogenous PTH.

The RACE long-term study is an open label study that was still ongoing at time of this assessment, extending the period of observation to a current maximum of 1003 days (cutoff date 3/1/14), and that supports the REPLACE study showing 34/45 (75.6%) subjects that met the triple efficacy endpoint at Week 52 (95% CI: 60.5, 87.1), 21/41 (51.2 %) subjects met the triple efficacy endpoint at Month 24 (95% CI: 35.1, 67.1) and 24/48 (50.0%) subjects met the triple efficacy endpoint at EOT (95% CI: 35.2, 64.8).

The PD C09-002 study is a single dose study that reports response of physiological parameters relevant for demonstrating the mimicking effect of rhPTH(1-84) vs the natural hormone in patients with hypoparathyroidism.

The REPLACE study has a rigorous study design adapted to safety considerations for the patients in both study groups, and has well defined and reliable methods for assessment of subject's response, including acceptable, pre-specified methods for analysis of the results.

Although the RACE study has an open label design, it has the advantage of its study duration and that it has a design that allows to mimic real life situations: after the starting dose, the rhPTH(1-84) dose could be increased/decreased by 25 µg to a maximum of 100 µg at any time, while adjusting oral calcium and active vitamin D regimens based on TSC levels.

3.3. Uncertainties and limitations about favourable effects

Initial lowering of urinary calcium and magnesium after administration of rhPTH(1-84) in PD study C09-002 was followed by return to baseline due to increasing serum levels: Over 24 hours, although there was an initial decrease by 65 – 68% with both doses of rhPTH(1-84) at 3 – 6 hours, values increased progressively to predose levels in the 16 – 24 hour sample. A different dosing scheme, continuous dosing, or a slow-release formulations was not considered. A more mechanistic PK-PD model is missing to characterize the exposure-response relationship determining the dose and dose regimen selection for clinical use (impact of covariates such as bodyweight, specific antibody presence). The applicant therefore is investigating this further post approval by means of an additional PK/PD study to inverstigate the appropriateness of the dosing regimen. This study, SHP634-101, is already planned. A model-based approach will need to be used in study design and data analysis to ensure an appropriate description of population PK, PK/PD and prediction of drug effects.

Overall, there is concern that the clinical development programme did not fully evaluate the pharmacokinetics and pharmacodynamics of Natpar in a population of subjects with hypoparathyroidism. For instance, the quick-release formulation of Natpar chosen by the company results in a peak parathyroid hormone concentration (about) 2 hours after administration that then decays with a half-life of (about) 3 hours. This profile does not mimic the diurnal variation seen with endogenous parathyroid hormone in healthy subjects. This difference may have been a contributing factor to the apparent lack of effect on serum [Ca++] found in (about) 16% of recipients of Natpar in the REPLACE study in spite of the expected rise in plasma parathyroid concentration: this is considered to reflect tachyphylaxis or desensitisation.

Initially, the SHL pen was proposed to be commercialised, but none of the pharmacodynamic or efficacy studies is performed with this pen. Study PAR-C13-004 showed that a high variability is recorded in the dose delivered to the subjects, ranging from approximately 40 mg to 80 mg for the Ypsomed pen and from approximately. 40 mg to 113 mg for the SHL pen (with a target dose of 72.1 mg). During the assessment of this application, the Applicant changed their intention to use the SHL pen in the to-be-marketed product to the Haselmeier pen (also referred to as Shire Q-cliq pen in this report), which is to be used in combination with the Duoject Mixing device. Although also for this pen a substantial variability in administered dose has been recorded, it should be noted that US post-marketing data concerning this product delivered with the Haselmeier pen indicated the frequency and nature of postmarketing adverse events (including pen complaints) are similar to what was seen in the clinical development programme. By using the same Haselmeier pen during the studies that will be done as post authorisation measures, the same variability will also be introduced in the results of these studies and, as such, it will be accounted for.

