CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125511Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

BLA: 125511	**Submission Date(s):** 10/23/2013
Brand Name (PROPOSED)	NATPARA®(rhPTH[1-84]) for injection
Generic Name	Parathyroid Hormone (1-84) Human Recombinant, NPSP558
Clinical Pharmacology and Pharmacometrics Reviewer	Manoj Khurana, Ph.D.
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OCP Divisions	Divisions of Clinical Pharmacology 2 & Pharmacometrics
OND division	Metabolism and Endocrinology Products
Sponsor	NPS Pharmaceuticals
Submission Type; Code	BLA; Orphan Drug Designation; Standard
Formulation; Strength(s)	Lyophilized powder for reconstitution. 25, 50, 75, and 100 mcg via subcutaneous injection
Proposed Indication	A replacement for endogenous parathyroid hormone for long-term treatment of hypoparathyroidism.

List of Figures and Tables

1 Executive Summary

The sponsor, NPS Pharmaceuticals, Inc. (hereafter NPS) is seeking approval for NATPARA® (Natpara; rhPTH[1-84] for injection). Natpara has been developed under IND 076514 as a replacement for endogenous parathyroid hormone (PTH[1-84]), indicated for the long-term treatment of Hypoparathyroidism. In the year 2007 the Agency granted Orphan Drug Designation to rhPTH[1-84] for the treatment of Hypoparathyroidism.

1.1 Recommendation

The Office of Clinical Pharmacology/Divisions of Clinical Pharmacology 2 (OCP/DCP-2) and Pharmacometrics (OCP/DPM) have reviewed the clinical pharmacology data submitted in support of BLA 125511 for Natpara® (rhPTH[1-84]) and recommend approval of this application. OCP recommends the following regulatory actions:

- **Restrict the indication to "For reduction in the oral calcium and vitamin-D supplement dose in management of patients with hypoparathyroidism"**
- **Labeling should reflect lack of benefit in controlling hypercalciuria.**

1.2 Phase IV Requirement

OCP recommends the following as a post-marketing requirement:

- Conduct a clinical trial to compare an alternative dosing regimen or dosing regimen with a slow release profile to the proposed once daily dosing regimen of Natpara, with an aim to control hypercalciuria while maintaining normocalcemia. Clinical trial simulations (incorporating variability and various titration strategies) should be conducted to substantiate the choice of dose and/or regimen. The details of the trial design including endpoints and dosing regimen should be discussed with the agency.

1.3 Summary of Important Clinical Pharmacology Findings

The Clinical Pharmacology and Pharmacometrics Review of this BLA revealed the following important findings:

Adequacy of the Proposed Dosage Regimen:

According to the proposed label, Natpara is intended for once daily (QD) administration by subcutaneous (SC) injection into alternating thighs. The proposed starting dose is 50 μg QD. Based on calcemic response, Natpara dose can be titrated at approximately 2- to 4-week intervals upward to doses of 75 μg and then 100 μg QD. Downward titration to a minimum dose of 25 μg QD can occur at any time.

When compared to the placebo group receiving standard care (combination of stable oral calcium and vitamin D dose), the proposed dosage regimen for Natpara was adequate in

reducing the calcium and vitamin D dose requirement while maintaining the albumin corrected total serum calcium within the 8-9 mg/dL target, albeit closer to the upper target limit. However, the once daily dosing regimen proposed by the sponsor is not adequate to control hypercalciuria.

It is important to note that in this clinical development program, no dose ranging studies were conducted for dose or dosing regimen selection of Natpara in patients with hypoparathyroidism before proceeding to the registration trial. Furthermore, (PKPD) studies were conducted while the Phase 3 trials were ongoing. A once daily dosing regimen of up to 100 µg dose from the current formulation does not provide optimal systemic exposures to control the excretion of calcium in urine. This is primarily due to short half-life (~ 3 hours) of Natpara which results in PTH concentrations returning to baseline by 10-12 hours, which is also acknowledged by the sponsor. The duration of stimulatory action of Natpara on calcium re-absorption is not long enough to control the excretion of calcium regardless of whether patients achieve normocalcemia.

To evaluate the adequacy of the dosage regimen (QD vs. a more frequent vs. slow release profile by formulation change) in balancing serum calcium and hypercalciuria, we utilized the methodology of a systems pharmacology model based simulations. Considering the complex nature of calcium homeostasis, a systems pharmacology model of calcium homeostasis[1] was adapted and utilized to understand the effect of changing the Natpara dosing regimen or hypothetically altering the formulation release profile on serum and urine calcium profiles. The systems pharmacology model was able to describe the time course of PTH, calcitriol, serum calcium, and 24-hour urinary calcium excretion after placebo or rhPTH treatment from the single and multiple QD dose PKPD trial. This provided confidence that the model could be used to simulate PTH and serum calcium profiles for various 'what if' scenarios, which were not evaluated in the clinical trials. The simulations demonstrate that conceptually, PTH hormone replacement therapy demands for exposures closer to physiological profile. A comparison of the model predicted serum calcium and 24-hour urinary calcium excretion data, obtained by evaluating various scenarios, demonstrate that it is feasible to achieve control on both serum calcium and 24-hour urinary calcium excretion with a lower and more frequent dosage regimen than QD or a QD dosing regimen with a slow release formulation.

As an example, for a typical hypoparathyroidism patient with 50% loss in PTH gland pool and a background daily intake of 2000 mg Ca and 1.5 µg Vitamin-D, the 24 hour urinary calcium without PTH treatment was predicted to be 771 mg/day [18.8 mmol/day > Upper Limit of Normal (ULN) of 300 mg/day or 7.3 mmol/day], which was projected to decrease to 443, 349, and 308 mg/day (10.8, 8.5, and 7.5 mmol/day, respectively; still

[1] A physiologically based mathematical model of integrated calcium homeostasis and bone remodeling. Mark C. Peterson and Matthew M. Riggs. Bone 46 (2010) 49–63.

>ULN) with 100 µg QD, 50 µg BID, and 50 µg QD - slow release profile rhPTH treatments, respectively (Figure 1a).

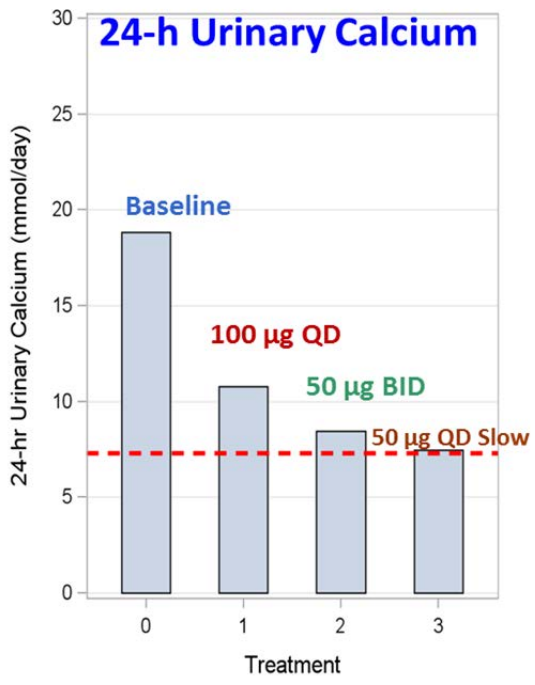
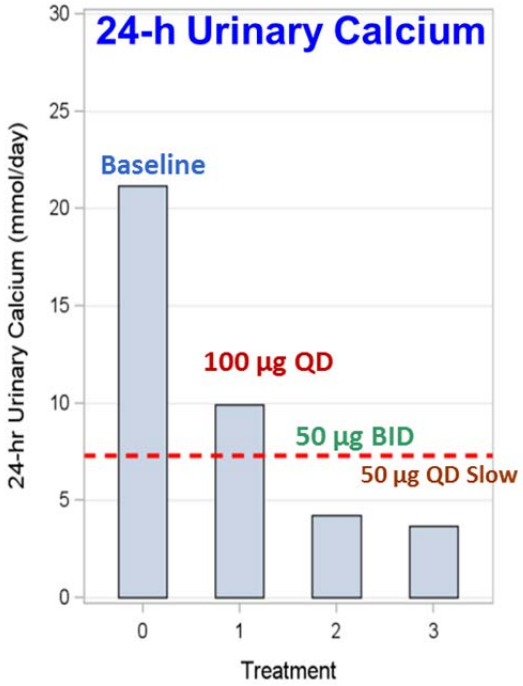
(a) Typical patient with 50% PTH Pool Reduction and taking 2000 mg Ca and 1.5 µg Calcitriol/day	**(b) Typical patient with 99% PTH Pool Reduction and taking 1000 mg Ca and 0.5 µg Calcitriol/day**
	

Figure 1 Model predictions reveal better control on hypercalciuria with more frequent administration or with a slow release PTH profile (at half the dose of QD) (See Figures 31-34 for additional details)

For a different scenario, assuming a typical patient with ~ 99% loss in PTH gland pool and a background daily intake of 1000 mg Ca and 0.5 µg Vitamin-D, the 24 hour urinary calcium without PTH treatment was predicted to be 861 mg/day (21 mmol/day; >ULN), which was projected to decrease to 410 mg, 164 mg, and 121 mg/day (10; >ULN, and 4, and 3 mmol/day; <ULN) with 100 µg QD, 50 µg BID, and 50 µg QD - slow release profile rhPTH treatments, respectively (Figure 1b).

It is worth noting that these model based predictions are for a typical patient without incorporating the PKPD variability and titration scenarios. Further predictions by incorporating variability and titrations will be needed to completely understand the impact of altering the dosing regimen or the formulation release profile on serum and urinary calcium profile. Nevertheless, the simulation results demonstrate that, in principle, the change in dosing regimen or alteration of the formulation release profile will be beneficial in reducing 24-hour urinary calcium while maintaining normocalcemia.

Furthermore, these results are consistent with the PKPD profile of Natpara that demonstrates that a once daily regimen of Natpara does not provide optimum duration of pharmacological action which may have also resulted in lack of benefit in terms of reducing urine calcium in the registration trial. These predictions are also consistent with the published literature, which indicates that more frequent administration[2] or slow SC infusion[3] delivery of rhPTH (1-34), a related but shorter peptide, was able to achieve control on calcium and urinary calcium excretion at roughly half the daily dose.

The FDA clinical pharmacology reviewers believe that adequate understanding of the reasons behind hypercalciuria and possible mitigation of this safety concern is essential for Natpara. Hypercalciuria is one of the primary safety concerns for the conventional therapy that results from using higher than usual calcium and vitamin-D doses. In general population, the relative risk of nephrolithiasis exponentially increases above a urinary calcium excretion of ~200-300 mg/day[4,5]. Furthermore, acknowledging that there are no formal guidelines for the therapy, medical literature recognizes the long term goals for the therapy in patients with hypoparathyroidism as: "*symptom control, a serum albumin-corrected total calcium level at the lower end of the normal range (approximately 8.0 to 8.5 mg per deciliter [2.00 to 2.12 mmol per liter]), a 24-hour urinary calcium level well below 300 mg, and a calcium–phosphate product below 55. Higher products can lead to precipitation of calcium–phosphate salts in soft tissues (e.g., kidney, lens, and basal ganglia)*"[6].

Overall, based on the review of PK/PD profile of Natpara, efficacy/safety results from the registration trial, and simulations conducted using a systems pharmacology model of calcium homeostasis ; it is evident that a lower and more frequent dosing regimen than QD or a QD dosing regimen with a slow release formulation will likely provide a better control on hypercalciuria. Therefore, the dose regimen should be further optimized to address the potential safety concerns associated with hypercalciuria.

Clinical Development Program:

The clinical program of Natpara essentially draws support from two clinical pharmacology studies that evaluated Natpara PK/PD in hypoparathyroidism patients, 3 BA/BE studies, one pivotal, placebo-controlled, phase 3 efficacy and safety trial CL1-11-040, and two uncontrolled studies.

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[2] Karen K. WINER et al. J Clin Endocrinol Metab 83: 3480–3486, 1998.

[3] Karen K. Winer et al. J Clin Endocrinol Metab 97: 391–399, 2012.

[4] Andrew F. Stewart and Arthur E. Broadus. The Regulation of Renal Calcium Excretion: An Approach to Hypercalciuria. Ann. Rev. Med. (1981) 32: 457-73

[5] Phillip M. Hall. Nephrolithiasis: Treatment, causes, and prevention. Cleveland Clinic Journal of Medicine Vol 76(10) 2009.

[6] Dolores Shoback, M.D. Hypoparathyroidism. N Engl J Med. (2008) 359:391-403

Recombinant human parathyroid hormone, rhPTH[1-84], was originally developed by the sponsor as a potential treatment for osteoporosis and was submitted to the Agency as a new drug application (NDA (b) (4)). The application was later withdrawn by the sponsor. A number of clinical pharmacology studies submitted by the sponsor were previously reviewed under this NDA (b) (4)

PKPD Characteristics of Natpara in Patients with Hypoparathyroidism:

Overall, PKPD data from short-term and long-term SC administration of Natpara up to 100 µg dose in the thigh, as assessed by serum and urinary PD markers, demonstrated the following:

- rhPTH[1-84] administration results in a dose-dependent increase in plasma PTH levels, which at peak far exceeded the observed normal physiological range of PTH (10-65 pg/mL). There was also a dose-dependent rise in serum calcium. This rise in serum calcium seems to be orchestrated by PTH effect on urinary calcium excretion (via cAMP activation) and gut absorption (via calcitriol increase).
- Natpara induced reduction in urinary calcium excretion (i.e. stimulatory action of Natpara on calcium re-absorption) is short-lived (10-12 hours) with single or multiple doses of up to 100 µg. This is primarily due to short half-life (~ 3 hours) of Natpara, which results in PTH concentrations returning to baseline by 10-12 hours. The PTH effects on serum calcium are driven by the duration of exposure rather than magnitude as demonstrated by the data. This could also be the artifact of saturation of the renal active transport system by the increased filtered load of calcium, which triggered by the PTH effect on increased serum calcium in the first-half of the 0-24 hour duration.

Natpara Efficacy/Safety Results:

In the registration trial CL1-11-040, based on the pre-specified composite end-point *(Responder was defined as fulfilling the following three criteria: ≥50% reduction in Oral Calcium dose + ≥50% reduction in Oral Vitamin D dose + albumin corrected total serum calcium maintained ≥baseline and ≤ULN)* the treatment difference in responder rate was 51.1 (39.9 – 62.3). Due to serious violations at one site identified during inspection, 10 subjects from that site (4 on placebo and 6 on active) were excluded. The overall conclusions did not change for the primary end point [treatment difference in responder rate was 52.26 (40.57, 63.95) after excluding data from this site] (see Statistical Review by Dr. Jennifer Clark dated 06/26/2014).

When compared to the placebo group receiving standard care (combination of stable oral calcium and vitamin D dose), the proposed dosing regimen for Natpara was adequate in reducing the calcium and vitamin D dose requirement (mean decrease of about 52% and 77%, respectively, from baseline (mean calcium and vitamin D doses of 2160 mg and 0.9

µg, respectively), while maintaining the albumin corrected total serum calcium within the 8-9 mg/dL target, albeit closer to the upper target limit.

In addition, at each visit there was substantial proportion of patients with 24-hour urinary calcium values (>50%) above the upper limit of normal (ULN) with Natpara treatment than placebo. From a safety perspective, mean 24-hour urinary calcium excretion remained above the ULN (300 mg/day) with the rhPTH[1-84] treatment while for placebo (standard of care, Ca/Vit D), mean 24-hour urinary calcium excretion remained within the normal range 50-300 mg/day). Hypercalciuria is one of the primary safety concerns with current standard of care (nephrolithiasis, soft tissue calcification, end organ damage) and thus an expectation from Natpara as a hormone replacement therapy, is that it provides additional benefit in terms of reducing urinary calcium excretion.

General ADME[7]:

Absorption: The absolute bioavailability of SC rh-PTH in the abdomen is 55%. The SC rhPTH pharmacokinetics (PK) is dose-proportional for the dose range of 0.5 to 5 µg/kg. Multiple SC rhPTH daily injections in the thigh do not lead to systemic PTH accumulation. rhPTH Cmax and AUC are 30 – 43% and 16 - 21% lower, respectively, upon SC rhPTH injection in the thigh vs. those in the abdomen.

Distribution: The volume of distribution at steady-state is 3.8 – 7.3 L.

Metabolism and Excretion: The sponsor did not study rhPTH's human metabolism and excretion properties but the previous review captured the extensive published literature on this topic. PTH metabolism is believed to occur non-specific enzymatically in the liver and then followed by excretion in the kidneys. Mean PTH terminal $t_{1/2}$ is 0.43 and ~2 hours after intravenous (IV) and SC rhPTH administration, respectively. Hence, SC rhPTH administration shows flip-flop kinetics, i.e., primarily driven by the rate of absorption from SC injection site.

Removal of PTH (1-84) via the liver and kidney accounts for about 90% of its clearance and PTH (1-84) has a plasma $t_{1/2}$ of 2 – 5 minutes. Liver's Kupffer cells metabolize PTH to different fragments such as the PTH (7-84) fragment. The PTH (7-84) fragment may inhibit PTH (1-84) action. The amino-truncated PTH fragments are predominantly cleared via the kidneys.

[7] Based on Clinical Pharmacology Review of NDA (b) (4) by Drs. S.W. Johnny Lau, Jaya Vaidyantahan, and Sang Chung in DAARTS dated 02/03/2006.

Intrinsic Factors (Body weight, Age, BMI, Gender, Race, and Antibody etc.) Affecting Exposure:

The population pharmacokinetic analysis was conducted for Natpara. The effects of various covariates e.g. disease status, CL_{CR}, body weight, age, BMI, race, and gender on Natpara PK parameters were evaluated in this analysis. The presence of antibody indicated a higher apparent volume of distribution and clearance (higher t1/2) in these subjects, although the low number of subjects (n=4) with specific antibodies did not allow robust statistical comparison among the groups. Overall, the findings do not warrant for any dose-adjustments of Natpara based on any of these covariates.

Renal Impairment: Modest increase in systemic exposure was observed in patients with mild and moderate RI. The data does not warrant a dose-adjustment. There was no information of albumin corrected total calcium. However, albumin-corrected total serum calcium should be closely monitored in patients with hepatic impairment.

Hepatic Impairment: Modest increase in systemic exposure was observed in patients with moderate HI. The data does not warrant a dose-adjustment. There was no information of albumin corrected total calcium. However, albumin-corrected total serum calcium should be closely monitored in patients with renal impairment.

Extrinsic Factors:

Effect of Co-administered Drugs on Natpara (Drug-drug Interactions): One clinical DDI investigation with alendronate indicated that PD (serum calcium) effect was diminished (up to 50%) despite of slightly elevated PTH concentrations upon co-administration with alendronate. Alendronate should not be co-administered with rhPTH[1-84] in patients with hypoparathyroidism.

Bioanalytical Methodology:

For the clinical pharmacology assessments, Natpara concentrations in plasma and urine were determined using an immunoradiometric (IRMA) assay [Scantibodies PTH(1-84) assay]. This was a two-site IRMA using polyclonal antibodies. The capture antibody is immobilized onto plastic beads and binds the C-terminal (39-84) region of PTH(1-84); the second antibody binds the N-terminal (1-6) region of PTH(1-84), which confers specificity for full length PTH(1-84), and is radiolabeled with ^{125}I for detection. The assay method is acceptable and adequately covers the concentration ranges observed in the clinical pharmacology studies. The assays were adequately validated for recovery, range, accuracy, precision, sensitivity, and specificity.

2 Question Based Review

2.1 General Attributes

Recombinant human parathyroid hormone, rhPTH[1-84], was originally developed by the sponsor as a potential treatment for osteoporosis and was submitted to the Agency as a new drug application (NDA [redacted] PREOS®). The application was later withdrawn by the sponsor.

Natpara [rhPTH[1-84] for injection] has been developed under IND 076514 as a replacement for endogenous parathyroid hormone (PTH[1-84]) indicated for the long-term treatment of Hypoparathyroidism. In the year 2007 the Agency granted Orphan Drug Designation to rhPTH[1-84] for the treatment of Hypoparathyroidism.

Another related (only first 34 amino acid) product, 1-34 amino acid N-terminal human parathyroid hormone (NDA 21-318, Forteo®, Eli Lilly and Company) was approved by the Agency in 2002 for treatment of postmenopausal women (PMW) with osteoporosis at 20 µg QD dose.

2.1.1 What are the highlights of chemistry of the therapeutic protein and the formulation as they relate to clinical pharmacology review?

rhPTH[1-84] is manufactured using a strain of *Escherichia coli* modified by recombinant deoxyribonucleic acid (rDNA) technology. Parathyroid hormone has 84 amino acid chain length and a molecular weight of 9425 daltons. The sequence of rhPTH[1-84] is identical to that of native human parathyroid hormone (hPTH) (Figure 2).

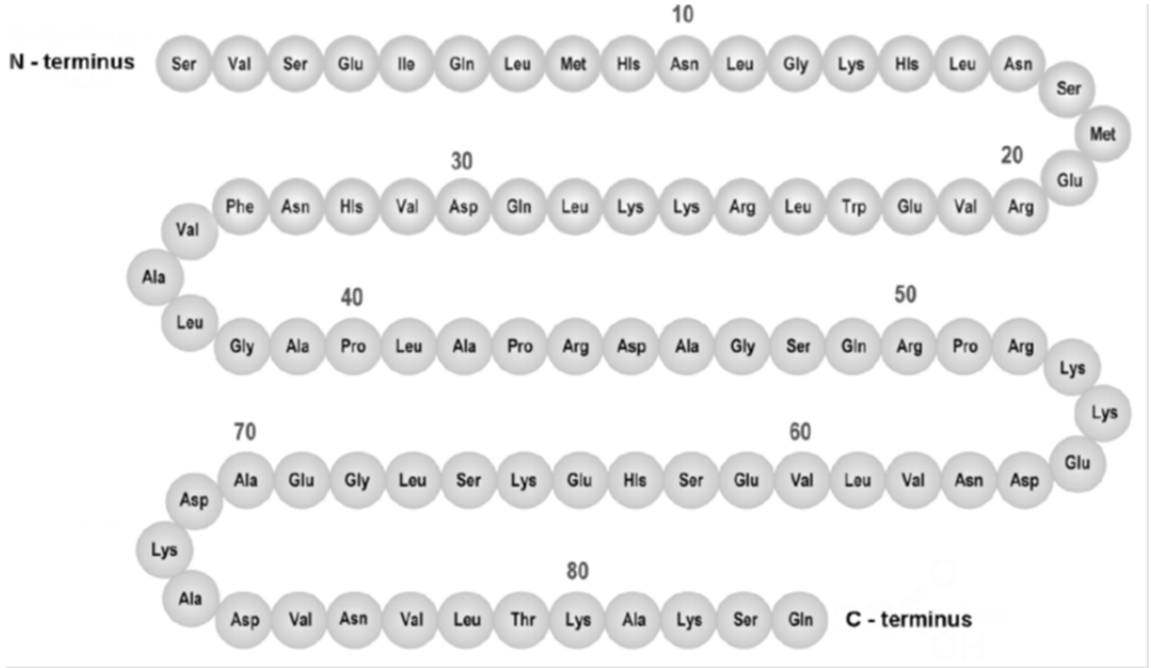


Figure 2 Amino Acid Sequence of Parathyroid Hormone

rhPTH[1-84] Drug Substance is a clear, colorless to light straw-colored liquid composed of rhPTH[1-84] (b) (4)

Natpara (rhPTH[1-84]) for injection is supplied as a multiple dose glass dual-chamber cartridge which is available in four nominal dosage strengths (25, 50, 75, and 100 µg/dose). 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 contained in one chamber, along with 1.13 mL of a sterile 3.2 mg/mL aqueous solution of m-cresol as the reconstitution diluent contained in the other chamber. Reconstitution results in a nominal solution concentration of (b) (4)

The disposable medication cartridge is designed for use with a reusable Natpara Mixing Device for product reconstitution and a reusable Natpara Q-Cliq™ pen injector for subcutaneous drug delivery. During the Natpara development program, Natpara Q-Cliq was also referred to as Natpara Reusable Pen (Haselmeier). The Natpara Q-Cliq is designed to deliver a fixed volumetric dose targeted at 71.4 µL. Using the Natpara Q-Cliq, each medication cartridge delivers 14 doses; each dose contains 25, 50, 75, or 100 mcg of rhPTH[1-84] depending on the product dosage strength.

Two devices, developed specifically for rhPTH[1-84] and containing the same commercial formulation was used in pivotal Phase 3 trial: the Natpara Mixing Device and Natpara Q-Cliq (formerly known as the Haselmeier system). A bioequivalence study was conducted to bridge the use of the Natpara Mixing Device and Natpara Q-Cliq to the pen injector manufactured by Ypsomed which had been used during the Hypoparathyroidism clinical development program. Only the Natpara Mixing Device and Natpara Q-Cliq are proposed for commercial use in this BLA.

2.1.2 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Natpara® (rhPTH[1-84]) for injection is a replacement for endogenous parathyroid hormone, indicated for the long-term treatment of Hypoparathyroidism.

Hypoparathyroidism is a rare endocrine deficiency that is characterized by absent or inappropriately low circulating parathyroid hormone (PTH) levels, in association with hypocalcemia, hyperphosphatemia, and hypercalciuria.

Parathyroid hormone (PTH), which is secreted by the parathyroid glands, has a variety of important physiological functions (Figure 3):

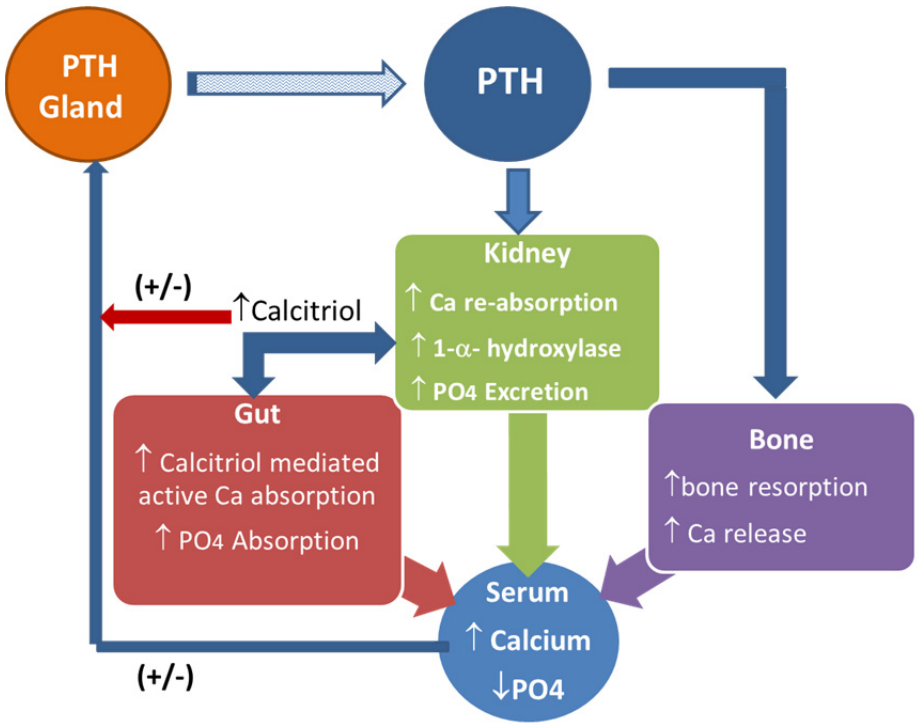


Figure 3 Parathyroid Hormone Mechanism of Action

- PTH regulates bone metabolism and serum levels of calcium and phosphate: when serum calcium is low, the parathyroid glands increase PTH secretion, when the serum calcium is high, the PTH secretion is reduced. 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.
- In kidney, PTH stimulates calcium reabsorption at the proximal tubule and excretion at the distal nephron. The overall effect of increased PTH is reduced urinary calcium excretion. Also in the kidney, PTH stimulates the 25(OH)D_3-1-α-hydroxylase that converts 25(OH) vitamin D into 1,25-dihydroxyvitamin D [1,25$(OH)_2$ vitamin D; calcitriol]. This active metabolite of vitamin D facilitates the absorption of calcium and phosphate from the intestine.
- In bone, PTH regulates the vast skeletal reservoir of calcium which amounts to 99% of total body calcium. This regulation occurs by effects on bone turnover (the process of bone formation and bone resorption known as bone remodeling).
- The net effect of increasing PTH levels is to increase serum calcium, reduce urinary calcium excretion, increase urinary phosphorus excretion, and reduce the serum phosphate level.
- In healthy subjects, the normal negative feedback mechanism is provided by the rise in serum calcium that inhibits PTH secretion, and in both healthy and

hypoparathyroidism patients, the increase in $1,25(OH)_2$ vitamin D that limits the activation by PTH on the 1-α-hydroxylase.

To understand the clinical consequences of Natpara exposure to human biological system, another key aspect is the calcium homeostasis from a mass balance perspective and role of PTH hormone in it. Figure 4 illustrates the day to day mass balance of calcium[8,9] in a typical adult.

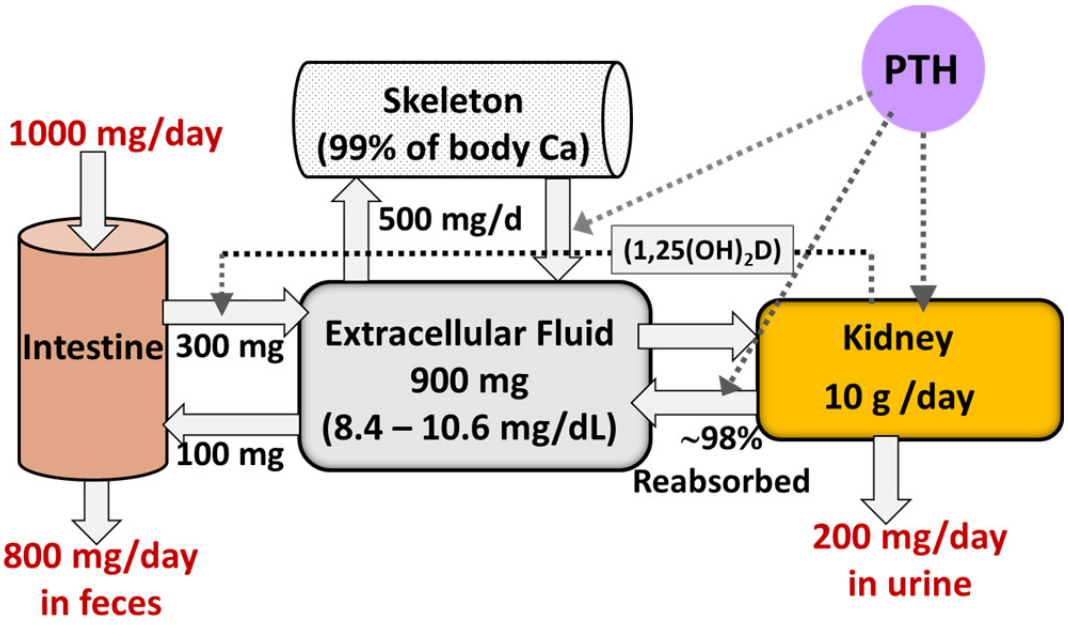


Figure 4 Mass balance of calcium homeostasis illustrated assuming 1000 mg daily oral intake of calcium: Regulation of calcium excretion by parathyroid hormone is one the key factor in defining the net influx and outflow of calcium and plays critical role in maintaining normocalcemia and normocalciuria

Kidney reacts quickly to PTH changes, where PTH exerts a direct action on distal nephron to decrease calcium excretion. In healthy individuals, on a daily basis about 10 g of calcium is filtered and ~90% of filtered calcium load is passively reabsorbed independent of PTH. PTH provides the fine tuning of calcium excretion in urine by controlling the active re-absorption of remaining calcium. This active transport process is biologically designed to be of low capacity and saturates at high filtered load (to prevent hypercalcemia). Considering the high filtered load of calcium, even small changes in fraction absorbed have potential to cause dramatic changes in amount of calcium excreted in urine. For this reason, patients with hypoparathyroidism with calcium in normal range generally excrete 3-fold higher calcium in absence of/low levels of PTH.[9]

[8] Adapted from: G A Clines and T A Guise. Endocrine-Related Cancer. (2005) 12: 549–583 and
[9] Chapter 43. Hormonal Regulation of Calcium Metabolism. H.M. Goodman in Essential Medical Physiology. Edited by – LR Johnson and JH Lyme

Physiological PTH secretion follows a diurnal pattern,[10,11] which is considered to be important in regulation of calcium homeostasis especially, for exerting a tight control on the urinary excretion pattern of calcium (See Figure 5 below).

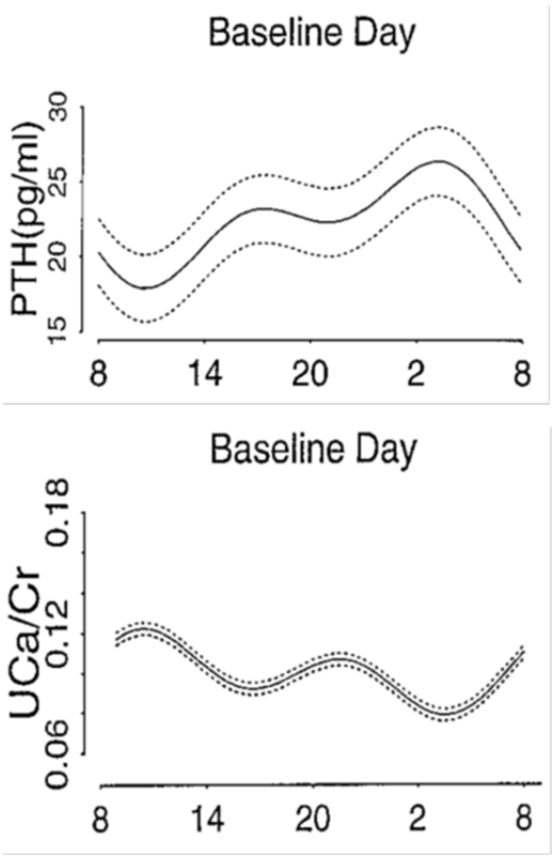
Circadian rhythm in PTH and Serum Calcium profile: Temporal pattern for the serum calcium is a mirror image for the PTH curve[12]	**Circadian rhythm in PTH and Urinary Ca Excretion profiles: Temporal pattern for the UCa/Cr curve is a mirror image of the PTH curve[13]**
Copyright Material	Mean (±2SD) in11 healthy men: 

Figure 5 Circadian rhythm of endogenous PTH, serum and urinary calcium

[10] Circadian rhythm in serum parathyroid hormone concentration in human subjects: correlation with serum calcium, phosphate, albumin, and growth hormone levels. W Jubiz, JM Canterbury, E Reiss, FH Tyler. J Clin Invest. 1972 Aug; 51(8):2040-6.

[11] The parathyroid hormone circadian rhythm is truly endogenous--a general clinical research center study. G el-Hajj Fuleihan , EB Klerman , EN Brown , Y Choe , EM Brown , CA Czeisler. J Clin Endocrinol Metab. 1997 Jan; 82(1):281-6.

[12] Circadian rhythm in serum parathyroid hormone concentration in human subjects: correlation with serum calcium, phosphate, albumin, and growth hormone levels. W Jubiz, JM Canterbury , E Reiss , FH Tyler. J Clin Invest. 1972 Aug; 51(8):2040-6.

[13] The parathyroid hormone circadian rhythm is truly endogenous--a general clinical research center study. G el-Hajj Fuleihan , EB Klerman , EN Brown , Y Choe , EM Brown , CA Czeisler. J Clin Endocrinol Metab. 1997 Jan; 82(1):281-6.

Acute symptoms of hypoparathyroidism are linked mainly to the low serum calcium levels (hypocalcemia) and are generally reversible. The key symptoms associated with hypocalcemia involve mainly the neuromuscular system: numbness, paresthesia, twitching, and tetany. More serious and potentially life-threatening effects of hypocalcemia such as seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm are also recognized in hypoparathyroidism.

2.1.3 What are the proposed dosage(s) and route(s) of administration?

Natpara is intended for once daily (QD) administration by subcutaneous (SC) injection into alternating thighs. The proposed starting dose is 50 μg QD. Based on calcemic response, Natpara dose can be titrated at approximately 2- to 4-week intervals upward to doses of 75 μg and then 100 μg QD. Downward titration to a minimum dose of 25 μg QD can occur at any time.

2.2 General Clinical Pharmacology

2.2.1 What are the features of the clinical pharmacology studies and the efficacy and safety trials used to support dosing or claims?

The Natpara clinical pharmacology and biopharmaceutics program for Hypoparathyroidism is supported by 2 PKPD studies [one conducted by the sponsor (C09-002), one for which the sponsor obtained right of reference (Mosekilde-IIT)], and 3 BA/BE studies (see Table 1). A number of studies submitted by the sponsor were previously submitted and reviewed under NDA (b) (4)

Table 1 Overview of Clinical Pharmacology, Biopharmaceutics, and Efficacy/Safety evaluation for Natpara

Study	Objective
PK and PD evaluation in patients with hypoparathyroidism	
C09-002	Safety and Tolerability, PK/PD following single dose administration of rhPTH[1-84]: escalating doses of 50 and 100 μg SC in the thigh in open label fashion; n=7
Mosekilde IIT PK/PD Sub-study	Randomized, double-blind, placebo-controlled PK, PD and tolerability study rhPTH[1-84]: 100 μg SC in the thigh (n=22), Placebo (n=17) in Hypoparathyroid subjects: PKPD data collected on last day of 6 month treatment
BA (PK and PD) evaluation in healthy	
PAR-C10-005	PK and BE following single dose administration; Randomized, open-label, two-treatment, two-period crossover rhPTH [1-84] 100 μg SC in the thigh using 2 different pen injector
CL1-11-007* [7]	PK, relative BA comparison between thigh and abdomen injection; Randomized, 3-way crossover, open-label rhPTH[1-84]: 100 μg SC, 18 healthy PMW
CL1-11-013* [7]	PK, absolute BA of SC dosing; Randomized, 2-way crossover, open-label rhPTH[1-84]: 100 μg SC in the abdomen and 15-minute IV infusion, 12 PMW

PK and PD evaluation in other populations including Special Populations	
CL1-11-009*[7]	PK, effect of hepatic impairment on BA healthy volunteers, rhPTH [1-84]: 100 µg SC in the abdomen, 24 (12 hepatic impaired and 12 normal hepatic function)
CL1-11-010*[7]	PK, effect of renal impairment on BA, rhPTH [1-84]: 100 µg SC in the abdomen, 32 (16 renal impaired and 16 normal renal function)
Efficacy and Safety Studies in patients with Hypoparathyroidism	
CL1-11-040 (REPLACE)	Placebo-controlled, Varying doses of 50, 75, and 100 µg SC in the thigh of rhPTH [1-84] daily, rh-PTH-90 or Placebo - 44
PAR-C10-007 (RELAY)	Randomized, dose-blinded efficacy and tolerability study evaluating fixed doses of 25 or 50 µg SC in the thigh of rhPTH [1-84] daily n=47 over 8 weeks
PAR-C10-009 (REPEAT)	Uncontrolled, open-label, safety and tolerability study evaluated varying doses of 50, 75, and 100 µg SC in the thigh of rhPTH[1-84] daily, over 24 weeks
Population pharmacokinetic analysis	
NPSP-PCS-101; Pop-PK	Population PK and PK/PD (Correlation analysis) and specific antibody effects on PK; Total 16 Studies: Hypoparathyroidism: n=136; Others: n=1410.

***Studies submitted and reviewed by the Agency under NDA** (b) (4)

2.2.2 Are active moieties and response endpoints measured in pivotal clinical trials and clinical pharmacology studies appropriate to assess PK/PD parameters and exposure response relationships?

PK: Measurement of plasma rh-PTH (Natpara) using an immunoradiometric (IRMA) assay was in clinical pharmacology studies and Phase 3 trials. See Section 3.3 for details**.**

PD: Serum calcium (total and albumin corrected), serum phosphate, cyclic-AMP, and 24-hour urinary calcium excretion were appropriate as PD measurement.

Efficacy: The primary efficacy endpoint in the pivotal Phase 3 trial was a composite of three criteria (see Figure 6 below).

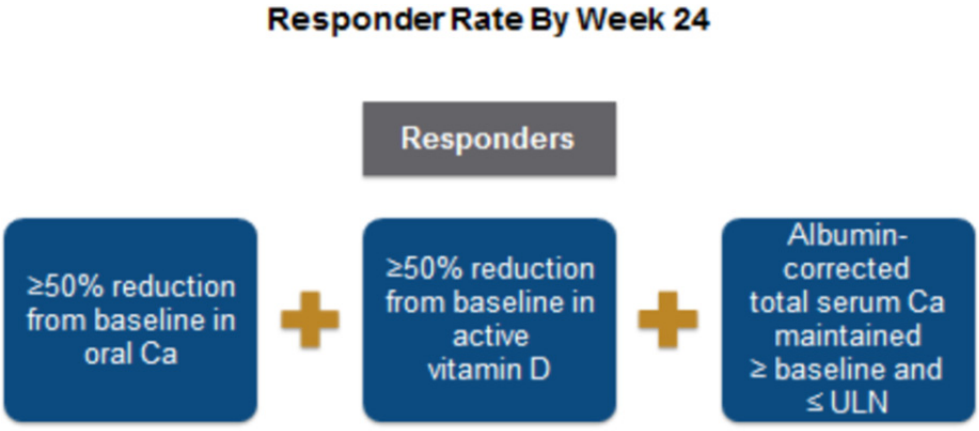


Figure 6 Definition of Responders - Primary end-point in Natpara Phase 3 Trials

2.2.3 What are the ADME characteristics of Natpara after SC administration?

The following relevant information is based on previous clinical pharmacology review[7] of the studies conducted in healthy post-menopausal women:

Absorption: The absolute bioavailability of SC rh-PTH in the abdomen is 55%. The SC rhPTH pharmacokinetics (PK) is dose-proportional for the dose range of 0.5 to 5 μg/kg. Multiple SC rhPTH daily injections in the thigh do not lead to systemic PTH accumulation. rhPTH Cmax and AUC are 30 – 43% and 16 - 21% lower, respectively, upon SC rhPTH injection in the thigh vs. those in the abdomen.

Distribution: The volume of distribution at steady-state is 3.8 – 7.3 L.

Metabolism and Excretion: The sponsor did not study rhPTH's human metabolism and excretion properties but the previous review captured the extensive published literature on this topic. PTH metabolism is believed to occur non-specific enzymatically in the liver and then followed by excretion in the kidneys. Mean rhPTH terminal $t_{1/2}$ is 0.43 and 1.49 hour after intravenous (IV) and SC rhPTH administration, respectively. Hence, SC rhPTH administration shows flip-flop kinetics, i.e., primarily driven by the rate of absorption from SC injection site.

Removal of endogenous PTH (1-84) via the liver and kidney accounts for about 90% of its clearance and the endogenous PTH (1-84) has a plasma $t_{1/2}$ of 2 – 5 minutes[14]. Liver's Kupffer cells metabolize PTH to different fragments such as the PTH (7-84) fragment[15]. The PTH (7-84) fragment may inhibit PTH (1-84) action. The amino-truncated PTH fragments are predominantly cleared via the kidneys.[16]

2.2.4 What are the pharmacokinetic and pharmacodynamic characteristics of Natpara after SC administration hypoparathyroidism patients and how do they relate to the dose?

Overall, PKPD data from short-term and long-term SC administration of Natpara up to 100 μg dose in the thigh, as assessed by serum and urinary PD markers, revealed the following:

- rhPTH[1-84] administration results in a dose-dependent increase in plasma PTH levels, which at peak far exceeded the observed normal physiological range of PTH (10-65 pg/mL). There was also a dose-dependent rise in serum calcium. This rise in serum calcium seems to be orchestrated by PTH effect on urinary calcium excretion (via cAMP activation) and gut absorption (via calcitriol increase).

[14] Marcus. Agents affecting calcification and bone turnover. In: *Goodman and Gilman's- The Pharmacological Basis of Therapeutics,* 10th ed., 2001, pp 1722.
[15] Potts et al. Parathyroid hormone: chemistry, biosynthesis, and mode of action. *Ad Protein Chem.* **35**: 323-96 (1982).
[16] Friedman. Agents affecting mineral ion homeostasis and bone turnover. In: *Goodman and Gilman's The Pharmacological Basis of Therapeutics,* Chapter 61, 11th ed., 2006.