In the pivotal REPLACE study, although 46/84 subjects achieved the primary endpoint, the pre-dose serum [Ca++] and 24hr urinary excretion of calcium and phosphate were similar in both Natpar and placebo groups at the end of study. The rate of subjects meeting the triple efficacy endpoint in the RACE study decreases from 34/45 (75.6%) subjects at Week 52 (95% CI: 60.5, 87.1), until 21/41 (51.2 %) Month 24 (95% CI: 35.1, 67.1). 11 subjects who met the triple efficacy endpoint in the REPLACE study at week 12 no longer met the 3 criteria at week 24. Mean serum calcium levels in the REPLACE study were still slightly decreasing in the active treatment group during the stabilisation phase between week 12 and week 24, and at week 24 after 8 weeks of stable dosing of rhPTH(1-84), despite mean additional calcium supplements being not decreased. Urinary calcium excretion was similar in the 2 treatment groups: -1.99 [± 4.85] mmol/24 hr in the rhPTH(1-84) group and -2.28 [± 4.27] mmol/24 hr in the placebo group (p = 0.439)

5% of subjects who were administered Natpar displayed neither an increase in plasma parathyroid hormone nor an increase in serum [Ca++]. This had previously been found by the applicant in studies CL1-11-007, CL1-11-009 and CL1-11-010. Possible explanations are non-compliance (it is understood that subjects would have been monitored at visit 13, making this seem unlikely; lso, the company reports a high rate of compliance), device failure (the event seems to occur whatever device has been used) or the presence of neutralising antibodies (the company reports that these are not found in recipients).

The number of hypocalcaemia events in the REPLACE study is not reduced in the active treatment group compared to the placebo group. In the rhPTH(1-84) group, 29/84 subjects (34.5%) had symptoms of hypocalcaemia reported as AEs compared to 15/40 subjects (37.5%) in the placebo group, during Week 16 to Week 24. The proposed dosing schedule and the serum calcium fluctuations post injections (which could be expected to be of lower extent if Natpar would be administered in divided doses) is underexplored.

QoL did not reach statistical significant improvement in the REPLACE study, nor in the Mosekilde ITT study. There was a numerical trend for between-group improvements in REPLACE for physical component scores (p = 0.097) and bodily pain (p = 0.105). No trends were observed in Mosekilde ITT.

The investigated population is largely female. Since male subjects appeared to have greater PTH exposure in study CL1-11-010 and since there is an effect of gender factor on the apparent volume of distribution in POP PK, the influence of gender factor on the rhPTH PK characteristics and its clinical relevance is not known. There are important uncertainties regarding the PK, efficacy and safety of rhPTH(1-84) in hypoparathyroidism treatment in patients from other ethnic origins than White, in older patients and in patients with severe renal & hepatic impairment.

The primary endpoint of the efficacy studies does not allow to assess any direct beneficial effect on the kidney comparing hormone replacement therapy to standard treatment. About 40% of subjects in the REPLACE study had evidence of renal impairment, however the effect of renal impairment on clinical outcome (or pharmacokinetics / pharmacodynamics) was not investigated during this study.

Cognitive testing, more specific QoL testing, and, at selected time points, measurements of pre- and post-dose serum calcium and phosphate (2-3 times per day) and a proper calcium clearance measurement was missing in the performed studies.

There is a lack of efficacy data of long-term placebo controlled studies beyond 24 weeks with regard to effect on bone and neutralizing antibodies, and a lack of long-term efficacy data overall allowing for assessment of clinical hard endpoints of hormone replacement therapy compared to standard treatment.

Various deficiencies identified will be addressed in the post-approval studies: alternative dosing, cognitive testing, QoL testing, calcium serum profile measurement, proper calcium clearance measurement, long-term data on clinical hard endpoints and neutralizing antibodies. These will be addressed in a randomised controlled clinical trial, agreed as a specific obligation of the applicant as part of the conditional marketing authorisation, comparing Natpar to Standard of Care and to alternative dosing (based on a preceding PK/PD study), and in a long-term registry study (PARADIGHM) collecting long-term clinical outcomes relevant in hypoparathyroidism (see section 2.7 risk management plan, pharmacovigilance plan, of this report).