- Natpara induced reduction in urinary calcium excretion (i.e. stimulatory action of Natpara on calcium re-absorption) is short-lived (10-12 hours) with single or multiple doses of up to 100 µg. This is primarily due to short half-life (~ 3 hours) of exogenously administered rhPTH[1-84], which results in PTH concentrations returning to baseline by 10-12 hours. The PTH effects on serum calcium are driven by the duration of exposure rather than magnitude as demonstrated by the data. However, the review team acknowledges that this could also be the artifact of saturation of the renal active transport system by the increased filtered load of calcium, which triggered by the PTH effect on increased serum calcium in the first-half of the 0-24 hour duration.

PK and PD are the fundamental principles behind successful drug therapy. However, they become utmost important when dealing with endocrine hormones, such as PTH, due to multiple physiological mechanisms that get affected by them and integrated nature of these mechanisms within the endocrine system in facilitating the treatment response. The importance of these principles to Natpara is described in the following section below.

Single escalating dose PK/PD in hypoparathyroidism patients (CL09-002): This study captured the short-term effects of rh-PTH administration in hypoparathyroidism patients on the PD markers of interest.

Natpara PK: The mean (±SE) plasma concentration-time profiles of rhPTH[1-84] from single SC doses of 50 and 100 µg are illustrated in Figure 7 below.

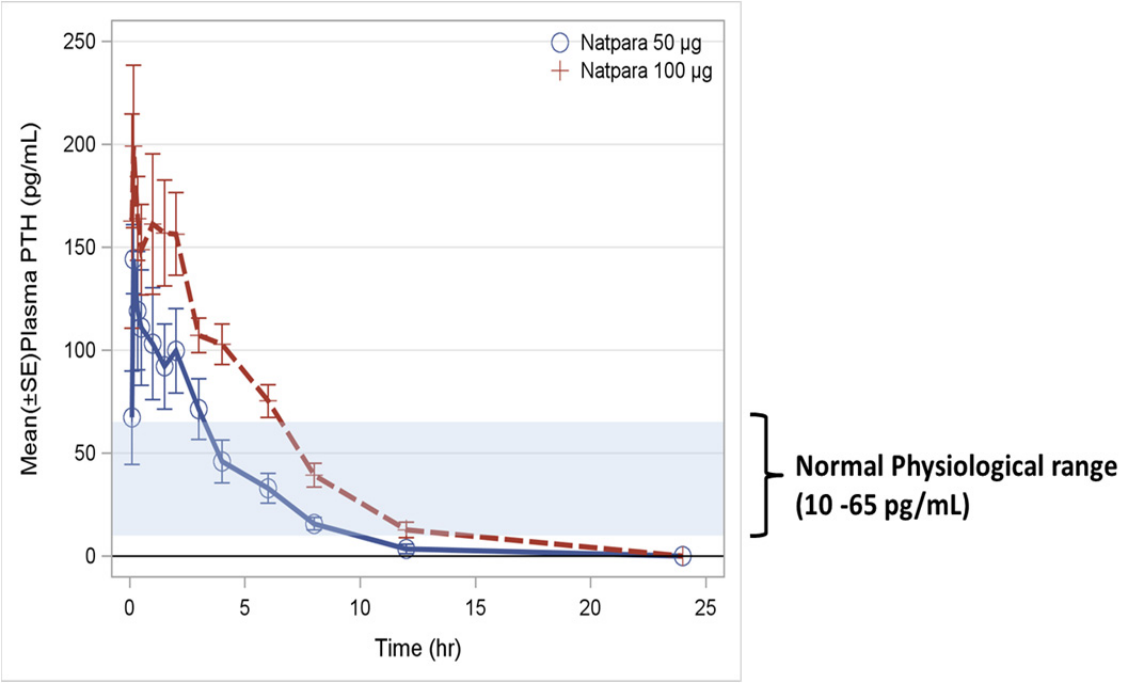


Figure 7 Mean plasma concentration versus time profile of Natpara (single 50 and 100 mcg SC doses in the thigh of same subjects, minimum 7 days washout) [Shaded area represents the normal physiological range of endogenous PTH]

Following the SC injection of Natpara in the thigh of subjects with hypoparathyroidism, plasma rhPTH[1-84] levels increased rapidly resulting in a double peak concentration profile similar to that seen previously: an initial peak occurred at 5 – 30 min and a second usually smaller peak at 1 – 2 hours after the injection. The baseline adjusted Cmax was 174 and 233 pg/mL and the baseline adjusted mean AUC0-last was 572 and 924 pg·hr/mL with the 50 µg and 100 µg doses, respectively (Table 2).

The rhPTH[1-84] concentrations exceeded the normal range of endogenous PTH in healthy (10-65 pg/mL; shown as shaded area in Figure 6) over 50% of the time when rhPTH[1-84] levels were above baseline. Plasma rhPTH[1-84] levels declined from the peak with a $t_{1/2}$ of approximately 3 hours with both doses and returned to pre-dose levels by 12 hours post-dose.

Table 2 Natpara PK parameters after 50 and 100 µg single SC dose in the thigh

PK Parameter	Treatment			
	50 µg NPSP558 SC (N = 6)		100 µg NPSP558 SC (N = 7)	
	Arithmetic Mean	SD	Arithmetic Mean	SD
$AUC_{0\text{-last}}$ (pg·h/mL)	572	123	924	175
$AUC_{0\text{-}\infty}$ (pg·h/mL)	636	122	1016	177
C_{max} (pg/mL)	174	49.7	233	126
$t_{1/2}$ (h)	3.02	1.26	2.83	0.721
CL/F (L/h)	81.0	14.7	102	21.1
V_{ss}/F (L)	357	171	488	172
T_{max} (h)[a]	0.250 (0.167, 2.00)		0.167 (0.0833, 1.50)	

N=Number, SD=Standard Deviation, SC=Subcutaneous

[a] Median (minimum, maximum) is presented for T_{max}

(Source: CSR for C09-002, Table 11-3, Page 63)

Natpara PD: The PD effects are described in the terms of effects of rhPTH[1-84] on serum 25-hydroxyvitamin D-1-hydroxylase activity via measurement of calcitriol [1,25$(OH)_2$D] , urinary cyclic-AMP, urinary calcium excretion and translational aspects on serum calcium.

Mean maximum increase in albumin corrected serum total calcium levels of ~9.5 mg/dL occurred at about 12 hours after the oral administration of calcitriol (0.5-0.75 µg) and calcium intake of ~2500 mg in each period (Figure 8). On rhPTH[1-84] treatment days with similar average calcium intake but without calcitriol, there was a dose-related increase in serum total calcium levels following rhPTH[1-84] injection. The maximum mean calcium levels, which also occurred at 12 hours, were approximately 9.8 mg/dL and 10.0 mg/dL, with the 50 µg and 100 µg doses of rhPTH[1-84], respectively.

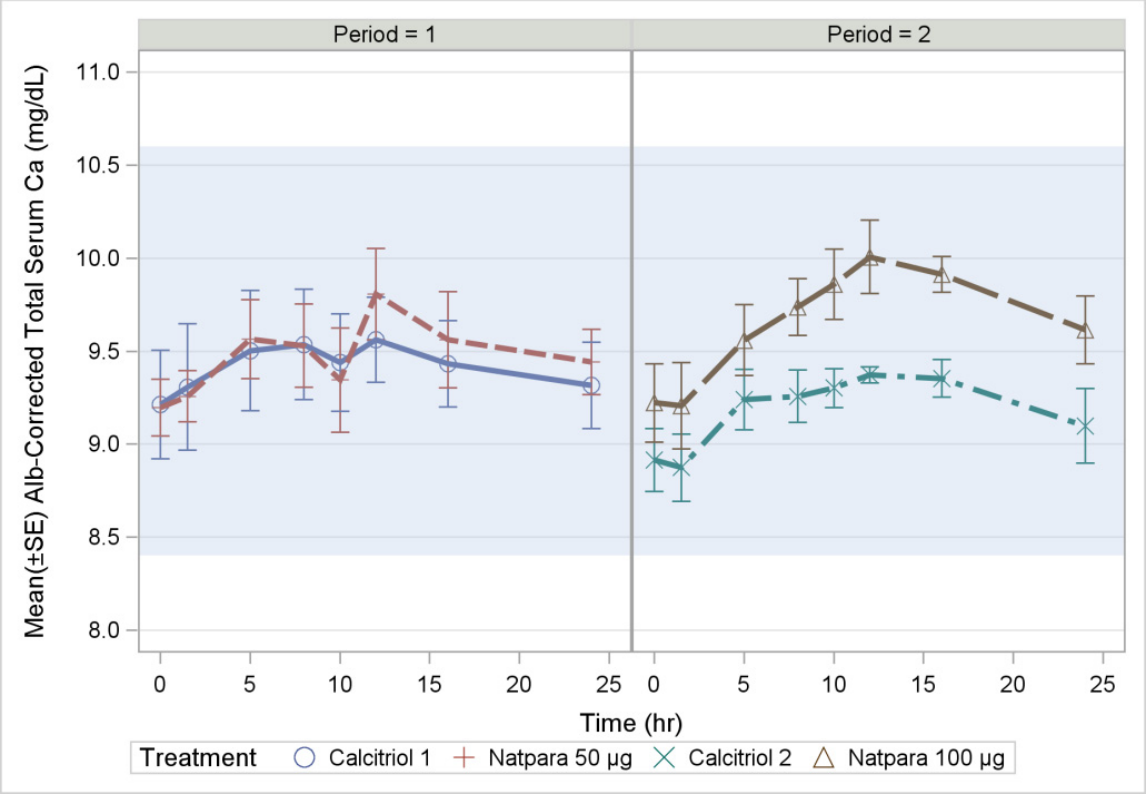


Figure 8 Mean (±SE) serum albumin-corrected total serum calcium versus time profile with calcitriol (left) and rhPTH[1-84] (right) 50 µg and 100 µg SC treatments

Mean increase in baseline-adjusted albumin-corrected serum total calcium levels of approximately 0.4 to 0.5 mg/dL occurred at about 12 hours after the oral administration of calcitriol in each period (Figure 9). There was a dose-related increase in albumin-corrected serum total calcium levels following rhPTH[1-84] injection. The maximum mean increases, which also occurred at 12 hours, were approximately 0.6 mg/dL and 0.8 mg/dL, with the 50 µg and 100 µg doses, respectively.

Mean (SD) net AUC (AUC_{above} – AUC_{below} baseline) for serum Ca increased in dose-dependent manner from 6.07 (6.25) with 50 µg to 11.4 (6.48) (mg*h/dL) with 100 µg dose. On corresponding calcitriol treatment visits (a day prior), the net AUC was 5.21 (5.63) and 7.63 (6.69) mg*h/dL) revealing that rhPTH[1-84] treatment contributed towards the serum calcium rise as calcitriol was not administered. The trend in total serum calcium was similar to the albumin-corrected serum calcium.

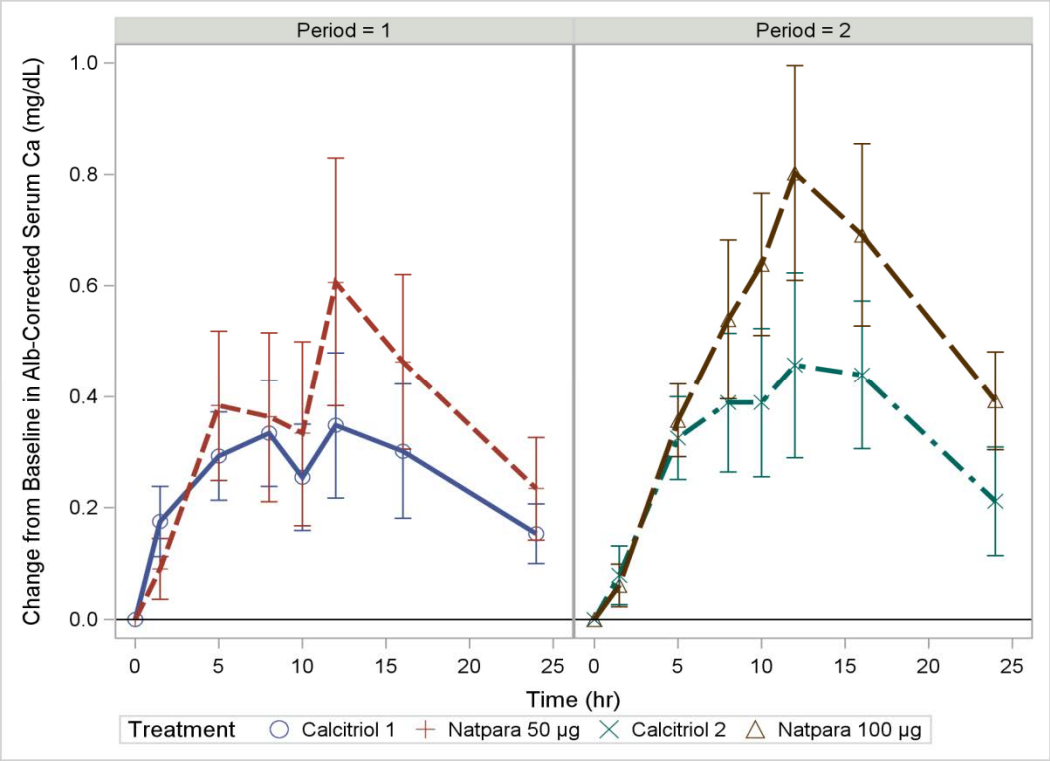


Figure 9 Mean (±SE) serum baseline adjusted albumin-corrected serum calcium versus time profile with calcitriol (left) and rhPTH[1-84] (right) 50 µg and 100 µg SC treatments

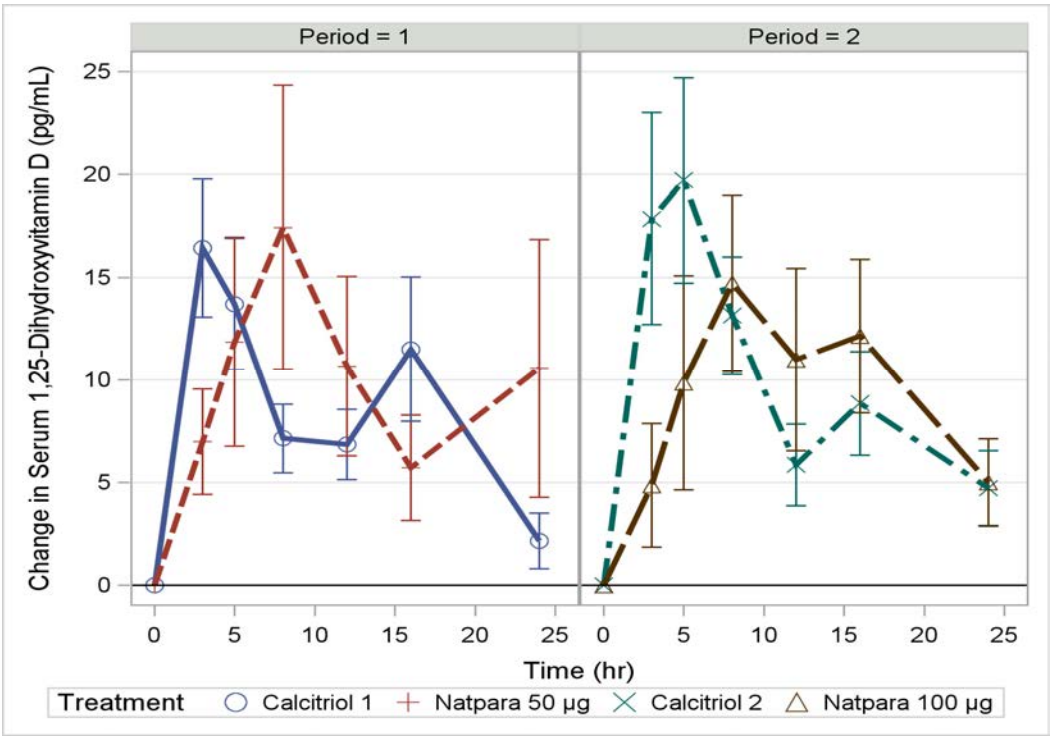


Figure 10 Mean (±SE) serum $1,25(OH)_2D$ versus time profile with calcitriol (left) and rhPTH[1-84] (right) 50 µg and 100 µg SC treatments

The median time of the maximum increase in serum $1,25(OH)_2D$ following oral calcitriol administration was 3 - 5 hours whereas it occurred at 8 – 16 hours following rhPTH[1-84] injection (Figure 10). Sponsor regarded this as a reflection of the time required for PTH to up-regulate 25-hydroxyvitamin D-1-hydroxylase activity. The mean maximum increase (Emax) in serum $1,25(OH)_2D$ following calcitriol administration was 20 pg/mL in both periods, whereas it was 27 pg/mL and 20 pg/mL, respectively, with the 50 μg and 100 μg doses of rhPTH[1-84]. The mean net AUC on baseline-adjusted serum $1,25(OH)_2D$ following calcitriol administration were 182 and 144 pg*h/mL in Period 1 and Period 2, respectively. On average, the AUC tended to be higher following rhPTH[1-84] administration (232 and 199 pg*h/mL, respectively, with the 50 μg and 100 μg doses. However, effect on serum $1,25(OH)_2D$ showed lack of dose-response.

Effect on Urinary PD Markers: Timed urine samples were collected throughout each study day for cyclic AMP, calcium, magnesium, phosphate and creatinine concentrations. The collection intervals were the same on Day -1 and Day 1 within each period. For each sample, the total amount of each analyte excreted was calculated and the amount excreted over the entire 24 hours was determined. The amount of cyclic AMP, calcium, magnesium and phosphate excreted in each collection interval relative to that of creatinine was also determined. In addition, the clearance of calcium, magnesium and phosphate was quantified. Finally, the fractional excretion (FE) of calcium, magnesium and phosphate were determined. FE is defined as clearance of the analyte divided by the glomerular filtration rate (GFR) and thus represents the percentage of each analyte filtered at the glomerulus that is excreted in urine. Creatinine clearance was used as a measure of GFR.

Calcium Excretion: The pattern of fractional excretion of calcium (FE_{Ca}) was very similar following oral calcitriol administration in Period 1 and Period 2. When rhPTH[1-84] was administered there was an immediate decrease in FE_{Ca} to a nadir in the 3 – 6 hour urine sample. When compared with the level observed in the 16 – 24 hour urine sample on Day -1, the magnitude of the maximum decrease in FE_{Ca} was very similar with both the 50 μg (68% decrease) and 100 μg (65% decrease) doses of rhPTH[1-84]. Thereafter, the FE_{Ca} increased progressively towards pre-dose levels. The rate of restoration of predose levels occurred more rapidly with the lower dose of rhPTH[1-84], but FE_{Ca} levels in the 16 – 24 hour sample after rhPTH[1-84] administration were very similar to those in the same urine sample on each Day -1 (Figure 11).

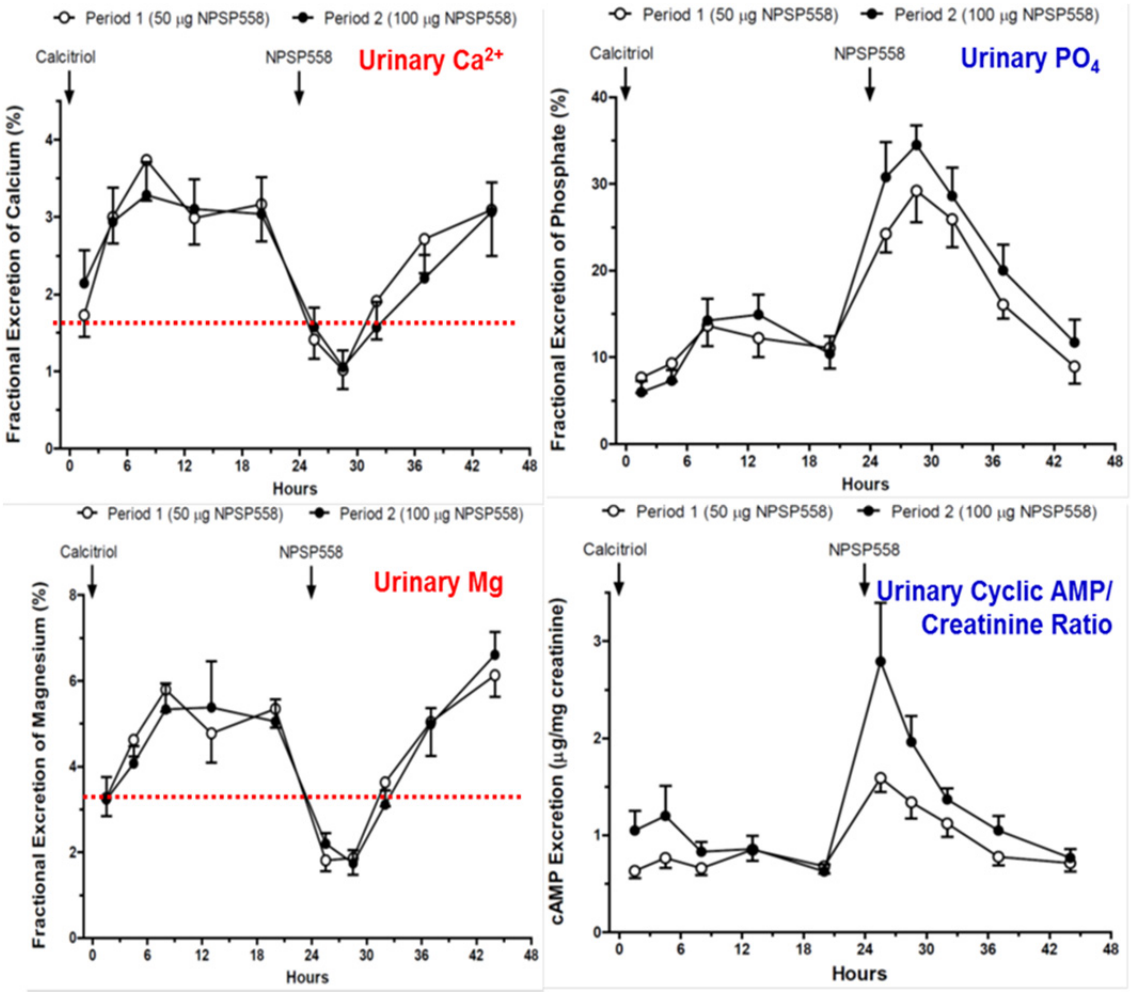


Figure 11 Mean (±SE) fractional excretion of urinary calcium (top left), phosphate (top right), magnesium (bottom left), and cAMP/creatinine ratio (bottom right) versus time profile with calcitriol (left) and rhPTH[1-84] (right) 50 µg (○) and 100 µg (●) SC treatments

(Source: Sponsor's Figure 11-16 on Page 92, 11-17 on Page 94, 11-18 on Page 97, and 11-19 on Page 99 of CSR C09-002)

Total 24-hour urinary calcium excretion was very similar on each Day -1. Treatment with rhPTH[1-84] reduced mean total calcium excretion by 13% (380 to 330 mg) and 23% (373 to 286 mg) with the 50 µg and 100 µg doses, respectively.