Table 18: Effects table – *favourable effects*

Effect	Short Description	Unit	rhPTH (1-84)	PBO	Uncertainties / Strength of evidence	References
Favourable Effects						
Triple endpoint	primary efficacy endpoint: reduction in calcium and active vitamin D metabolite supplements while maintaining calcium serum level within desired range	%	54.8 CI: 43.5-65.7	2.5 CI: 0.1-13.2	p < 0.001 > 18 months post-diagnosed clinical relevance of triple endpoint questioned calcium serum levels still decreasing at week 24 no clinical hard endpoints (soft tissue calcifications, end-organ damage) largely female & white, very few patients ≥ 65 years PTH profile does not mimic the diurnal variation of endogenous parathyroid hormone in healthy subjects	REPLACE, 50/75/100 µg rhPTH(1-84) at week 24 RACE, 25/50/75/100 µg rhPTH(1-84) at month 24, cut-off 3/1/2014 Mosekilde IIT C09-002, single dose rhPTH(1-84)
	Phosphate serum levels, change	mmol/L	-0.16 (±0.25)	-0,01 (±0.22)	p ≤ 0,004, significantly decreased	REPLACE
	Calcium-phosphate product in serum	$mmol^2/L^2$	2.808 (±0.4657)	3.204 (± 0.4429)	p < 0.001, significantly decreased	REPLACE
	Urinary calcium level	mmol/24 hr	-1.99 [± 4.85]	-2.28 [± 4.27]	not significantly different important for renal effects However, hypercalciuria[1]: 53.2% PTH subjects and 39.4% placebo subjects Chronic: 10% of patients hypercalciuria at all visits in open-label long-term trial	REPLACE
BMD	Bone Mineral Density		Decreased	Stable	Relevance, long-term fracture prevalence lacking	REPLACE
BTMs	Bone Turnover Markers		Increased	Stable	clinical long-term relevance questioned	REPLACE
QoL	Quality of Life				No in-between group difference	REPLACE and Mosekilde

3.4. Unfavourable effects

Most of the adverse events reported in response to Natpar (such as paraesthesia, headache, fatigue) appear to be caused by hyper- or hypocalcaemia.

Calcium fluctuations

Serum Ca^{2+} fluctuated up to 0.7mmol/L over 24 hours after each administration of study drug.

Issues of hypo- and hyper-calcaemia and fluctuations in serum calcium have been addressed by advice in the proposed SPC.

Hypercalcaemia

During the titration period of the placebo-controlled REPLACE study, hypercalcaemic events occurred more frequently in the rhPTH(1-84)-treated subjects than in the placebo treated subjects: 12/84 (14.3%) rhPTH subjects (13 events) and 1/40 (2.5%) placebo subjects (1 event) reported hypercalcaemia. The ACSC laboratory values support this trend.

One PTH-treated patient (1.2%) and no placebo treated patient had a TESAE with interruption of the study drug. All hypercalcaemic events resolved. The majority have a duration of 7 days or less. Patient with longer durations or more severe events need short interruption of the study drug regimen or down titration.

During the stable period of the REPLACE Study, during which there was no further uptitration of the PTH dose, 8/84 (9.5%) of rhPTH(1-84)-treated subjects had 8 AEs of hypercalcaemia compared to no placebo subjects. Hypercalcaemic events were primarily mild or moderate and resolved quickly. One subject had a severe event which resulted in an interruption of the rhPTH(1-84) dose and a subsequent dose reduction.

Also in the open-label long-term RACE study seven subjects experienced 11 mild or moderate events of hypercalcaemia that eventually resolved by an interruption of the study drug, a reduction in study drug dosing and/or a change of supplement dosage.

Hypocalcaemia

During the titration period of the placebo controlled REPLACE Study, hypocalcaemic events occurred more frequently in the placebo-treated subjects than in the rhPTH-treated subjects, which can be attributed to the protocol-mandated reduction in oral calcium and active vitamin D.

In the stable period of the REPLACE study, hypocalcaemia rates for both the AE and ACSC criteria were higher in the rhPTH(1-84) subjects than in placebo subjects: 19/84 (22.5%) subjects in the rhPTH(1-84) group experienced an AE of hypocalcaemia compared to 4/40 (10.0%) subjects in the placebo group. The incidence rate per subject per visit of ACSC < 1.88 mmol/L is 10.8%, which means that 1 out of 10 subject visit of patients in the PTH group presented ACSC values < 1.88 mmol/L, compared to 6 out of 100 in the placebo group.