To further understand the calcium sparing effect and the role of urinary excretion changes, the urinary excretion data was analyzed using non-compartmental analysis (WinNonlin 6.3 module in Phoenix® 6.3.0.395; Pharsight Corporation) to compute the calcium excretion rate by mid-point of collection interval. Reviewer's analysis of urinary excretion data is presented in Figure 12 below.

Depending upon the reference point, this data reveals different magnitude of effect on urinary calcium excretion. For instance, sponsor compared the data over 0-3 hour interval

with PTH treatment to 16-24 hour interval with the calcitriol treatment that preceded the PTH treatments. In contrast, when all the excretion profiles are overlaid, the excretion rate over 0-3 hour interval does not differ across 4 treatment visits. The 0-3h collection interval data from the calcitriol treatment visits seems to be a reasonable baseline as subjects were on a stable calcium and calcitriol dose in the study. There is a reduction in calcium excretion rate during the 3-6 hour collection, which gradually rises to the magnitude seen with calcitriol treatment by 12 hours. This reveals that the duration of stimulatory action of rhPTH[1-84] on urinary calcium reabsorption is short-lived (10-12 hours for 50 and 100 mcg dose). These effects marry well with the observed PK profile, where, the rhPTH[1-84] concentrations return to baseline by 12 hours.

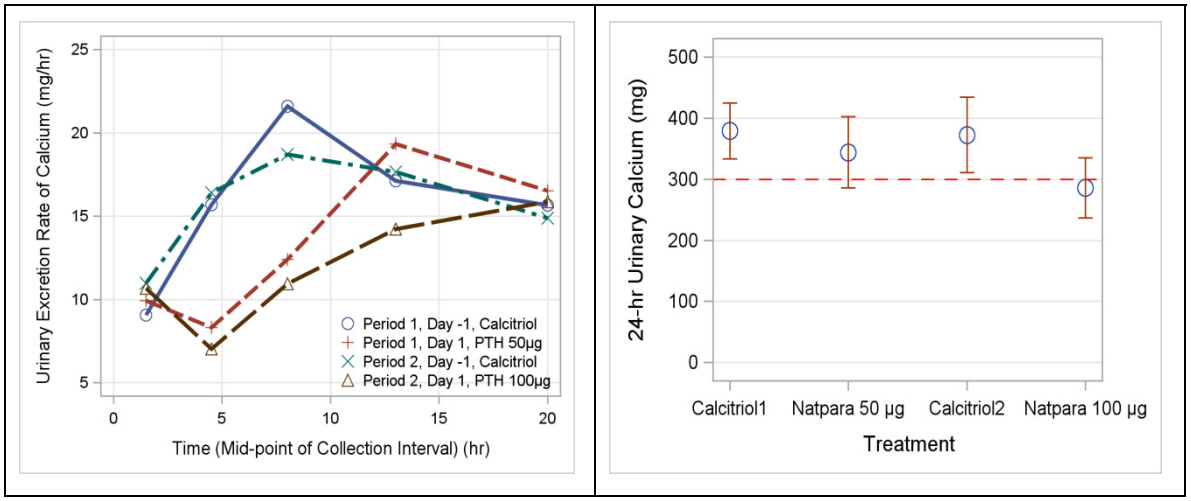


Figure 12 Mean urinary excretion rate of calcium versus time (left) and Mean (±SE) 24-hr urinary calcium excretion (right) by visits specific for calcitriol, and rhPTH[1-84] 50 µg and 100 µg SC treatments

To understand the results of this PKPD study which evaluated the effect of short-term administration of PTH, the scientific insight on intricate complexities in the PTH – cAMP – Calcitriol – Calcium interplay is very important. In his review of the published data, David Fraser captured and explained the intricate complexities in the regulation of 25-hydroxyvitamin D-1-hydroxylase by PTH[17]. According to the *in vitro* and animal studies, PTH has a trophic effect on the 1-hydroxylase activity that is mediated by cAMP and this effect is biologically designed to be saturable at high PTH levels (*in vitro*) and short-lived so as to keep calcitriol production under control. In addition, decreased intracellular calcium can also independently activate the enzyme as well as excess phosphate levels[17].

[17] Regulation of the Metabolism of Vitamin D. DAVID R. FRASER. PHYSIOLOGICAL REVIEWS. Vol. 60, No. 2, April 1980

Lambers et al[18] reviewed the information on coordinated control of renal calcium handling. PTH receptors have been detected throughout the nephron, thus enabling the body to directly control active calcium reabsorption in the kidney via PTH. PTH stimulates renal calcium handling by co-regulating the expression of the calcium transport proteins, TRPV5, calbindin-D28K, and NCX1. However, they acknowledged that regulation of expression of the calcium transport proteins is a relatively slow process, and mentioned that activation of adenylyl cyclase, accumulation of cyclic adenosine 3',5'-monophosphate (cAMP) and subsequent stimulation of protein kinase A is a fast non-genomic response that operates in the kidney and is sufficient for an immediate, short-term PTH-stimulated active calcium reabsorption in the kidney.

Relative to calcitriol administration on each Day -1, administration of the 50 and 100 μg doses of rhPTH[1-84] increased total cyclic AMP excretion by 43% and approximately 59%, respectively, and cyclic AMP-to-creatinine ratio by approximately 38% and 66%, respectively (Figure 11).

Collectively, the results from this PKPD study are in agreement with the scientific arguments and mechanism postulated in the literature from animal experiments. There was a short-term rise in cAMP excretion in urine in first 3 hours, reflective of its increased formation in kidney as an immediate effect of rhPTH[1-84] challenge. This was subsequently translated as a short-term reduction in calcium excretion rate in urine and an increase in calcitriol levels that peaked around 6 hours with both the doses resulting in a rise in serum calcium (peaked at 10-12 hours). The apparent short-lived effect on reduction in urinary excretion of calcium is a combination of several factors. While the non-genomic nature of rhPTH[1-84] response is one factor, the rise in calcium due to PTH stimulated influx of calcium from other sources (e.g. gut and bone) can drive the excretion rate up again in absence of adequate PTH levels to control urinary excretion of calcium. This is evident from the observed data as calcium urinary excretion rate peaked in 12-16 hour collection interval (Figure 12), and in serum peak calcium concentration occurred at 12 hours followed by a steady fall (Figure 9).

Mosekilde-IIT PKPD sub-study in Hypoparathyroidism Patients:

This study captured the effects of rh-PTH administration after long-term use (last day of 100 μg SC QD for 6 months) in hypoparathyroidism patients on the PD markers of interest. This was a 1-day pharmacokinetic/pharmacodynamic (PK/PD) study, conducted on the last day of the 24-week, randomized, double-blind, placebo-controlled, parallel-group IIT in subjects with hypoparathyroidism receiving active or native vitamin D and calcium supplementation. Subjects fasted on the morning of their last study day of the IIT. Following a morning SC injection of 100 μg of rhPTH(1-84) or placebo in the thigh, blood sampling for determination of plasma rhPTH(1-84), total calcium, albumin,

[18] Coordinated control of renal Ca2+ handling.TT Lambers, RJM Bindels, and JGJ Hoenderop. Kidney International (2006) 69, 650–654. Published online 11 January 2006.

magnesium, and phosphate, as well as urine collection for total calcium, magnesium and phosphate were performed at specified intervals from baseline through 24 hours.

Figure 13 below shows mean (±SD) plasma concentration-time profile of endogenous PTH(1-84) and exogenous rhPTH[1-84] after multiple once daily SC administration of placebo or 100 µg rhPTH[1-84] dose in the thigh, respectively (assessed on last day of 24 week treatments).

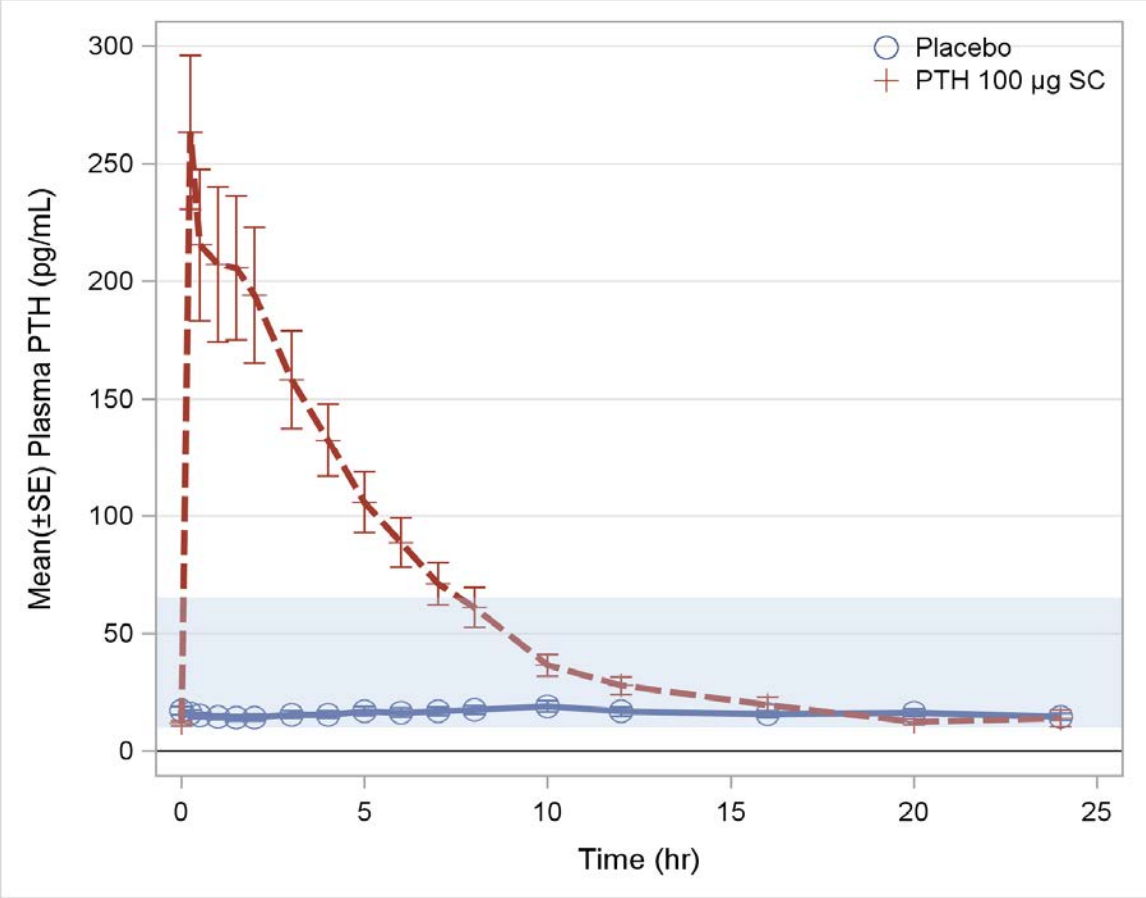


Figure 13 Mean (±SD) plasma concentration-time profile of endogenous PTH(1-84) and exogenous rhPTH[1-84] after multiple once daily SC administration of placebo or 100 µg rhPTH[1-84] dose in the thigh, respectively (assessed on last day of 24 week treatments)

The pharmacokinetics of rhPTH[1-84] was similar after administration of a single 100 µg dose and after multiple doses at steady-state on last day of 6 month treatment with QD regimen. Following SC administration, peak levels reached at approximately 0.4 h after dosing. Plasma concentration-time profiles showed a monophasic decline with mean terminal elimination half-life of 2 hours. Consistent with the half-life, no accumulation was observed at steady-state.

The summary statistics of pharmacokinetic parameters for rhPTH[1-84] are presented in Table 3 and 4 below.

Table 3 Pharmacokinetic parameters of unadjusted rhPTH[1-84] data on last day of multiple once daily SC doses of 100 µg over 24 weeks

PK Parameter	rhPTH(1-84) 100 µg SC (N = 22)
	Geometric mean (CV% geometric mean)
$AUC_{0\text{-last}}$ (pg•h/mL)	1311 (54.3)
C_{max} (pg/mL)	228 (85.4)
	Median (min, max)
t_{max} (h)	0.36 (0.22, 2.08)

(Source: CSR for Mosekilde-IIT Study, Table 11-2, Page 28)

Table 4 Pharmacokinetic parameters of baseline-adjusted rhPTH[1-84] data on last day of multiple once daily SC doses of 100 µg over 24 weeks

PK Parameter	rhPTH(1-84) 100 µg SC (N = 22)
	Geometric mean (CV% geometric mean)
$AUC_{0\text{-last}}$ (pg•h/mL)	950 (93.2)
$AUC_{0\text{-}\infty}$ (pg•h/mL)	1124 (69.6)[a]
C_{max} (pg/mL)	210 (99.6)
$t_{½}$ (h)	2.00 (60.4)[a]
CL/F (L/h)	89.0 (69.6)[a]
V_z/F (L)	256 (130.4)[a]
	Median (min, max)
t_{max} (h)	0.36 (0.22, 2.08)

$AUC_{0\text{-last}}$ = area under the concentration-time curve from 0 to the last measurable concentration; $AUC_{0\text{-}\infty}$ = area under the concentration-time curve from 0 to infinity; C_{max} = maximum plasma concentration; N = number of subjects; SC = subcutaneous; $t_{½}$ = terminal elimination half-life; CL/F = apparent total body clearance; V_z/F = apparent volume of distribution
[a]N=19

(Source: CSR for Mosekilde-IIT Study, Table 11-3, Page 29)

Actual and baseline-adjusted mean Cmax concentrations of rhPTH(1-84) in plasma were relatively similar (228 pg/mL and 210 pg/mL, respectively). Drug exposure (AUC0-last) derived from unadjusted and baseline-adjusted concentrations were 1311 pg*h/mL and 950 pg*h/mL, respectively. Clearance (CL/F), half-life (t1/2), and volume of distribution (Vz/F) of rhPTH(1-84) were 89.0 L/h, 2.00 h, and 256 L, respectively. These parameters were comparable to those observed in C09-002 study. Although, a high degree of variability (CV%>30) was apparent in rhPTH[1-84] CL/F and Vd/F in this study.

rhPTH[1-84] PD: The PD effects are described in the terms of effects of rhPTH[1-84] on serum calcitriol, urinary calcium excretion and translational aspects on serum calcium and summarized in Figure 14.

Mean (95% confidence bands) plasma concentration-time profile of PTH, total vitamin D (calcitriol), serum calcium, 24-hr urinary excretion (median), and serum phosphate after multiple once daily SC administration of placebo (top) or 100 µg rhPTH[1-84] dose in the thigh (assessed on last day of 24 week treatments) are presented in Figure 14 below.

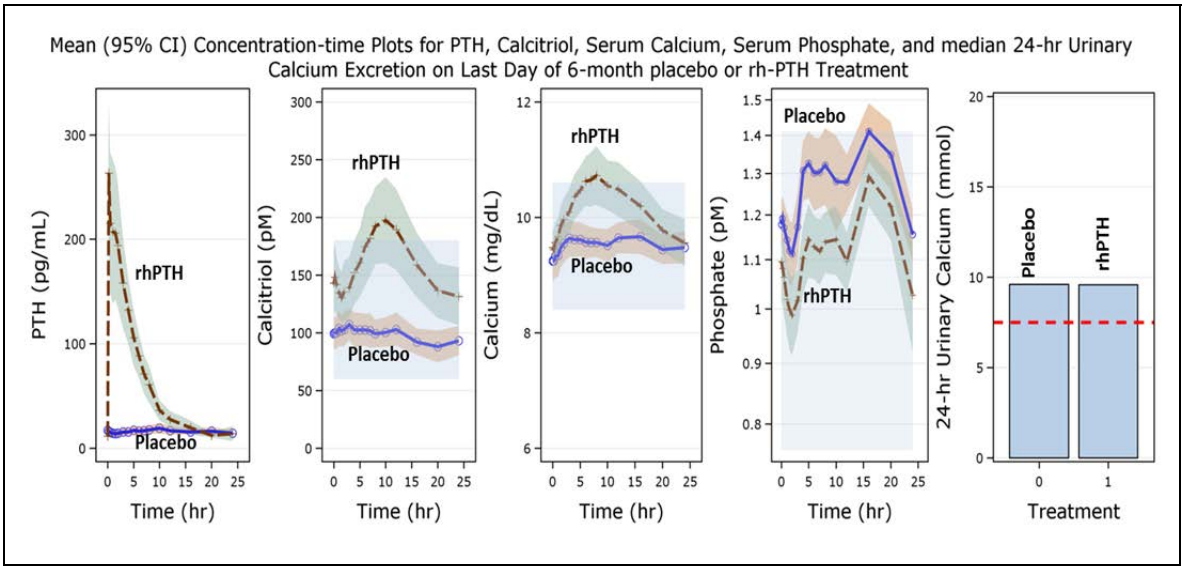


Figure 14 Mean (95% confidence bands) plasma concentration-time profile of PK – endogenous/exogenous PTH) and PD – total vitamin D (calcitriol), serum calcium, 24-hr urinary excretion (median), and serum phosphate after multiple once daily SC administration of placebo (top) or 100 µg rhPTH[1-84] dose in the thigh (assessed on last day of 24 week treatments)

According to the sponsor's conclusions, plasma concentrations of calcium, albumin-corrected calcium, and magnesium reached a peak at approximately 8 hours after rhPTH[1-84] administration then returned to approximately baseline levels at the 24-hour time point. Plasma phosphate concentration decreased in the first 2 hours after rhPTH[1-84] administration, then increased over the 24-hour period before returning to approximately baseline level at 24 hours, probably due to the ingestion of alphacalcidol during the PK/PD assessment day. In subjects receiving placebo, no clear relationship between plasma PTH(1-84) concentrations and PD biomarkers in plasma was evident, probably due to the intermittent ingestion of calcium and alphacalcidol by all placebo-treated subjects.

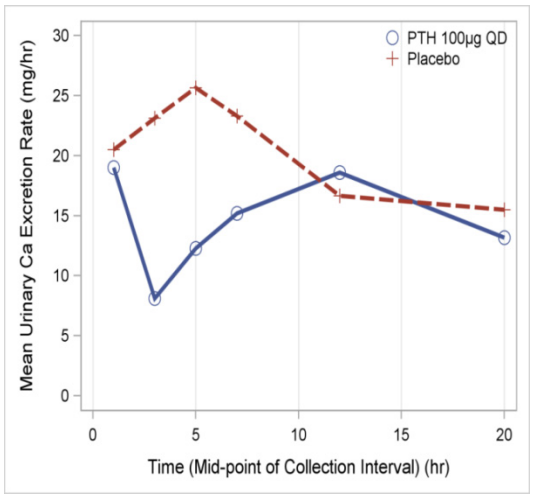
However, data clearly demonstrates that PTH administration on top of background calcium and vitamin D administration attains serum calcium that are towards the high end of upper limit of normal (ULN=2.65 mmol) although, the increase was approximately 0.3 mg/dL from baseline. Since subjects were taking alphacalcidol it is difficult to tease out the trophic effect of PTH on calcitriol, the fact that rhPTH[1-84] treated subjects were at a higher baseline of Vitamin D than placebo subjects shows that rhPTH[1-84] must have exerted the trophic effect on 1-alpha-hydroxylase. Notably, alphacalcidol does not

depend on the renal activation and rather activated by hydroxylation in liver[19]. Although, not mentioned in the study reports, the publication based on this study by Sikjaer et al[20] documented that subjects took variety of Vitamin D preparations, which makes the interpretation of Vitamin D levels difficult.

Effect on Urinary PD Markers: Timed urine samples were collected throughout each study day for calcium, magnesium, phosphate and creatinine concentrations. Sponsor concluded that urinalysis conducted during the study did not produce meaningful results. Resulting figures are skewed due to the inclusion of data for a subject who took large amounts of oral supplementation throughout the analysis period and due to broad collection periods, which ranged from 2 hours to 8 hours.

However, Agency's analysis of urinary calcium excretion data (WinNonlin 6.3 module in Phoenix® 6.3.0.395) reveals that there was a short-term decrease in the excretion rate of calcium from baseline in the 2-4 hours collection interval, which subsequently returned to baseline (similar to placebo value as well) by 10-12 hours. This was very much consistent with the observations from C09-002 study.

Reviewer's analysis of urinary excretion data to compute the calcium excretion rate by mid-point of collection interval is presented in Figure 15 below.



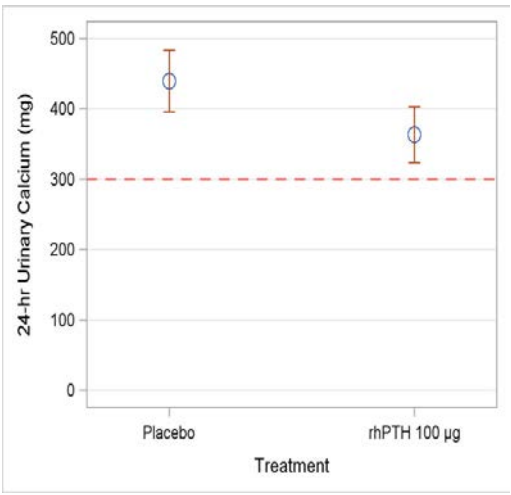


Figure 15 Mean urinary excretion rate of calcium versus time (left) and Mean (±SE) 24-hr urinary calcium excretion (right) on last day of 6 month placebo and rhPTH[1-84] 100 µg QD SC treatments

[19] Superiority of alfacalcidol compared to vitamin D plus calcium in lumbar bone mineral density in postmenopausal osteoporosis. Nuti R, Bianchi G, Brandi ML, Caudarella R, D'Erasmo E, Fiore C, Isaia GC, Luisetto G, Muratore M, Oriente P, Ortolani S. Rheumatol Int. 2006 Mar;26(5):445-53. Epub 2005 Nov 10.
[20] The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, Mosekilde L, and the Hypoparathyroid Study Group. J Bone Miner Res 2011; 26:2358–2370.

Remarkably, the median cumulative amount of calcium excreted in urine (9.8 mmol/day exceeding the ULN of 7.3 mmol/day in males or 6.25mmol/day in females) was similar between placebo and rhPTH[1-84] treatment groups. Since PTH treatment group attained a higher peak serum calcium level than placebo amidst comparable baseline, the similarity in cumulative amount excreted in urinary excretion and urinary excretion rate data shows that the 100 µg QD dose is not able to provide a control on the urinary excretion beyond 10-12 hours over a day's duration.

Overall, PKPD data from short-term and long-term SC administration of rhPTH[1-84] at 100 µg dose in the thigh, as assessed by serum and urinary PD markers, revealed the following:

- On average, the systemic exposure increased in a dose-dependent manner for 50 and 100 µg doses. The peak rhPTH[1-84] concentrations of 174 and 233 pg/mL, respectively were achieved at about 15 minutes post-dose. The concentrations subsequently declined with a half-life of 3 hours, which was about twice longer than reported with abdominal injection.
- rhPTH[1-84] administration results in a dose-dependent increase in serum calcium. This rise in serum calcium seems to be orchestrated by PTH effect on urinary calcium excretion (via cAMP activation) and gut absorption (via calcitriol increase). However, discrete assessments of serum and urinary markers have limited utility versus if sponsor had attempted a mechanistic model to relate these markers.
- Duration of stimulatory action of rhPTH[1-84] on urinary calcium reabsorption is short-lived (~10-12 hours for 50 and 100 mcg dose). This is full concordance with the PK profile, where, the concentrations return to baseline by 12 hours.

2.3 Exposure Response

2.3.1 Does PK/PD and efficacy/safety data support the proposed QD administration of Natpara in Hypoparathyroidism patients?

No, based on the review of PK/PD profile of Natpara, efficacy/safety results from the registration trial, and simulations conducted using a calcium homeostasis model, it is evident that a lower and more frequent dosing regimen than QD will likely provide a better control on hypercalciuria. Additional simulations mimicking a slow release PTH profile indicated that a better control on both serum calcium and excretion of calcium in urine with a QD administration of half the dose in comparison to the PD response from 100 µg dose of the proposed product.

The reviewers believe that adequate understanding of the reasons behind hypercalciuria and possible mitigation of this safety concern is essential for Natpara. Hypercalciuria is one of the primary safety concerns for the conventional therapy that results from using

higher than usual calcium and vitamin-D doses. Therefore, the dose regimen should be further optimized to address the safety concerns for hypercalciuria.

It is important to note that no adequate dose ranging studies were conducted for dose selection of Natpara before proceeding to the registration trial and PKPD studies were conducted while the Phase 3 trials were ongoing. Once daily dosing regimen up to 100 µg do not provide optimal systemic exposures to control the excretion of calcium in urine. This is primarily due to short half-life (~ 3 hours) of Natpara which results in PTH concentrations returning to baseline by 10-12 hours. The duration of stimulatory action of Natpara on calcium re-absorption is not long enough to control the excretion of calcium regardless of whether patients achieve normocalcemia.

Natpara Efficacy in Hypoparathyroidism:

The proposed dosage regimen was adequate in reducing the calcium and vitamin D dose requirement while maintaining the albumin corrected total serum calcium within the 8-9 mg/dL target, albeit closer to the upper target limit. However, mean 24-hour urinary calcium excretion remained above the ULN (300 mg/day in males or 250 mg/day in females) with the rhPTH[1-84] treatment versus placebo (standard care) where, 24-hour urinary calcium excretion remained within the normal range 50-300 mg/day).

The efficacy and safety of rhPTH[1-84] was evaluated in a randomized, double-blind, placebo-controlled, Phase 3 study in adult subjects with hypoparathyroidism.

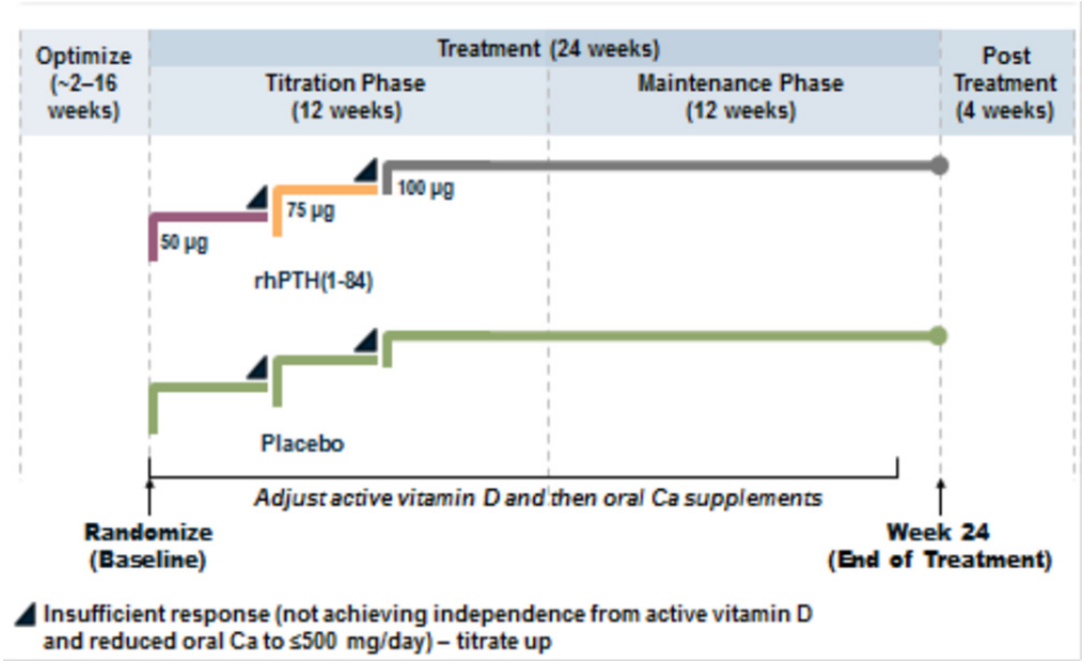


Figure 16 Phase 3 Trial Design (Source: Fig 9-1 in CL1-11-040 CSR page 52)

The key features of the Phase 3 study (Figure 16) were as follows:

- Study consisted of an optimization period of 2 to 16 weeks duration to ensure a common baseline. During the optimization period, supplemental calcium and active vitamin D therapies were standardized and stabilized in terms of dosage form and time of administration to achieve a clinically acceptable, stable, serum albumin-corrected total calcium level prior to randomization.
- Subjects who completed the optimization period and met the following criteria were ready for randomization: (a) daily dose of calcium citrate was 1,000 mg or greater and the daily dose of active vitamin D was 0.25 μg or greater, or the daily alphacalcidol dose was 0.50 μg or greater; (b) 2 successive study visits separated by a 2-week interval were characterized by (i) no more than a 25% change in the daily doses of both calcium citrate and active vitamin D and (ii) the second of 2 serial albumin-corrected total serum calcium concentrations (as reported by the central laboratory) was higher or comparable to the prior albumin-corrected total serum calcium value; (c) the albumin-corrected total serum calcium concentration was between 7.5 mg/dL and the laboratory ULN.
- Optimization was followed by a 24-week treatment period with randomization (2:1) to once daily SC treatment with either rhPTH[1-84] or placebo. The initial dosage was rhPTH[1-84] 50 μg or matching placebo SC QD which could be up-titrated in those subjects with a demonstrably insufficient response, first to 75 μg or matching placebo SC QD and subsequently to 100 μg or matching placebo SC QD. All subjects were subjected to the same titration criteria. Subjects self-administered or underwent administration by a designee of either rhPTH[1-84] or placebo SC QD in the morning on alternate thigh. Active vitamin D was taken in the morning after study drug injection and oral calcium was taken as needed throughout the day.
- Following randomization and study drug initiation with either rhPTH(1-84) 50 μg or placebo, subjects underwent staged reductions in calcium and active vitamin D supplementation (according to a recommended titration algorithm starting with a 50% reduction in active vitamin D) while maintaining or normalizing their predose, albumin-corrected total serum calcium concentrations. Intra-subject dose escalation occurred with either rhPTH[1-84] or placebo in order to maintain the blind.
- Escalation of the rhPTH[1-84] dose to 75 μg SC QD occurred at Week 2, if subjects were taking supplements that could be down-titrated. If supplements could be further reduced, while subjects were on the 75-μg dose of rhPTH[1-84], up-titration to 100 μg SC QD was conducted at Week 4 (Visit 9).
- This final intra-subject dose escalation to an rhPTH[1-84] dose of 100 μg SC QD was performed in accordance with the NPS guideline for titration of supplements. An additional week was allowed at each up-titration interval, if the subject required additional time to clinically adapt to treatment changes, in the opinion of the investigator. No further up-titration of study drug was to occur after Visit 9. The entire titration period was performed in conjunction with frequent measurements of

albumin-corrected total serum calcium and urine calcium. Following titration of study drug and the majority of the titration of study supplements, the final 12 weeks were considered the stable period (maintenance phase).

The mean (SD) albumin corrected serum calcium and 24-hr urinary calcium excretion profile over the trial duration for placebo and rhPTH[1-84] treatments are shown in Figure 17. The primary analysis results are summarized in Table 8 below.

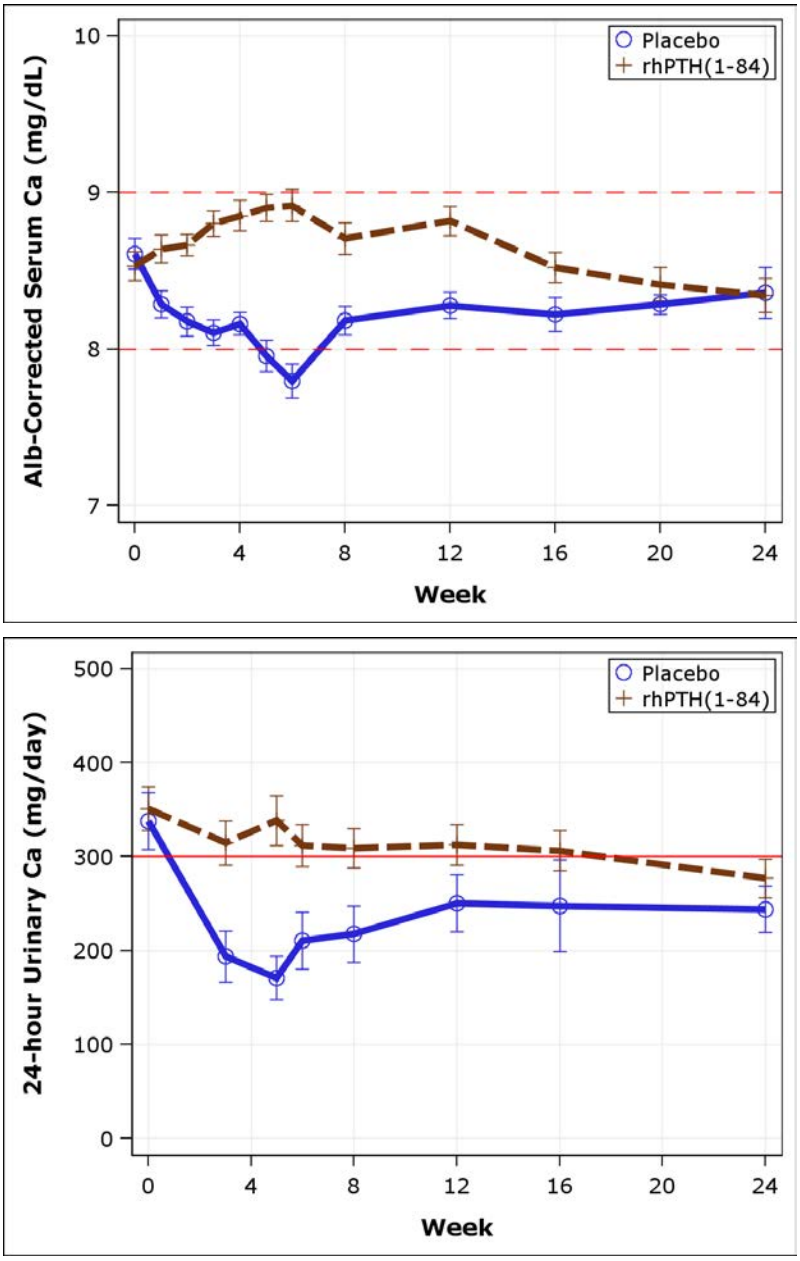
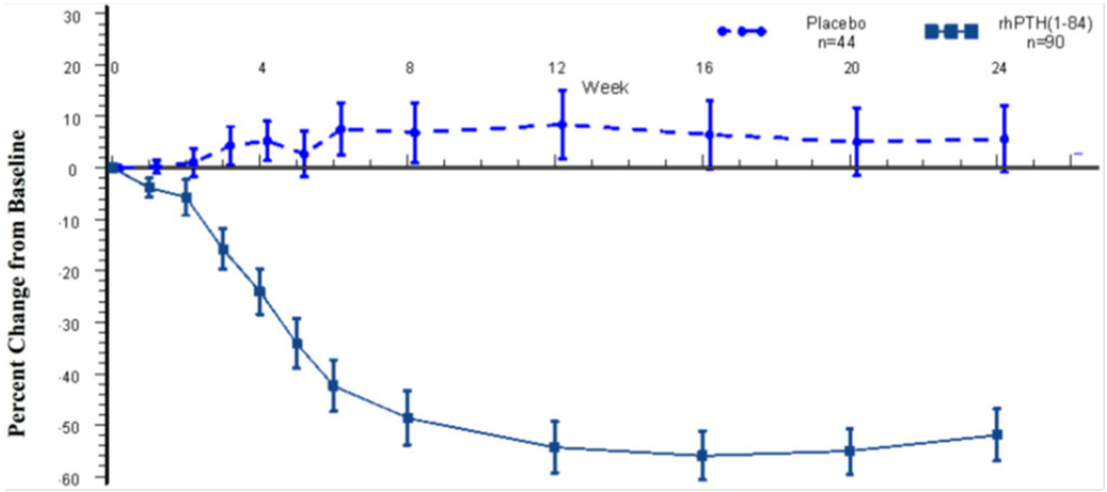


Figure 17 Time-profiles for mean (SD) albumin corrected serum calcium (top) and 24-hr urinary calcium excretion (bottom) with placebo (blue) and rhPTH[1-84] (red) treatments in Phase 3 trial CL1-11-040

On average, albumin corrected total serum calcium was maintained within the pre-specified target (8-9 mg/dL) for both placebo and rhPTH[1-8] treatments (Figure 17) with placebo profile being closer to the lower target limit of 8 mg/dL and closer to the upper target limit of 9 mg/dL for rhPTH[1-84]. This was also reflected in the mean 24-hr urinary calcium profile remaining below and above the upper limit of normal (300 mg/day) for placebo and rhPTH[1-84], respectively over majority of the duration of trial.

This suggests that at least on average, placebo treatment provided closer to the desired profile in terms of balancing normo-calcemia and normo-calciuria.

% Change in daily oral calcium dose (Investigator-prescribed data)



%Change in daily Vitamin D dose (Investigator-prescribed data)

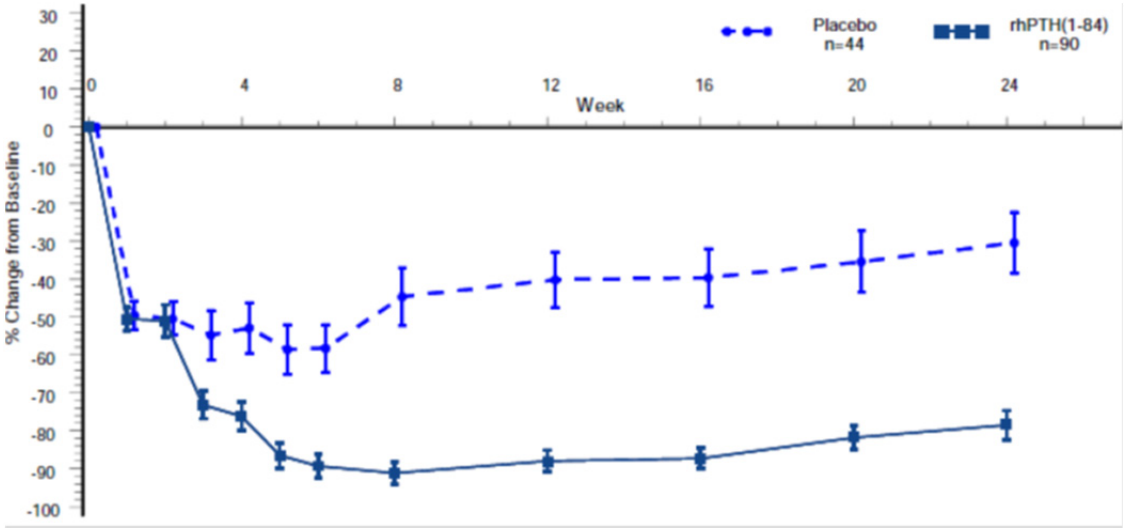


Figure 18 Time-profiles for mean (SE) percent change in calcium (top) and vitamin D (bottom) daily dose by treatment in Phase 3 trial CL1-11-040

[Source: Figures 11-6 and 11-5, CSR for CL1-11-040 Page 129 and 128, respectively]

From a replacement perspective, the observed serum calcium and 24-hr urinary calcium profile resulted from a background reduction in daily calcium and vitamin D dose, which was greater with PTH treatment when compared to placebo (Figure 18).

Based on the pre-specified composite end-point the treatment difference in responder rate was 51.1 (39.9 – 62.3) (see Table 5 below).

Table 5 Statistical analysis result of responder analysis in Phase 3 trial*

	Placebo (N= 44)		rhPTH(1-84) (N= 90)			
Status	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	Treatment Difference (95% CI)[b]	p-value[c]
Responder	1 (2.3)	(0.1, 12.0)	48 (53.3)	(42.5, 63.9)	51.1 (39.9, 62.3)	< 0.001
Non-Responder	43 (97.7)		42 (46.7)			

CI = confidence interval; ITT = intent-to-treat; N, n = number of subjects
Note: Percentages are based on the number of ITT subjects in each treatment arm.
[a] Based on exact 95% CI for the responder rate.
[b] Treatment difference is calculated as responder rate of rhPTH(1-84) minus the responder rate of placebo, the 2-sided asymptotic 95% CI is based on normal approximation.

*Due to major protocol violations in the data from one of the clinical site 1002 were deemed unreliable. Therefore, the efficacy analysis was re-run by the statistical reviewer after excluding the 10 subjects (4 on placebo and 6 on active). The results indicated **3%** and **55%** subjects being responders in the placebo and active treatments, respectively with a treatment difference in responders of **52.26 (40.57 – 63.95)** (*see Table 5 in Statistical Review by Dr. Jennifer Clark in DAARTS dated 06/26/2014*).

Hypercalciuria: Safety aspect of Once Daily regimen

Based on the efficacy/safety results from the registration trial along with the PK/PD information of Natpara (C09-002 and Mosekilde-IIT), Natpara doses up to 100 µg once daily do not provide optimal control on the excretion of calcium in urine in all subjects. PKPD data reveals that this is primarily due to short half-life (~ 3 hours) of Natpara which results in PTH concentrations returning to baseline by 10-12 hours, similar to what sponsor have acknowledged in the clinical pharmacology summary document (Section 2.7.2 Summary of clinical pharmacology studies, pages 41 and 124).

It is important to note that the proposed dosage regimen was adequate in reducing the calcium and vitamin D dose requirement while maintaining the albumin corrected total serum calcium within the 8-9 mg/dL target, albeit closer to the upper target limit.

Excessive calcium excretion in urine is considered as a risk factor for renal damage with the conventional treatment of hypoparathyroidism with high calcium and vitamin D

doses. Pak et al[21] reported quantitative threshold for hypercalciuria that is associated with increased risk of nephrolithiasis in general population. Their analysis showed the optimal cutoff point for urinary calcium excretion was 172 mg/day on a restricted diet (a value that approximates the traditional limit of 200 mg/day) at which, a clear demarcation was seen between urinary calcium excretion of kidney stone formers with absorptive hypercalciuria type I and normal individuals.

On average, with rhPTH[1-84] treatment 24-hr urinary calcium excretion was higher than ULN. The 24-hr urinary calcium excretion data was not available at intermediate visits for all subjects. However, with this caveat in mind the data in hand was further analyzed to assess the extent of hypercalciuria in the Phase 3 trial population to understand this safety aspect of Natpara dosing regimen.

Figures 19 and 20 present the proportion of subjects with hypercalciuria by treatment over duration of trial, and Mean (95% confidence band) 24-hr urinary calcium excretion in normocalciuria and hypercalciuria (24-h Urinary Calcium > 300 mg) situations by treatment over duration of trial, respectively for Phase 3 trial CL1-11-040.

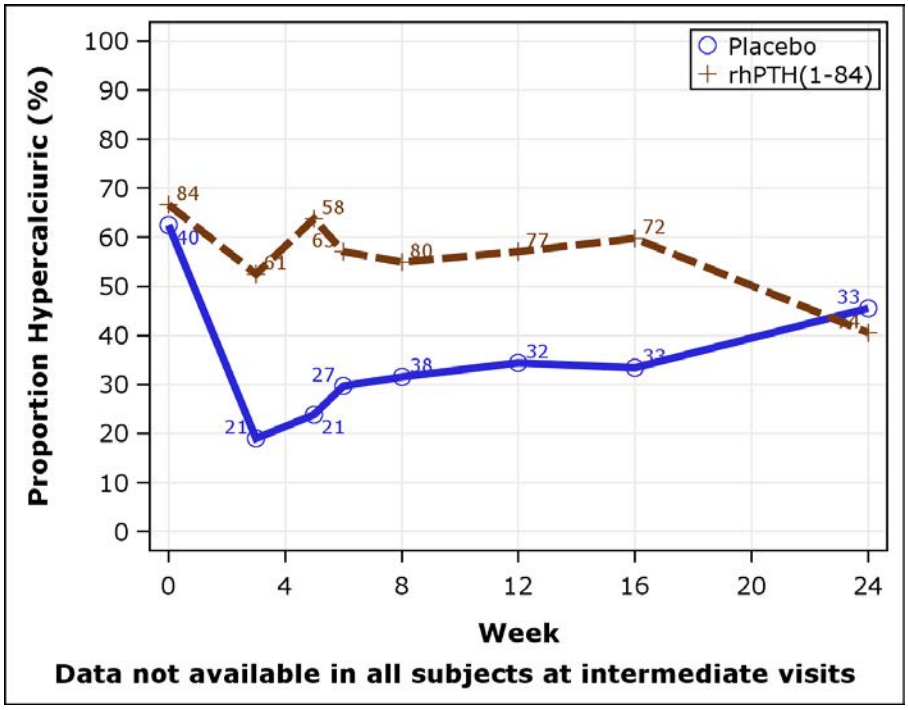


Figure 19 Proportion of subjects with hypercalciuria by treatment over duration of trial (Phase 3 trial CL1-11-040)

Keeping in mind that data was not available at intermediate visits, there was a trend for more hypercalciuria in rh[PTH] treatment than placebo similar to the trend indicated by

[21] Defining hypercalciuria in nephrolithiasis. Charles Y.C. Pak et al. Kidney International (2011) 80, 777–782.

the mean 24-hr urinary calcium excretion profile (Figure 19). Interestingly, the magnitude of 24-hr urinary calcium excretion was similar on average between placebo (standard of care) and rhPTH[1-84] treatments when the values were classified and summarized by normocalciuria or hypercalciuria (Figure 20).