Events occurring in this phase of the study were generally of short duration and were easily managed by adjustment of oral supplements. Four PTH-treated subjects experienced on-treatment hypocalcaemia that required treatment with intravenous calcium gluconate. All of the events were considered to be serious or significant, but resolved by the end of study.

About 15% of rhPTH(1-84)-treated subjects with ACSC < 1.88 mmol/L had hypoparathyroidism symptoms within ±7 days of the reported occurrence.

After discontinuation of study drug, 27/84 (32.1%) rhPTH-treated subjects (31 times) and 4/40 (10.0%) placebo-treated subjects (4 times) experienced hypocalcaemia. In 5 rhPTH-treated subjects and in 1 placebo subject, the post-treatment hypocalcaemia required treatment with IV calcium gluconate. One of the events was not resolved by the end of study.

Hypercalciuria

During the stable period of the REPLACE study, 8/84 (9.5%) rhPTH-treated subjects had an AE of hypercalciuria compared to 2/40 (5.0%) placebo subjects. This effect is also seen in the 24-hour urinary calcium ≥ 7.5 mmol/24 hr. None of the events were serious or led to discontinuation.

The effect on urinary calcium excretion is confirmed in the long-term open-label study. Ten percent of the patients have persistent hypercalciuria.

Vital signs and cardiovascular safety

Shortening of the QT interval is an effect of the change in serum calcium concentration that is consequent to administration of Natpar. Elevations of serum calcium in the efficacy and safety studies in hypoparathyroidism demonstrated the known effects of shortening the QTc interval.

Immunological events

16 of the 87 subjects with hypoparathyroidism who were tested using the validated MSD method and were treated with rhPTH(1-84) developed positive specific antibodies to PTH. None of these subjects had a systemic hypersensitivity reaction or any immunogenicity-related event related to rhPTH(1-84) treatment.

Interactions

The inotropic effects of digoxin are affected by serum calcium levels. Because rhPTH(1-84) transiently increases serum calcium, patients receiving digoxin should use rhPTH(1-84) with caution.

There is a pharmacodynamic interaction with all medications that may potentially have impact on the calcium/phosphate metabolism (thiazides, corticosteroids, etc.)

3.5. Uncertainties and limitations about unfavourable effects

Calcium fluctuations

The long-term effects of wide fluctuation in 24-hr post-dose serum [Ca++], as found in the REPLACE study, are not known. These arise as either recurrent peak calcium concentrations achieved or from the repeated rise and fall of serum calciumwhich could be aggravated by the variability introduced by the pen (see section pen complaints, below).

Hypercalcaemia

Hypercalcaemia has been assessed based on pre-dose serum [Ca^{2+}]. Serum [Ca^{2+}] levels are higher 6-10 hours post dose in the PTH-treated group and are expected to be maximal 10-12 hrs post-dose. The only clinical efficacy and safety study by the company that addressed post-dose hypercalcaemia using laboratory values is Study CL1-11-040 and only at visit 13 of this study. 35/75 subjects are shown to be hypercalcaemic at 6-10 hrs post dose i.e. serum [Ca++] >2.55mmol/L. Three subjects in the rhPTH group had ACSC ≥ 2.98 mmol/L. Post-dose hypercalcaemia has not been adequately investigated by the Applicant.

The occurrence of hypercalcaemia has been observed in monitoring conditions and in 'real live' the incidence could be higher and the outcome more serious.

Hypocalcaemia

Several factors might contribute to the higher incidence of hypocalcaemia in the rhPTH(1-84)-treated group in the stable phase of the REPLACE study. There will be an artificially lower incidence of hypocalcaemia events in the placebo group by protecting them for the study protocol. rhPTH(1-84) subjects were not allowed to increase their rhPTH(1-84) dose to compensate for their loss in oral calcium and active vitamin D supplementation. There was a decrease in 25-OH VitD levels seen in some patients in the rhPTH(1-84) subject group.

The incidence of hypocalcaemia at discontinuation of the study drug is of concern in non-compliant patients, in which serum calcium levels won't be monitored. Studies with diabetic patients have shown frequent omission of injections: 14% in type I diabetics and up to 28% in type 2 diabetics. (Farsaei *et al.*, Prim Care Diabetes. 2014; (4):338-45)

Vital signs and cardiovascular safety

ECGs were obtained only prior to administration of study drug or shortly afterwards. It is understood that serial ECGs (or continuous monitoring) were not obtained. A high frequency of serial 12-lead ECG monitoring will be performed in a planned PK/PD study.