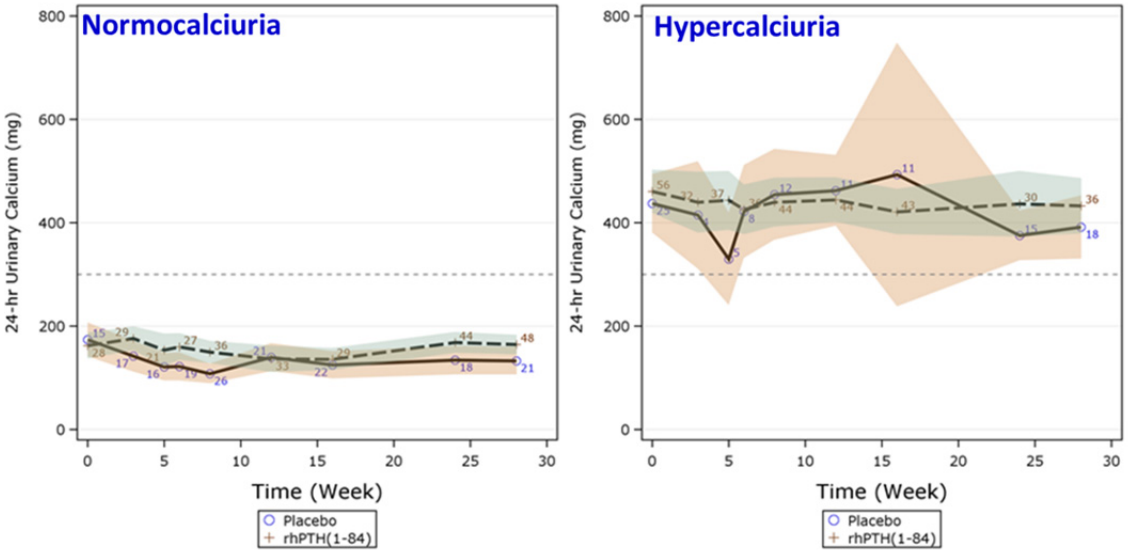


Figure 20 Mean (95% confidence band) 24-hr urinary calcium excretion in normocalciuria and hypercalciuria situations by treatment over duration of trial (Phase 3 trial CL1-11-040)

Further, there was a trend of higher proportion of patients with hypercalciuria at more than two visits than placebo (Figure 21 below).

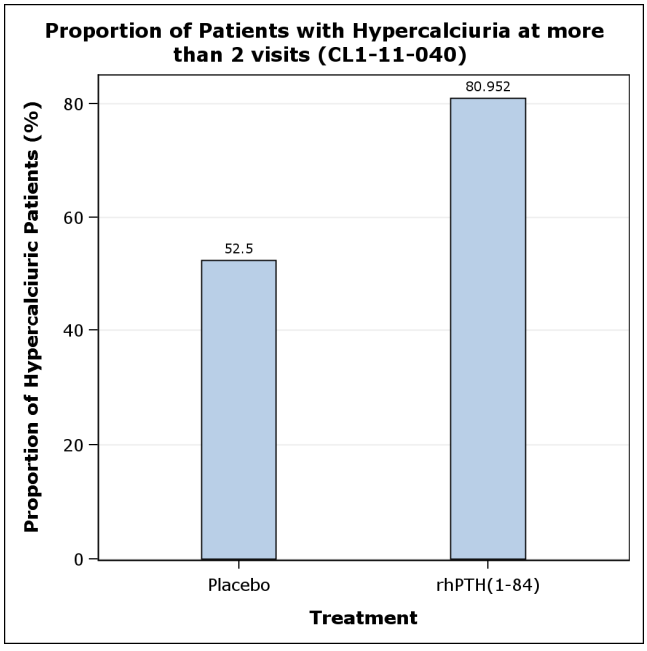


Figure 21 Proportion of patients with hypercalciuria at more than 2 visits by treatment over duration of trial (Phase 3 trial CL1-11-040)

In addition, in the placebo controlled trial the AEs incidences were higher with the rhPTH[1-84] treatment for hypercalcemia, hypocalcemia, vomiting, pain in extremity, anxeity symptom, and palpitations in comparison to placebo (Figure 22).

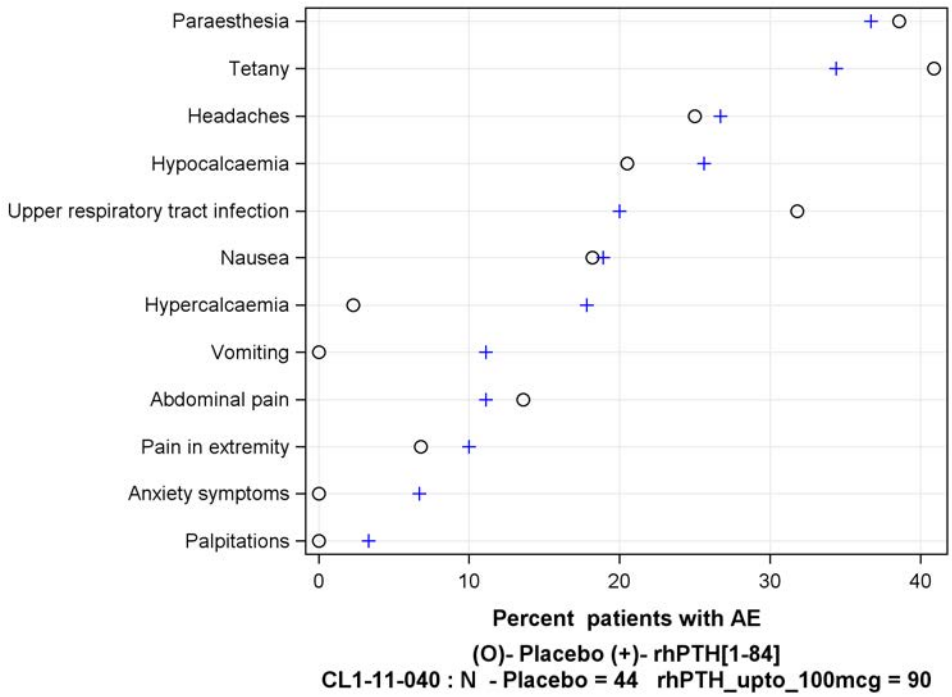


Figure 22 Percent patients with select AEs of interest (Reported in ≥ 5% of Total rhPTH[1-84] treated Subjects) (Phase 3 trial CL1-11-040)

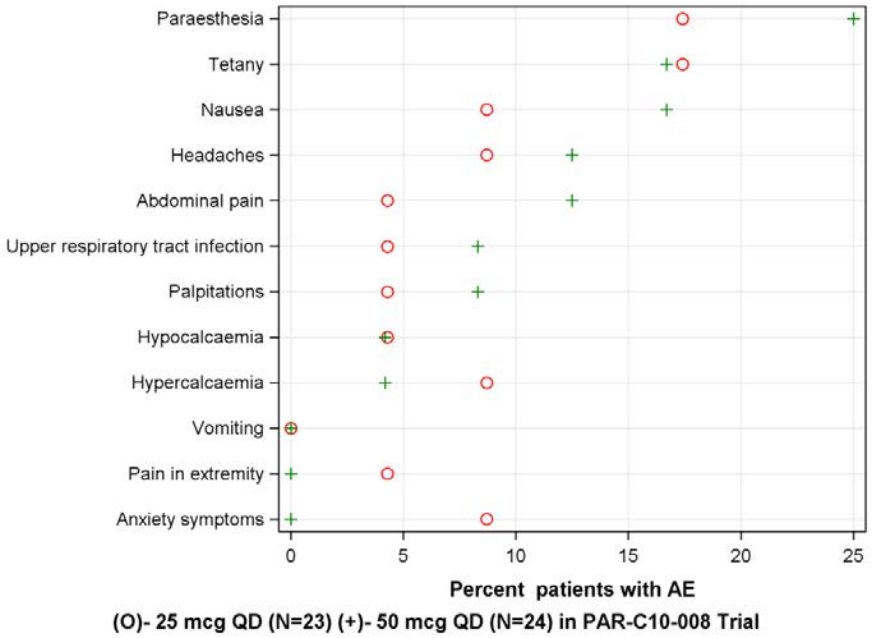


Figure 23 Percent patients with select AEs of interest (Reported in ≥ 5% of Total rhPTH[1-84] treated Subjects) (Phase 3 trial PAR-C10-008)

Although, there was no placebo control and 100 µg data in PAR-C10-008, the dose-dependent increase in some AEs was evident between flat doses of 25 and 50 µg QD (Figure 23).

2.3.2 Is a different dosing regimen required to optimize the safety and efficacy of Natpara specifically with regards to balancing serum calcium and 24-hr urinary excretion?

Yes, the results of modeling and simulation using a systems pharmacology model for calcium homeostasis demonstrate that a more frequent dosing regimen or a slow release profile of rhPTH[1-84] was predicted to achieve better control on hypercalciuria compared to the current QD dosage regimen. The factors that may lead to or could identify a patient's susceptibility to hypercalciuria during Natpara treatment need to be further investigated.

Potentially, one could utilize a mechanistic population PKPD analysis to explain the relationship between PTH PK – urinary calcium/phosphate excretion-serum calcium/phosphate profiles to get an answer to this question. However, considering that PTH has multifaceted effects that are mediated through several pathways, simultaneous modeling of such data, if not impossible, is a daunting task especially considering that there are three variables that changed in the clinical testing of the treatment: PTH, Calcium, and Vitamin D dose. A systems pharmacology approach was used since calcium homeostasis is affected by several factors including PTH, oral calcium, vitamin D, etc. and has several feedback mechanisms. The model was intended to address the following:

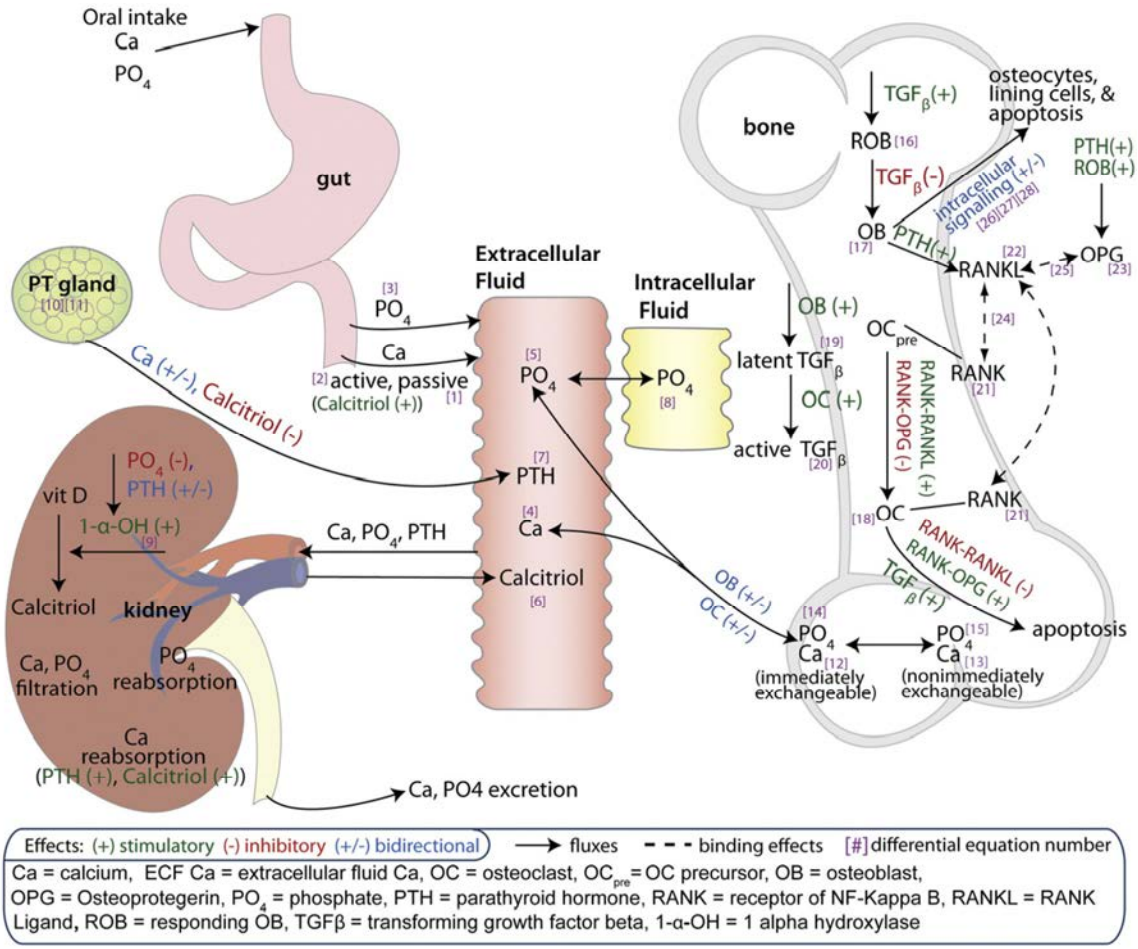
- Adequacy of the model in describing PTH PKPD profile for both serum calcium and urinary calcium excretion simultaneously from a QD regimen.
- Capability of the model in evaluating alternate dosing scenarios (more frequent dosing or a QD dosing with slow release profile) from a PKPD perspective in the disease to determine if more frequent dosing regimen is optimal for controlling calcium excretion in urine. The intention of evaluating a more frequent dosing regimen or a regimen with slow release profile is to provide exposures for Natpara which are close to physiological levels along with adequate exposure coverage during the 24 hour period.

Systems Pharmacology Model:

There are a number of calcium homeostasis models available in the literature including a comprehensive minimal mathematical model of calcium homeostasis by Raposo et al[22]. The fundamental philosophy behind these and subsequent models was pretty much the same as explained in a nice and simple way by *Raposo et al* -"*The model is in itself a*

[22] A Minimal Mathematical Model of Calcium Homeostasis. J. F. Raposo, L. G. Sobrinho, and H. G. Ferreira. J Clin Endocrinol Metab 87: 4330–4340, 2002

product of evidence-based thought, because it is a synthesis from a minimal set of analytical descriptions of quantifiable published processes and data". We adapted a subsequent comprehensive model published by Peterson and Riggs[1] (Implement in R and code available in public domain) for our purpose.



[Figure from: Mark C. Peterson and Matthew M. Riggs. Bone 46 (2010) 49–63]

Figure 24 Calcium homeostasis model[1] has the capability to simulate the hypoparathyroidism disease state (reduction in circulating PTH and corresponding changes in serum calcium and osteoclast osteoblast activity)

This systems pharmacology model (See Figure 24) combined three previously published models to include – (a) calcium homeostasis components, which describe the kinetics of Ca, PO4, and relevant endocrine factors (PTH, calcitriol, 1-α hydroxylase and Parathyroid gland capacity [similar structural aspects as Raposo *et al*[22]], (b) bone resorption and formation kinetics mediated by PTH, the RANK–RANKL–OPG axis, and TGF-β, and (c) osteoblastic intracellular signaling. Of note, the model included the renal calcium handling component [included expressions for both the filtered load and tubular

reabsorption] that was defined having a 'renal threshold' for calcium, above which there is a linear increase in Ca excretion with increased plasma Ca concentration[1].

Our objective was to use a simulation based strategy in getting an answer to the above mentioned questions. We evaluated a modified version (Our modifications included rhPTH[1-84] PK, Vitamin D dose input, and 24-hour urinary excretion output) of Peterson and Riggs's model by simulating and graphical comparison to the external data available from this BLA submission (data that was not used for development of this model). A fit-for-purpose model validation strategy was adapted (Figure 25). Upon gaining confidence in the model we simulated various 'what if' scenarios and compared it with the QD PKPD profile.

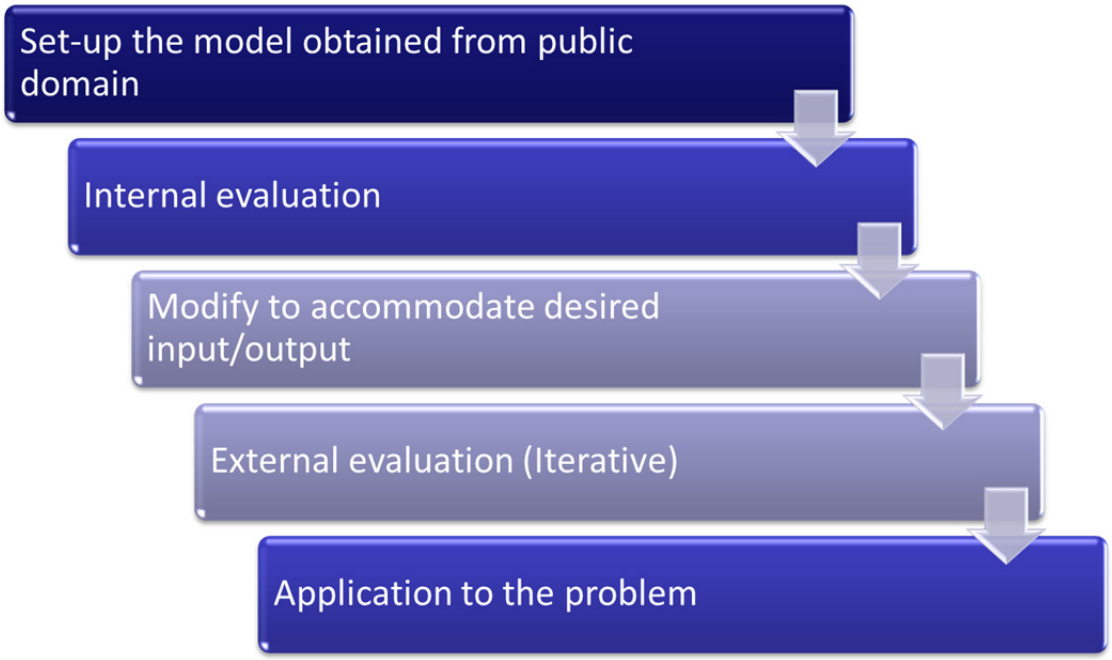


Figure 25 Schematic of the fit for purpose model validation strategy

Peterson *et al* used their model to demonstrate that their model was able to simulate a typical hypoparathyroidism patient (Primary hypoparathyroidism instituted in the model as an immediate 50% lowering of endogenous production of PTH from parathyroid gland[1]).

Using the publically available information, we implemented the model and confirmed that model was able to simulate a hypoparathyroidism state (Figure 26) and our results matched with what was reported in the publication. This constituted the internal evaluation of the model.

Following the internal evaluation, we performed external evaluation of the model, i.e., we used the model to predict placebo and rhPTH(1-84) PK, serum and urinary calcium output as PD effect and compared it with the observed data from the single dose (C09-002) and multiple dose (Mosekilde-IIT) PK/PD studies.

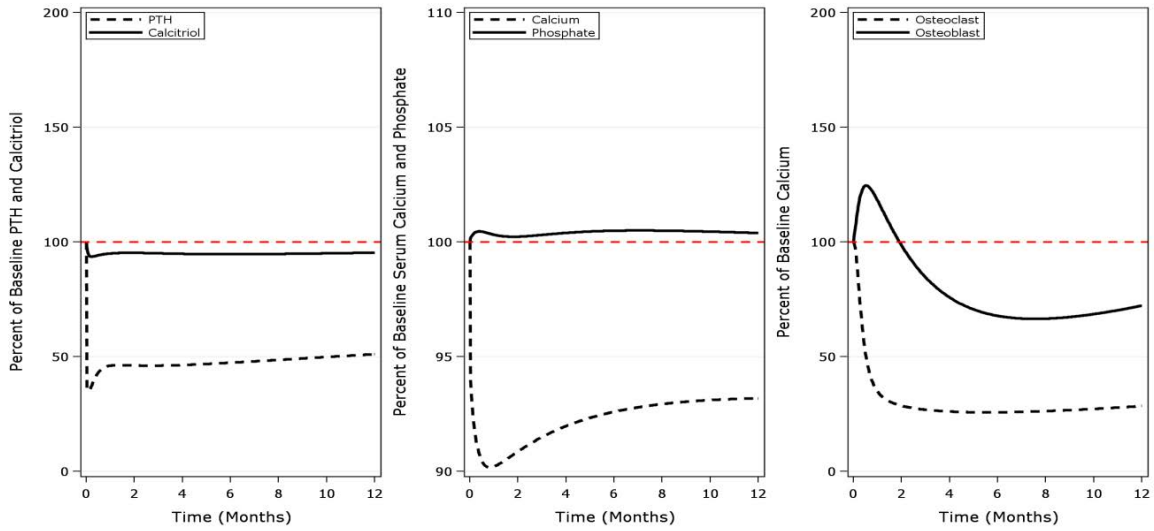


Figure 26 Calcium homeostasis model has the capability to simulate the hypoparathyroidism disease state (reduction in circulating PTH and corresponding changes in serum calcium and osteoclast osteoblast activity)

The results for the external model evaluation are presented in Figures 27 to 31 below. Each figure presents the observed mean (95% confidence bands) and model projected (solid line) data for rhPTH, calcitriol, serum calcium, and 24 hour urinary excretion (cumulative amount) after single dose in Study C09-002 (Figures 27 and 28) or for the last day of 6-month QD treatment simulation with placebo (Figure 29) and rhPTH (Figure 30) indicating that model reasonably described the PKPD data observed in Mosekilde-IIT study.

The assumptions are explained in Appendix 4.2 Section 4.2.2.

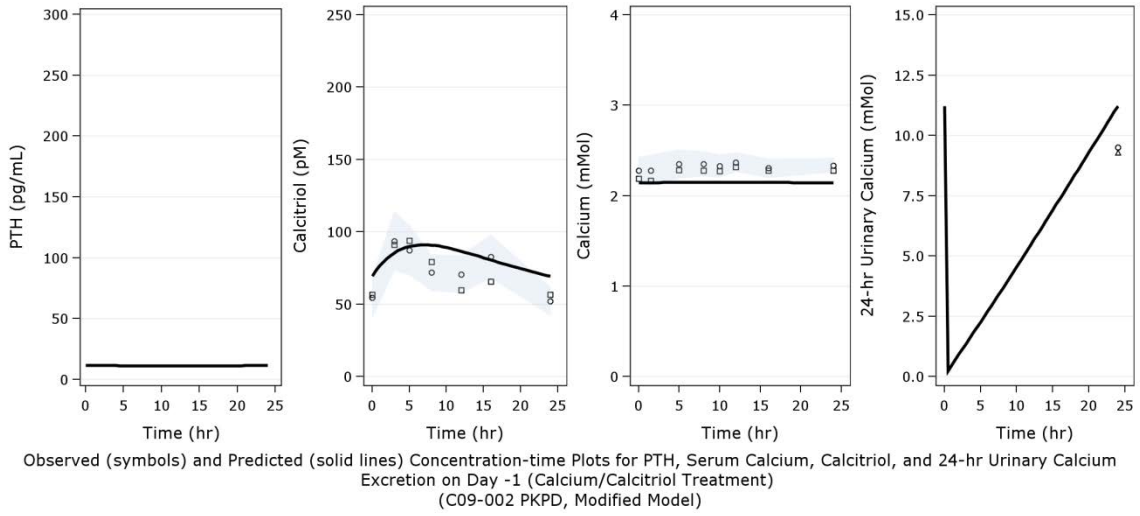
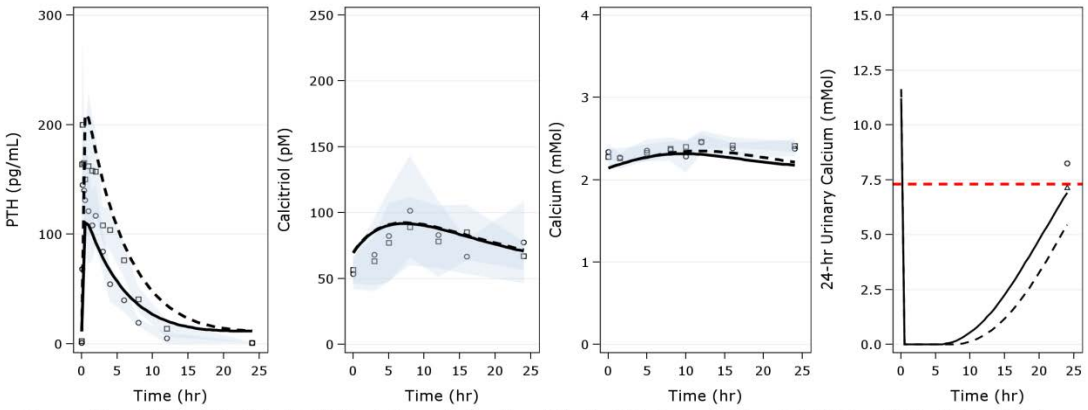
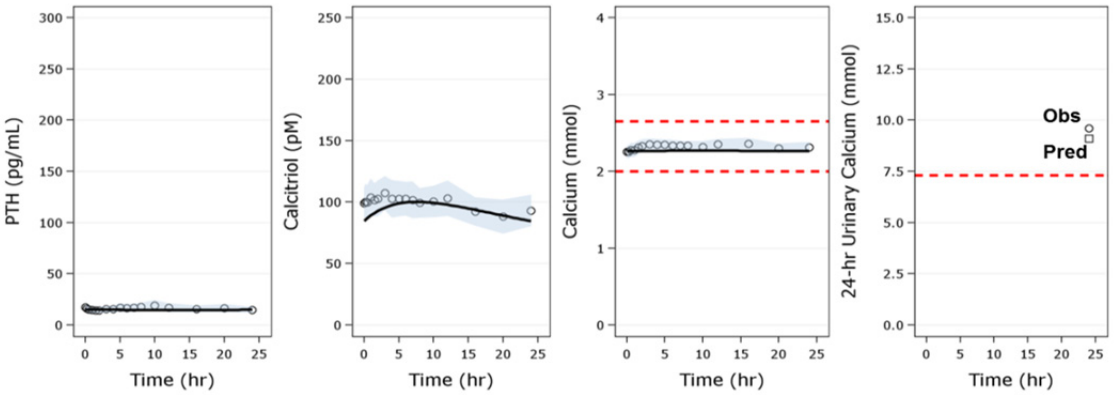


Figure 27 Evaluation of model – model reasonably predicts the observed data for placebo treatment in PKPD study C09-002 (PTH were BLQ in placebo)



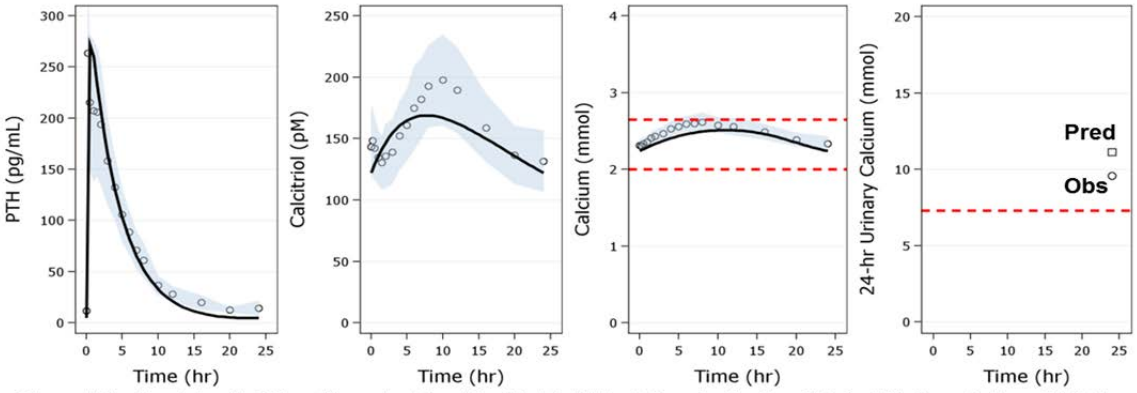
Observed (symbols) and Predicted (solid lines) Concentration-time Plots for PTH, Serum Calcium, Calcitriol, and 24-hr Urinary Calcium Excretion on Day 1 (50 mcg PTH) and Day 2 (100 mcg PTH)Treatment
(C09-002 PKPD, Modified Model)

Figure 28 Evaluation of model – model reasonably predicts the observed PK and PD data for rhPTH[1-84] treatment in PKPD study C09-002



Observed Mean(symbols with 95% confidence bands) and Predicted (solid lines) Concentration-time Plots for PTH, Serum Calcium, Calcitriol, and 24-hr Urinary Calcium Excretion on Last Day of 6-month Placebo Treatment
(Mosekilde-IIT, Modified Model)

Figure 29 Evaluation of model – model reasonably predicts the observed PK and PD data for placebo treatment in Mosekilde-IIT PKPD study



Observed Mean(symbols with 95% confidence bands) and Predicted (solid lines) Concentration-time Plots for PTH, Serum Calcium, Calcitriol, and 24-hr Urinary Calcium Excretion on Last Day of 6-month rhPTH[1-84] Treatment
(Mosekilde-IIT, Modified Model)

Figure 30 Evaluation of model – model reasonably predicts the observed PK and PD data for rhPTH[1-84] treatment in Mosekilde-IIT PKPD study

Simulation of Alternate Dosing Regimens or Dosing Regimen with Slow Release Profile

Once we established confidence on the model based on above mentioned internal and external model evaluations, simulations for QD, BID regimen and a QD regimen with slow release profile were conducted for various 'what if' scenarios and serum calcium and 24-hour urinary calcium excretion profiles were compared versus the reference QD profile. The intent was to test the hypothesis that a more frequent administration (same total daily dose) or QD regimen with slow release profile will provide PTH levels that reasonably mimic the physiological PTH profile (Figure 5) and thus offer better control on urinary calcium excretion while balancing serum calcium. We also compared the performance of these dosing regimens at two levels of PTH pool reduction: 50% and 99% reduction (both are clinically feasible situations).

The following scenarios were simulated using the validated systems pharmacology model for calcium homeostasis incorporating the rhPTH PK. To demonstrate the concept, the following simulations were conducted for a typical subject with the conditions described below:

Table 6 Overview of the projection scenarios using the systems pharmacology model for calcium homeostasis

Scenario #	Assumption of 50% loss in PTH gland pool (Similar to Mosekilde-IIT Population) 6 month treatment simulation			Assumption of 99% loss in PTH gland pool (Extreme Clinically Realistic Scenario) 6 month treatment simulation		
	PTH µg Dose (Frequency)	**Oral Ca (mmol/d)**	**Oral Calcitriol (µg)**	**PTH µg Dose (Frequency)**	**Oral Ca (mmol/d)**	**Oral Calcitriol (µg)**
1	100 QD	50	1.5	100 QD	50	1.5
2	50 BID	50	1.5	50 BID	50	1.5
3	100 QD	25	0.5	100 QD	25	0.5
4	50 BID	25	0.5	50 BID	25	0.5
Assuming a different slow release PK profile (1/10th absorption rate constant than current)						
5	50 QD	50	1.5	50 QD	50	1.5
6	50 QD	25	0.5	50 QD	25	0.5

The predicted serum calcium (mmol) and 24-hour urinary calcium excretion (mmol/day) for different dosing regimen is presented below in Figures 31 to 34 below. In the figures below, the shaded region in the left and middle plot represent the normal range of PTH and serum calcium, respectively, while the red dashed line in the plot on the right represents the ULN of 24 hour urinary calcium.

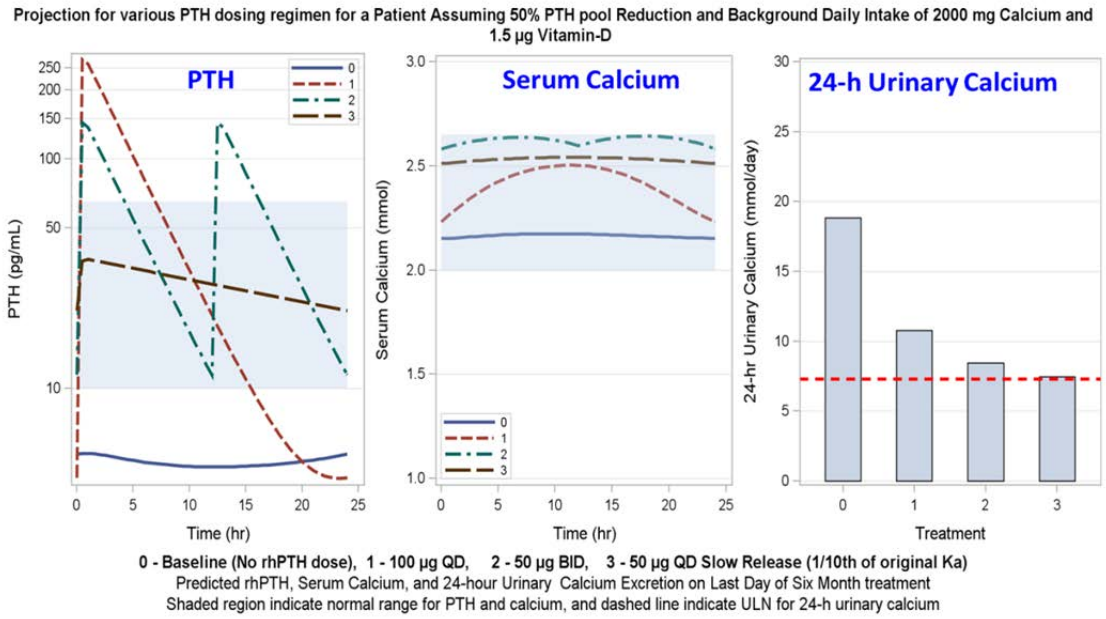


Figure 31 Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 1000 mg oral Calcium and 0.5 µg Vitamin D in a patient representing 50% PTH pool reduction

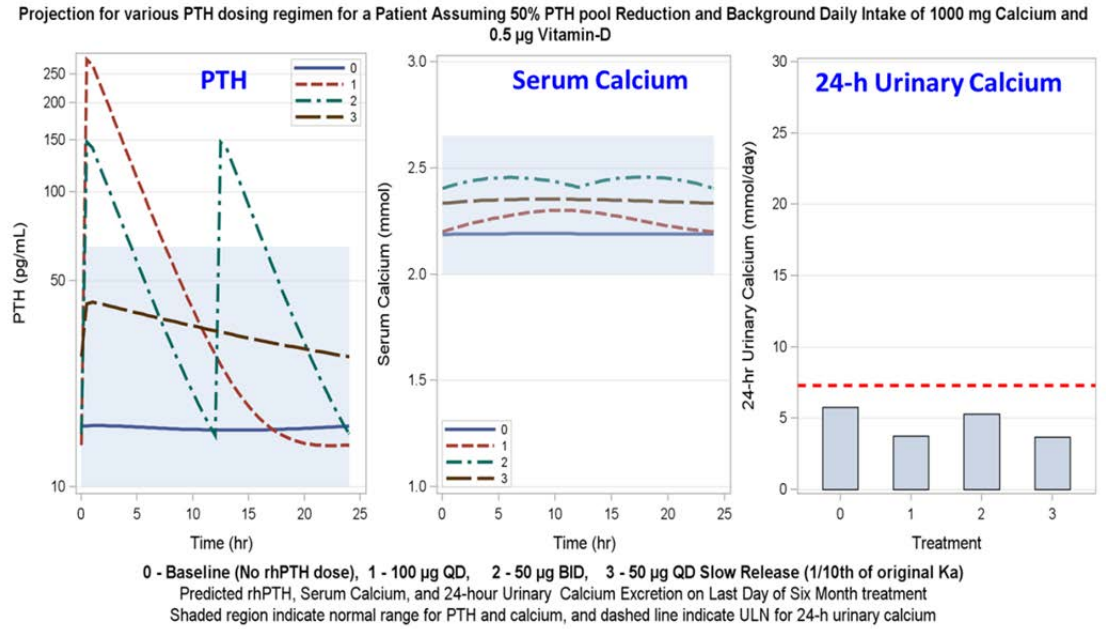


Figure 32 Simulations show that 100 µg QD achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose, however, or a slow release rhPTH profile achieves this target at 50 µg QD dose assuming background intake of 1000 mg oral Calcium and 0.5 µg Vitamin D in a patient representing 50% PTH pool reduction

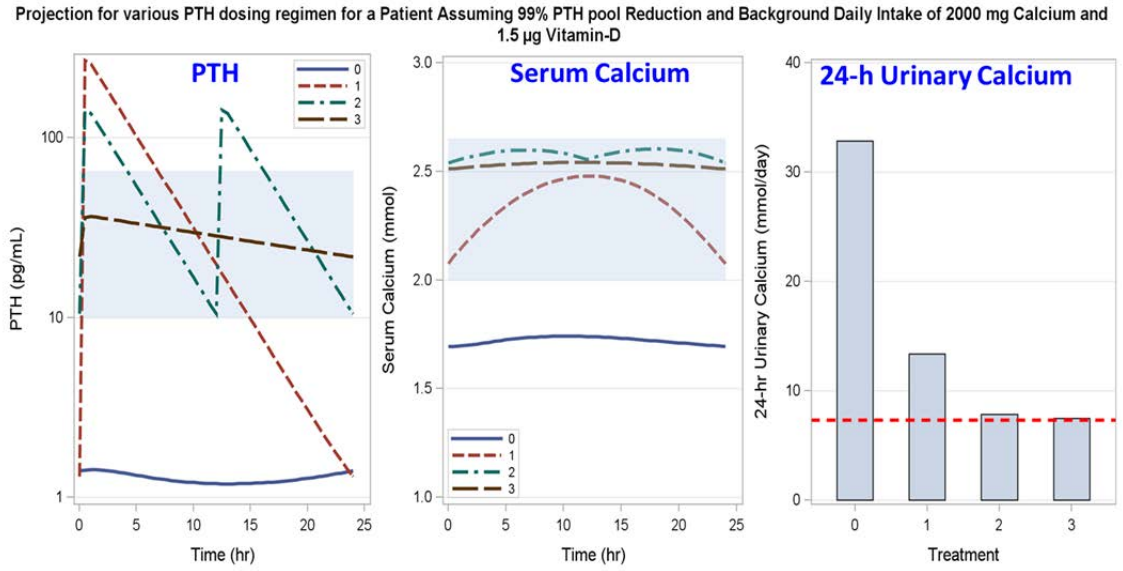


Figure 33 Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 2000 mg oral Calcium and 1.5 µg Vitamin D in a patient representing 99% PTH pool reduction

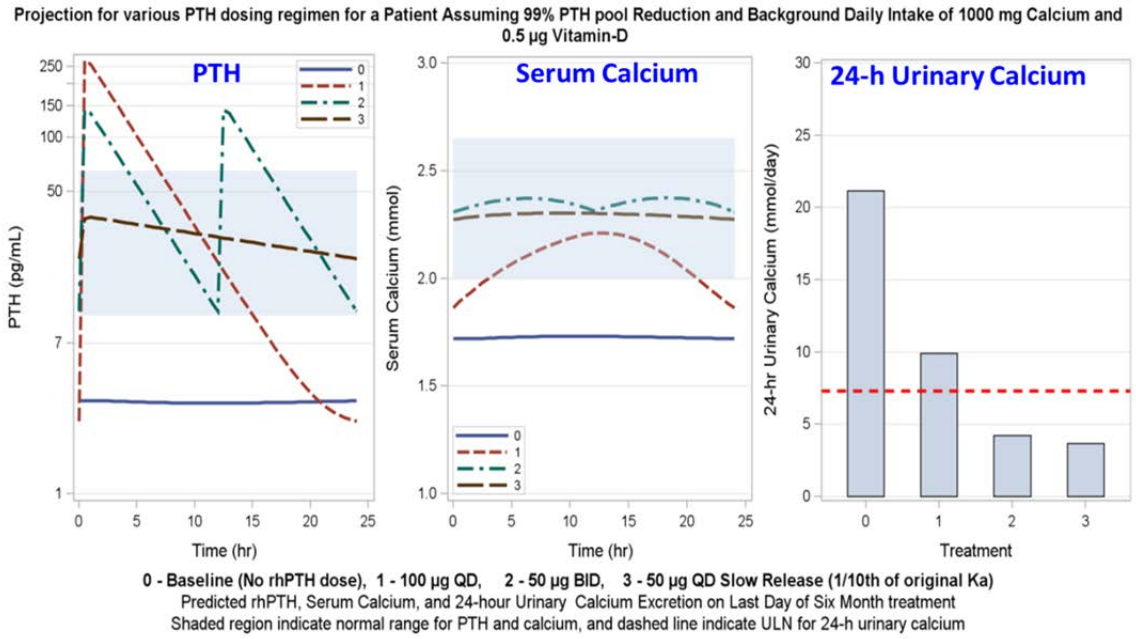


Figure 34 Simulations show that 50 µg BID or 50 µg QD dose with slow release profile achieves better control on serum calcium and urinary calcium excretion versus 100 µg QD dose background intake of 1000 mg oral Calcium and 0.5 µg Vitamin D in a patient representing 99% PTH pool reduction

The simulations demonstrate that on average in a typical individual with normal renal function (GFR 100 mL/min) and on daily oral intake of 25 mmol (1000 mg) calcium and 0.5 µg calcitriol, it is feasible to achieve better control on 24 hour urinary calcium excretion (<7.3 mmol) and serum calcium (within normal range 2-2.65 mmol or 8.4-10.6 mg/dL) with more frequent administration of total daily dose of 100 µg, especially (50 µg BID) in both set of assumptions for 50% and 99% reduction of PTH pool. Further, under the assumption of a hypothetical product that provides slow release of PTH ($1/10^{th}$ the absorption rate constant of current formulation, this target was achieved at a lower 50 µg QD dose.

Limitations of the Simulation Exercise:

The simulations had some limitations as highlighted below:

- Simulations have not tested titration and rather tested one or two factors at a time (e.g. effect of one PTH dose level and daily calcium intake and Vitamin-D dose level).
- The simulations represent the data at mean level and do not incorporate or address the variability that might be introduced by the factors affecting rhPTH pharmacokinetics or factors that may influence the response. The model have the capability to test the extremes (e.g. we tried to test one of the variability component – degree of baseline PTH gland function, though not much is known about the true quantitative magnitude of this factor in the patient population; we simulated the data assuming either 50% loss of PTH gland function or 99% loss).
- Clinically, there is heterogeneity in the choice of Vitamin-D (e.g. calcitriol, calciferol, alphacalcidol or other analogs) that was used as standard treatment. However, the model operates on the assumption of systemic levels of calcitriol (either stimulated by PTH or from exogenous administration). It is unknown if all forms of Vitamin-D have similar inhibitory potential on residual PTH secretion or on stimulating the calcium reabsoprtion. It is beyond the scope of current model and simulations to account for these variations.

Published Evidence on Utility of Alternate Dosage Regimen in Management of Patients with Hypoparathyroidism

The pharmacologically active rhPTH[1-34] peptide has been evaluated by Karen Winer *et al*[2] in a randomized, controlled comparison of rhPTH(1-34) QD versus BID (0.7 µg/kg per day starting dose) in patients with Hypoparathyroidism. The study demonstrated that in patients with acquired or idiopathic hypoparathyroidism, serum calcium was maintained within the normal range (Figure 35). The total daily PTH dose was markedly reduced with the twice-daily regimen (twice daily 46±52 µg/day vs. once daily 97±60 µg/day, P<0.001).