Immunological events

The antibody testing strategy employed by the company (to detect antibodies in recipients that develop against study drug and E. coli protein) is regarded as incomplete.

There is concern that the immunological response of those subjects who are hypoparathyroid for reasons other than post-neck surgery will be different in type and magnitude from those who had hypoparathyroidism post-neck surgery.

Osteosarcoma

Based on experience with parathyroid hormone related products, there is concern that long-term exposure to Natpar may be associated with the development of osteosarcoma. The long-term data available for rhPTH(1-84) are limited. A potential risk of osteosarcoma has been described for the related drug teriparatide (rhPTH(1-34)).

In the FDA adverse event reporting system, 8 cases of osteosarcoma were identified in patients with a history of teriparatide use. Pathology results consistent with a diagnosis of osteosarcoma were provided for 4 of the 8 cases. It is difficult to draw conclusions on the causality based on limited data, but there are at least 4 reported cases on a population estimated to be less than 1 million, i.e. more than the background incidence rate.

An increased risk for osteosarcoma cannot be excluded. Beyond routine pharmacovigilance, this concern is being addressed in the SmPC section 4.3 by contraindicating the use of the product for patient groups with a potentially higher risk to develop an osteosarcoma and by a warning in section 4.4 of the SmPC against the use of the product in young adults.

Long-term effects

For a product with intended chronic use, the number of patients receiving long term treatment is limited, there are 47 patients with hypoparathyroidism treated for 1 year and 41 patients treated for 3 years. The patient cutoff was 30 September 2014.

Long-term data on clinical (efficacy and) safety will be collected in the PARADIGHM registry. Data on clinical hard endpoints should be recorded (bone, soft tissue calcifications and renal function), together with data on hypercalciuria, QoL.

Missing data in subpopulations

There is no clinical data available in pregnant or lactating women, patients with severe renal or severe hepatic insufficiency.

The elderly population is too limited to draw conclusions, only 6 patients were 65 years of age or older, no subjects were 75 years of age or older.

Pen complaints

The Applicant decided, during the procedure, to change its intended pen for commercialisation from the SHL pen to the Haselmeier pen (also referred to as Shire Q-cliq pen in this report). The Ypsomed pen was used in the studies in hypoparathyroidism (Studies CL1-11-040, PAR-C10-007, PAR-C10-008, and PAR-C10-009). The Haselmeier pen is being used in study PAR-C10-008. Also with the Haselmeier pen a substantial variability in delivered dose weights has been observed, but it is to be noted that this pen was used in the commercialisation of the same product in the US (Natpara) and since then, post-marketing data indicated the frequency and nature of postmarketing adverse events (including pen complaints) are similar to what was seen in the clinical development programme. The simulated use validation study PAR-C12-003 shows there is a risk for underdosing with the Haselmeier pen following incorrect use of the pen. Underdosing can be corrected by intake of oral Calcium and active vitamin D supplements following the appearance of symptoms. It is recommended to use also the Haselmeier pen for the studies included as post authorisation measures. As such, the variability will also be taken into account in the further post-approval development of this product.

Table 19: Effects table – *unfavourable effects*

Effect	Short Description	Unit	rhPTH (1-84)	PBO	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Hypercalcaemia – titration period	Number of subjects with TEAE[1]	%	14.3	2.5	1 serious adverse event in PTH group	REPLACE
Hypercalcaemia – stable period	Number of subjects with TEAE[1]	%	9.5	0	Will real life conditions increase the incidence of hypercalcaemia and increase the severity of the outcome? Possible underestimation due to timing of measurement	REPLACE
Hypocalcaemia – stable period	Number of subjects with TEAE[2]	%	22.5	10.0	Long-term effects of wide serum Ca^{2+} fluctuations are not known.	REPLACE
Hypocalcaemia – upon treatment discontinuation	Number of subjects with TEAE[2] (PT of hypocalcaemia and blood calcium decreased)	%	32.1	10.0	5 PTH subjects and 1 placebo subject requiring treatment with IV calcium gluconate High risk in non-compliant – unmonitored – patients	REPLACE
Osteosarcoma					Based on the potential risk for the related product PTH(1-34).	

Notes:

[1]TEAE Hypercalcaemia: PT of hypercalcaemia or blood calcium increased

[2]TEAE Hypocalcaemia: PT of hypocalcaemia or blood calcium decreased

3.6. Benefit-risk assessment and discussion

3.6.1. Importance of favourable and unfavourable effects

There is a clear and substantial effect of Natpar to decrease daily calcium and vitamin D requirements in hypoparathyroidism patients, demonstrated in the pivotal efficacy studies REPLACE and RACE. There is uncertainty, however, about how well this decrease of supplements addresses the actual clinical need in patients that are well-controlled on standard therapy of active vitamin D metabolite and calcium supplementation. At present, based on the primary endpoint, a favourable clinically relevant effect cannot be discerned in the hypoparathyroid population that is well-controlled on standard therapy, but is relevant in a patient population needing large amounts of oral supplements or not adequately controlled with standard therapy (unmet need).

PD studies indicate that there is a mimicking of the natural hormone on several physiological parameters. However, only QD dosing is considered, which raises uncertainty about the possibility of having more effective dosing or dosing regimen of rhPTH(1-84) than was actually utilized in the efficacy studies.

The reduction of calcium-phosphate product in serum is seen as beneficial. Serum phosphate measurements over the course of 24 hours were however not examined. As the PD effect on phosphate only lasted for 8-12 hours out of 24 hours, questions about the dosing schemes are raised. Clinical effect on ectopic calcifications on the longer term is needed to confirm its significance.

Renal calcium excretion is another important parameter, but 24 hour calcium excretion did not show an improvement with Natpar vs. control. Improvement in 24 hour calcium excretion is an important treatment goal because hypoparathyroidism can result in impaired renal function. This will be further investigated in a randomised controlled clinical trial, agreed as a specific obligation of the applicant as part of the conditional marketing authorisation, comparing Natpar to Standard of Care and to alternative dosing (see also section 2.7 risk management plan, pharmacovigilance plan, of this report).

The primary endpoint used in the studies does not allow to assess any direct effect on one of the main target organs: i.e the kidney. These direct effects are assessed as secondary endpoint, but a clear treatment effect has not been demonstrated. Data also failed to show a quality-of-life benefit, which may be due to the number of patients investigated, but is considered to be a very important uncertainty. On the other hand, beneficial effects on bone turnover markers and bone mineral density are demonstrated. Clinical outcomes in terms of bone strength and function are however unknown. No long-term placebo-controlled studies are available that show that the currently proven beneficial effects are maintained long-term or that show improvement on hard clinical endpoints relevant for these patients. Data on clinical hard endpoints, including bone, soft tissue calcifications and renal function, will be captured in a registry study (PARADIGHM) included as a post authorisation commitment.

Administration failure, tachyphylaxis or desensitisation are possible, but will become apparent if an increase in doses of oral supplements is needed. Therefore it is considered acceptable.

The consequences of the wide fluctuations in serum [Ca++] over the course of 24hrs after each administration are uncertain. So far, no long-term effects on the kidney and cardiovascular system are seen. Additional potential kidney effects are important in this population, but it is difficult to assess the impact of this uncertainty on the benefit-risk.
On the short term this can result in extreme hypercalcaemia, which may cause severe symptoms, including palpitations. As the aim is to control serum calcium levels, this is an important safety endpoint. The facts that the post-dose 24-hour calcium has been insufficiently investigated and in real

world conditions the incidence could be higher make the risk for hypercalcaemia even more important. The SmPC contains advice to mitigate this risk.

Hypocalcaemia events are more commonly expected to occur in this population with hypoparathyroidism than hypercalcaemia and can mostly be managed by adjustment of oral supplements. Few SAE or significant events occurred that required treatment with IV calcium gluconate. Severe hypocalcaemia may produce tetany and convulsions. As the aim is to control serum calcium levels, this is an important safety endpoint.

The occurrence of hypocalcaemia upon drug discontinuation is a major concern in non-compliant patients.

Osteosarcoma is very difficult to cure and has very serious consequences, but the risk for occurrence is considered minimal and further reduced by the contra-indications in patients with an increased baseline risk of osteosarcoma.

3.6.2. Balance of benefits and risks

It is clearly recognized that hypoparathyroidism is a state of deficiency of parathyroid hormone in which the current treatments do not replace that hormone or restore its function. The concept of providing the missing hormone as a replacement is a rational therapeutic option.

The design of the pivotal trial shows a clear and substantial effect of rhPTH(1-84) to decrease daily calcium and active vitamin D metabolite requirements in hypoparathyroidism patients.

The significant decrease of the serum calcium-phosphate product suggests potential further benefits.

A reduction of 24-hour urinary calcium has not been shown, although exogenous PTH would be anticipated to have the same effect on urinary calcium as endogenous PTH.

The studies did not show an improvement of quality of life or cognitive data.

In hypoparathyroidism patients that are well-controlled with their standard therapy the effects shown are insufficient to counterbalance the lack of a significant decrease in urine calcium levels compared to standard treatment, the lack of an effect on QoL, the absence of a demonstration of long-term effects on clinical hard endpoints and the observed increase in hyper- and hypocalcaemia, and the remaining uncertainty of the long-term safety and this patient population is therefore not included in the indication of this product.

However, the benefit/risk is considered positive in the restricted patient population that is not adequately controlled on standard conventional therapy. Standard therapy may include oral calcium, active vitamin D, magnesium, thiazide diuretics, and/or phosphate binders. Patients who are not adequately controlled with such standard therapy may be candidates for the treatment with Natpar but should be treated by health care professionals experienced in the management of patients with hypoparathyroidism. A guideline sponsored by the European Society of Endocrinology for the treatment of chronic hypoparathyroidism in adults has been published recently (Bollerslev, J., et al., European Journal of Endocrinology, 2015, G1-G20). Guidelines such as these may serve as guidance for treatment goals under such therapies.

In order to confirm the positive B/R of Natpar administered QD in patients with chronic hypoparathyroidism that are not adequately controlled with standard therapy alone, i.e. the approved indication, the MAH has committed to conduct a randomised controlled trial comparing Natpar to Standard of Care and to alternative dosing (optimal dosing resulting from a PK/PD study), investigating the appropriateness of the dose, cognitive data and QOL, as well as other parameters of calcium-

phosphate metabolism, including calcium serum profile, serum phosphate and renal calcium clearance (specific obligation of the applicant as part of the conditional marketing authorisation, see also section 2.7 risk management and section 4 recommendation).

The risk of post-dose hypercalcaemia should be further investigated, but is currently mitigated by close monitoring as described in the SmPC. Guidance has been added in the SmPC for initiation and titration of Natpar and oral supplements, including that treatment should be stopped or reduced and reassessed if pre-dose serum calcium raises above the ULN (2.55 mmol/L).

3.6.3. Additional considerations on the benefit-risk balance

There is a clear effect of rhPTH(1-84) on the reduction of required calcium and active vitamin D metabolite supplements. The importance of this statistically highly significant effect is however counterbalanced by the fact that the added clinical value is not known for patients who are already stabilized on calcium levels by the supplements that are currently used. Therefore, the use of Natpar is now being limited to a restricted patient population, in which treatment with calcium and vitamin D metabolites is insufficient to obtain stable serum levels of calcium or when uptitration in calcium and vitamin D supplements to obtain adequate calcium plasma levels is hampered by intolerable adverse events which may seriously affect these patients' quality of life.

The overall B/R of Natpar is positive in the restricted population of patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone. Further data will be obtained in a randomised controlled clinical trial, agreed as a specific obligation of the applicant as part of the conditional marketing authorisation, to further substantiate the positive benefit/risk in this patient population to confirm appropriateness of QD dosing versus standard of care and versus alternative dosing regimens using cognitive testing, measures of serum calcium and phosphate post-dose and proper calcium clearance measurements. Post-approval, long-term efficacy and safety of the product will also be investigated in a long-term registry study (PARADIGHM)capturing data on clinical hard endpoints, including bone, soft tissue calcifications and renal function (see also section 2.7 risk management plan, pharmacovigilance plan, of this report).

Conditional marketing authorisation

As comprehensive data referring to the safety and efficacy of the product are not available, a conditional marketing authorisation was proposed by the CHMP during the assessment, after having consulted the applicant.

The product falls within the scope of Commission Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a seriously debilitating disease and is designated as an orphan medicinal product. The currently available standard treatment of hypoparathyroidism with calcium and active vitamin D has major deficiencies as it is not a physiological replacement of the missing endogenous parathyroid hormone and does not allow a complete normalisation of the calcium and phosphate metabolism. Patients insufficiently controlled on such standard therapy experience intolerable adverse events, such as periodic events of muscle cramps, tetanic events and cognitive deficits, which can seriously affect these patients' quality of life. Patients with hypoparathyroidism on standard treatment are also at risk of suffering long term extra osseous calcifications, particularly of the kidney, brain and eye lens.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.

- It is likely that the applicant will be able to provide comprehensive data: The applicant will conduct a 26-week randomised controlled clinical trial to confirm the positive benefit/risk of Natpar in terms of safety and efficacy in the approved patient population in the EU. The study will investigate quality of life, collect cognitive data, and investigate physiological parameters of calcium and phosphate metabolism.The study is intended to confirm the positive B/R and the appropriateness of the QD dosing regimen of Natpar in patients with chronic hypoparathyroidism that are not well controlled on standard therapy alone, which is the currently approved indication. The randomised controlled trial will compare Natpar to Standard of Care and to an alternative dosing scheme. Outcomes will include clinical endpoints like cognitive status, hypoparathyroidism related symptoms and health-related quality of life, which are considered essential, in combination with confirmation of QD dosing. Renal handling of calcium, reduction of hyperphosphataemia and fluctuations of serum calcium will also be measured because they are critical for the adverse events with current standard of care. These clinically important outcome parameters are considered confirmatory vs. the intermediate endpoints captured in the studies submitted in this application. This is a short study in the approved patient population and provision of comprehensive data seems likely.
- Unmet medical needs will be addressed: Natpar is identical to human parathyroid hormone and is therefore a replacement therapy for the lack of endogenous parathyroid hormone in patients with hypoparathyroidism. Currently, no other hormone replacement therapy for hypoparathyroidism is authorised. Currently available standard treatment of hypoparathyroidism with calcium and active vitamin D has major deficiencies as it is not a physiological replacement of the missing endogenous parathyroid hormone and does not allow a complete normalisation of the calcium and phosphate metabolism. Patients insufficiently controlled on such standard therapy experience intolerable adverse events, such as periodic events of muscle cramps, tetanic events and cognitive deficits, which can seriously affect these patients' quality of life. Patients with hypoparathyroidism on standard treatment are also at risk of suffering from long term extra osseous calcifications, particularly of the kidney, brain and eye lens.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required: The demonstrated reduction of doses of active vitamin D metabolites and calcium needed to adjust the calcium and phosphate parameters of patients with hypoparathyroidism together with partial improvement of some parameters of calcium-phosphate metabolism, and the lack of any other approved therapeutic option to replace the missing parathyroid hormone in case of severely debilitating consequences of the disease outweighs the risk inherent in the fact that additional data are still required.

3.7. Conclusions

The overall B/R of Natpar is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Natpar is favourable in the following indication:

Natpar is indicated as adjunctive treatment of adult patients with chronic hypoparathyroidism who

cannot be adequately controlled with standard therapy alone.

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
Non-interventional PASS: In order to collect long-term data on clinical efficacy and safety, the MAH should submit the results of a study based on data deriving from a registry of patients with hypoparathyroidism and who are treated with NATPAR. The MAH should collect data on clinical hard endpoints (bone, soft tissue calcifications and renal function), together with data on hypercalciuria and quality of life. The final clinical study report should be submitted by:	The MAH shall plan to include regular progress reports of the registry in the PSUR. 31 December 2035.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Commission Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to further confirm the efficacy and safety of NATPAR in the treatment of patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone, the MAH should conduct a randomised controlled trial comparing NATPAR to Standard of Care and to alternative dosing according to an agreed protocol. The clinical study report should be submitted by:	30 June 2023

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.