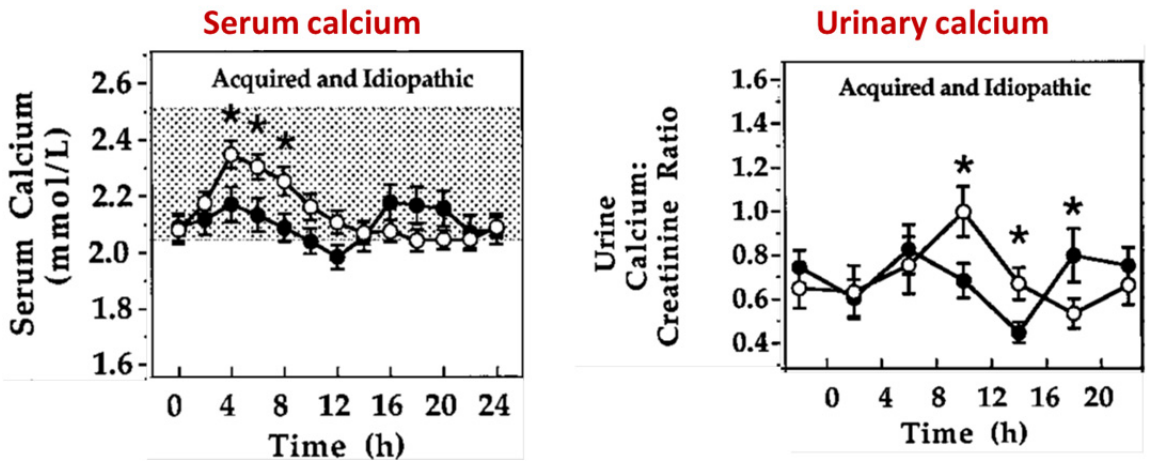


Figure 35 Mean (±SE) serum calcium and urine calcium/creatinine ratio with QD and BID regimen of rhPTH(1-34) (Figure Adapted from Karen K. WINER et al. J Clin Endocrinol Metab 83: 3480–3486, 1998)

In another study continuous SC infusion using a pump delivery was compared BID regimen of rhPTH(1-34)[3].

The data demonstrated that both serum calcium and 24-hour urinary calcium excretion were controlled with the pump delivery in comparison to the BID regimen (see Figure 36). Mean±SD daily rhPTH(1-34) dose was 65% less during pump versus BID delivery (13±4 vs 37±14 µg/day, P<0.001).

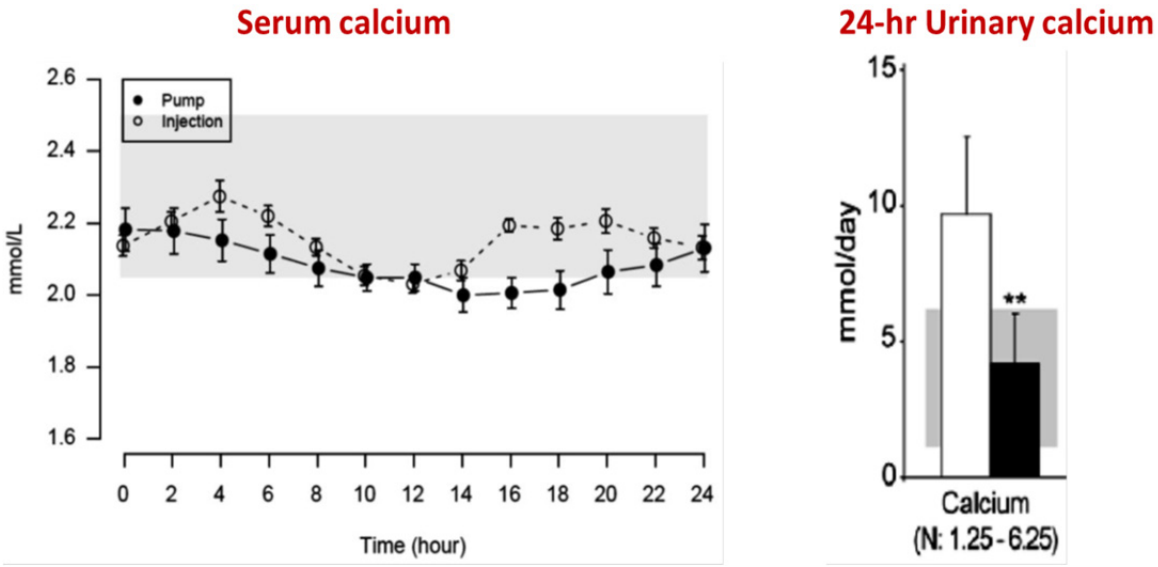


Figure 36 Mean (±SE) serum calcium and urine calcium/creatinine ratio with QD and BID regimen of rhPTH(1-34) (Figure Adapted from Karen K. Winer et al. J Clin Endocrinol Metab. 97: 391–399, 2012)

2.2.6 Does Natpara prolong the QT or QTc Interval?

Based on the clinical pharmacology review of NDA (b) (4) the rhPTH was devoid of any QT prolongation concern.

2.4 Intrinsic Factors

2.4.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?

The effect of various covariates e.g. body weight, Age, disease state (hypoparathyroidism and osteoporosis), BMI, Gender, CLCR and Race was assessed in the population pharmacokinetic analysis. The details are mentioned under **Appendix 4.2.1**.

Sponsor's analysis identified only body weight as a covariate for rhPTH[1-84] CL/F and V/F. However, no dose adjustments are proposed as the product is titrated based on calcemic response. The body weight effect on CL/F and V/F was not apparent from diagnostic plots from the sponsor's base model and data showed a modest correlation (Figure 37).

While body weight was identified by the sponsor as most significant covariate, the review team considers that the inclusion of this covariate seems to have only a statistical basis, as the inclusion of this covariate only explained 0.7% and 8% of the inter-individual variability in CL/F and V/F, respectively.

According to the sponsor's analysis, no clinically relevant effect of age, gender, disease status, BMI or race on Natpara PK was evident from the data. However, age, gender, disease can independently affect the physiological functions involved in calcium homeostasis and therefore, clinical data should also be weighed in for dosing decisions.

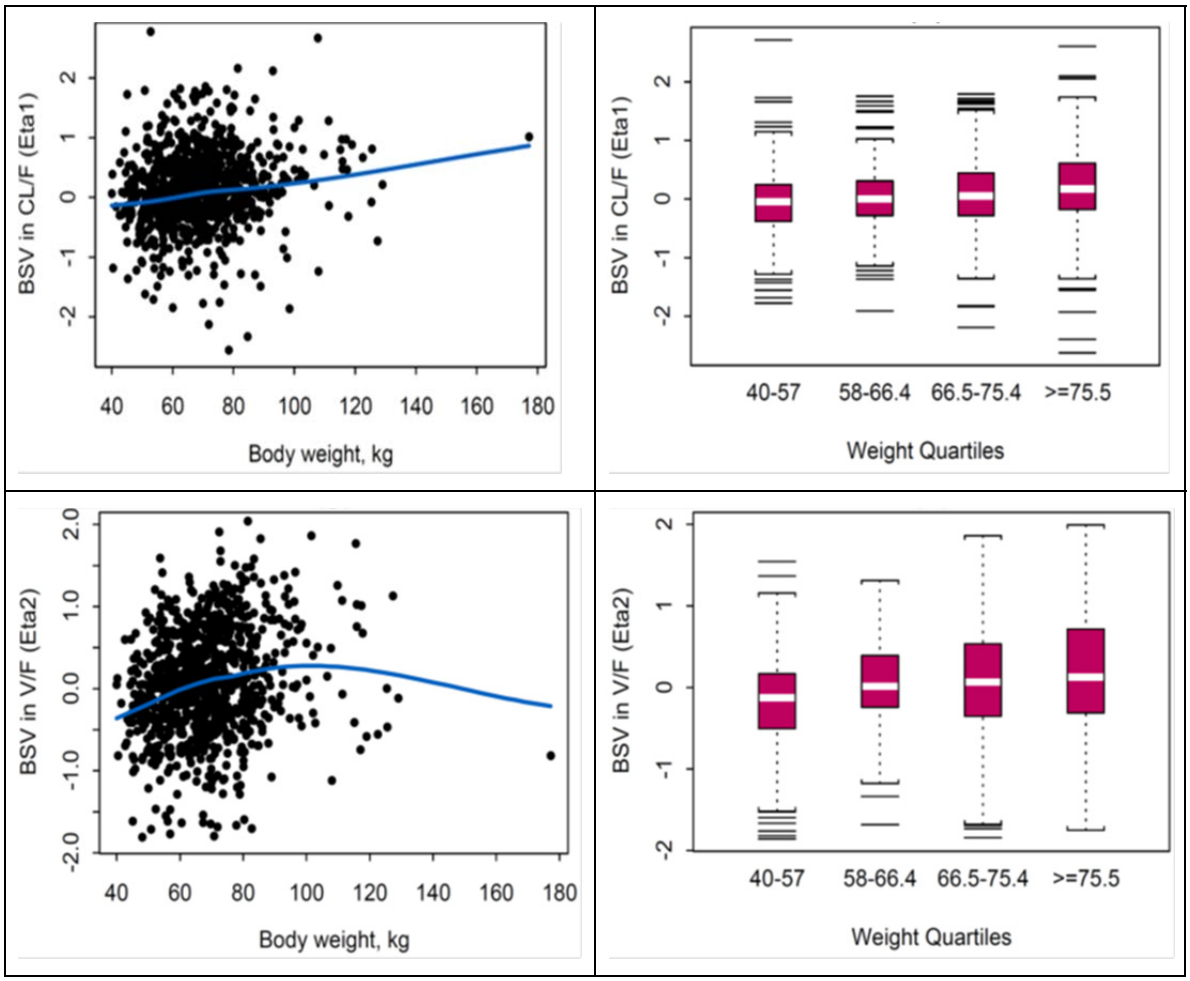


Figure 37 Effect of body weight on Natpara CL/F and V/F from population pharmacokinetic model

2.4.2 Does the hepatic function affect Natpara pharmacokinetics and pharmacodynamics?

Based on the previous clinical pharmacology review of the hepatic impairment study[7], subjects with moderate hepatic impairment (Grade B: total Child-Pugh score of 7 - 9) had 20% higher baseline-corrected PTH C_{max} and $AUC_{0\text{-last}}$ values than those for healthy subjects.

Adding on to the previous clinical pharmacology review[7], the total serum calcium profile did not differ between the two groups (Figure 38). Although, the data also did not show a significant rise in total calcium from baseline, and albumin corrected calcium concentration data was not available. Therefore, no dose adjustment is recommended based on PK changes observed in patients with moderate hepatic impairment. However, albumin corrected serum total calcium should be closely monitored.

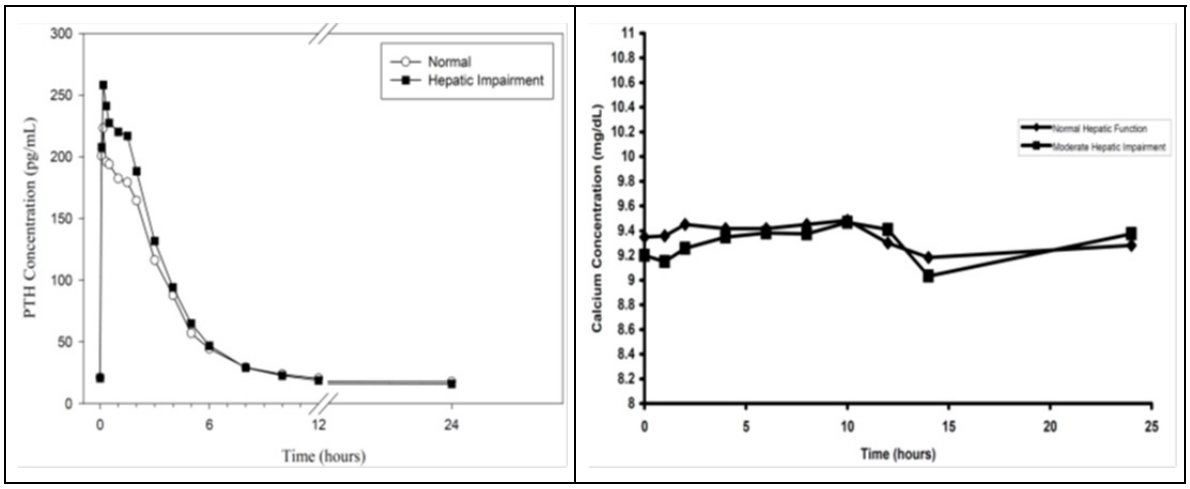


Figure 38 Effect of hepatic impairment on rhPTH[1-84] PK (left) and PD (right) profile

2.4.3 Does the renal function affect Natpara pharmacokinetics and pharmacodynamics?

Based on the previous clinical pharmacology review of the renal impairment (RI) study[7], both baseline corrected PTH $AUC_{0\text{-last}}$ and C_{max} are not significantly different when compared between subjects with moderate RI and healthy subjects, as well as when compared between subjects with mild RI and healthy subjects.

Adding on to the previous review, however, there are some interesting aspects of PTH handling by kidney. Martin et al[23] reported the animal data shows that renal uptake of the biologically inactive fragments of i-PTH is dependent upon glomerular filtration; while the biologically active forms of i-PTH (intact bovine-PTH[1-84] and synthetic b-PTH[1-34]) are handled mainly by peritubular uptake. This could explain the marked accumulation of biologically inactive PTH fragments in patients with renal failure. Also, this can shed some light on the overall effectiveness of PTH in modulating urinary calcium handling and vitamin D activation; the latter is naturally reduced with degree of severity in renal impairment.

The PD data was analyzed after regrouping the subjects into normal renal function, mild RI, and moderate RI (sponsor had grouped them as mild to moderate versus normal). The total serum calcium profile differed between the three groups with a trend for systematic decline in response with increasing severity of RI (Figure 39). The albumin corrected calcium concentration data was not available.

Further, based on individual level data there were a number of subjects who did not show any increase in serum calcium from baseline. Therefore, proportion of subjects who did

[23] The Renal Handling of Parathyroid Hormone: Role of Peritubular Uptake and Glomerular Filtration. K J MARTIN, K HRUSKA, J LEWIS, C ANDERSON, and E SLATOPOLSKY. The Journal of Clinical Investigation. Volume 60, October, 1977: 808-814.

not show any increase from baseline calcium was computed and compared amongst the three groups. This proportion increased with severity of RI supporting the decline in response to the rhPTH challenge (Figure 40). Applicability of this data to the patients with hypoparathyroidism is complex as RI in subjects with normal parathyroid gland function would usually cause hyperparathyroidism and can be expected to have different calcium handling.

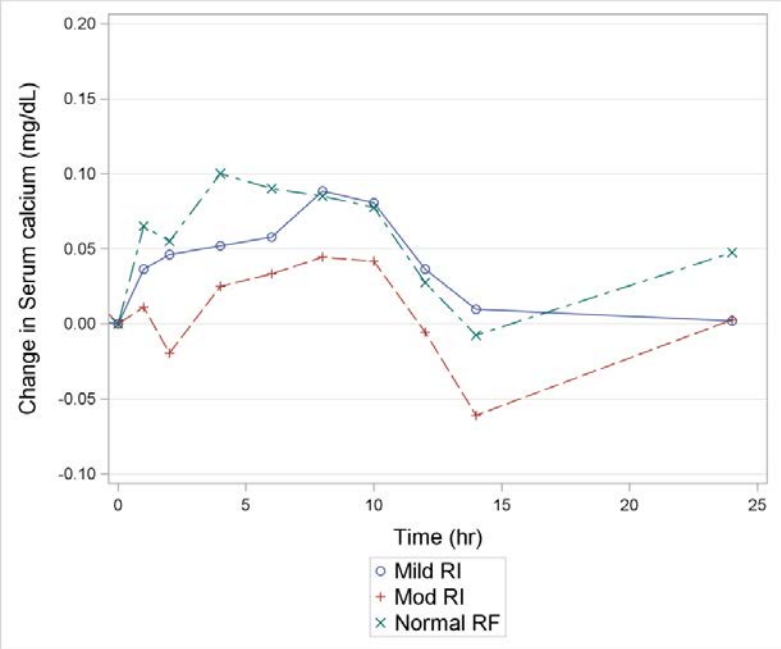


Figure 39 Mean change from baseline in total serum calcium by renal function

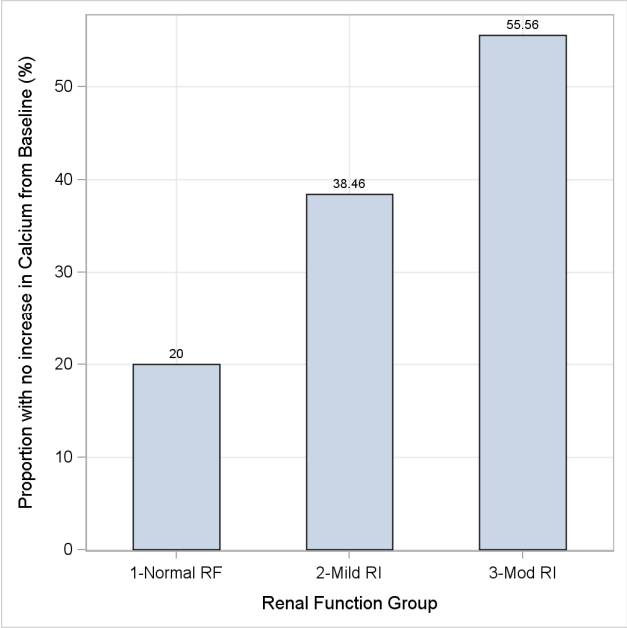


Figure 40 Proportion of subjects with no increase in calcium from baseline (data labels are % subjects)

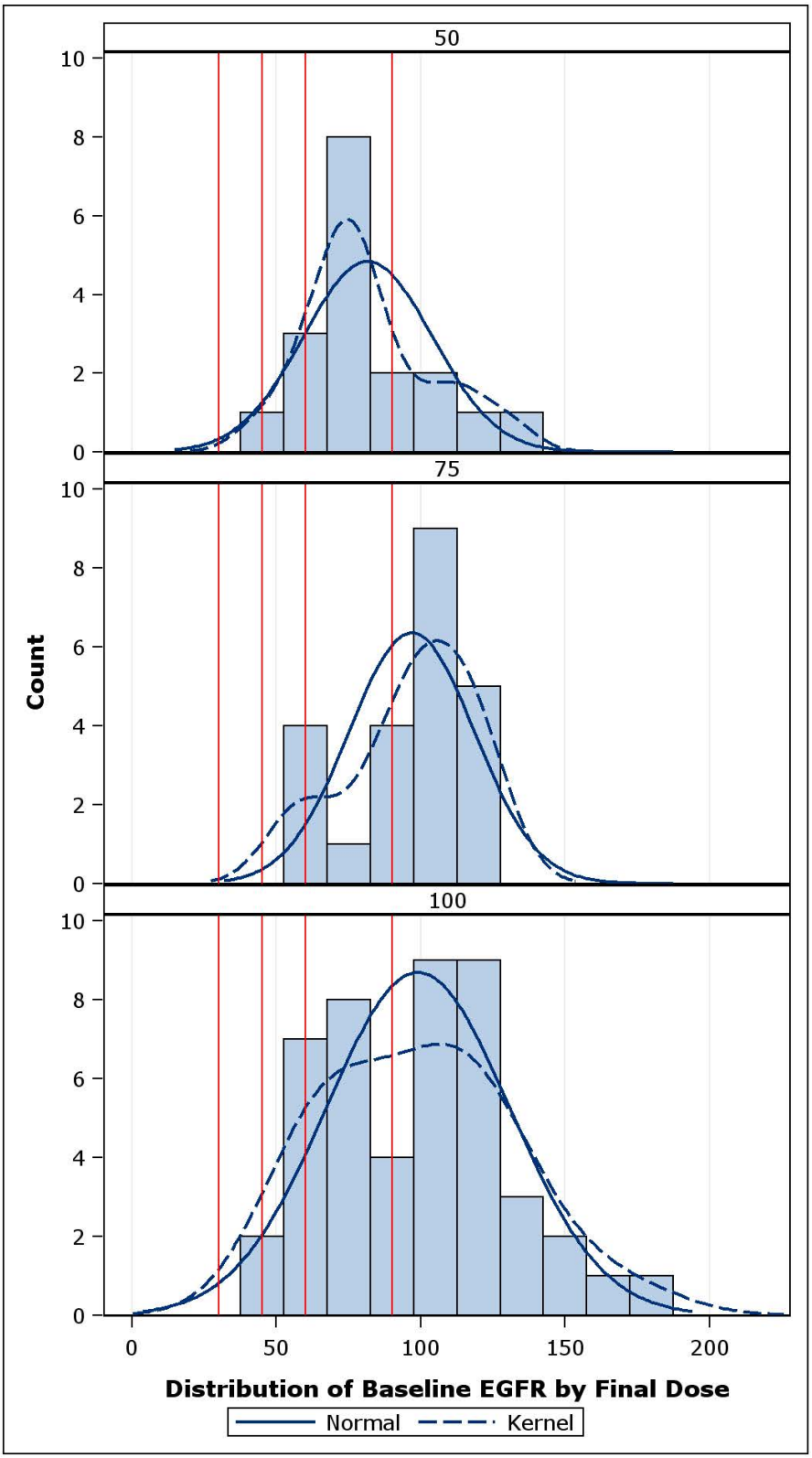


Figure 41 Distribution of baseline eGFR by final dose

However, in Phase 3 trial CL1-11-040, except a slight rightward shift in the central tendency, there was no significant trends with regards to distribution of baseline eGFR values between final rhPTH[1-84] dose (trial included patients with mild and moderate RI) to confidently say that dose requirements were influenced by eGFR status and pin-point a requirement for dose-adjustment (Figure 41). However, albumin corrected serum total calcium should be closely monitored in patients with renal impairment.

2.5 Extrinsic Factors

2.5.1 Drug-Drug Interactions

2.5.2.3 What is the effect of co-administered drugs on the pharmacokinetics and pharmacodynamics of Natpara?

Sponsor submitted one clinical DDI investigation with alendronate, which was conducted as a sub-study in post-menopausal women at 100 mg dose [PaTH Study (PTH and alendronate in combination for the treatment of osteoporosis submitted with NDA (b) (4)]. Mean PK and serum calcium data by treatment is presented in Figures 42 and 43, respectively.

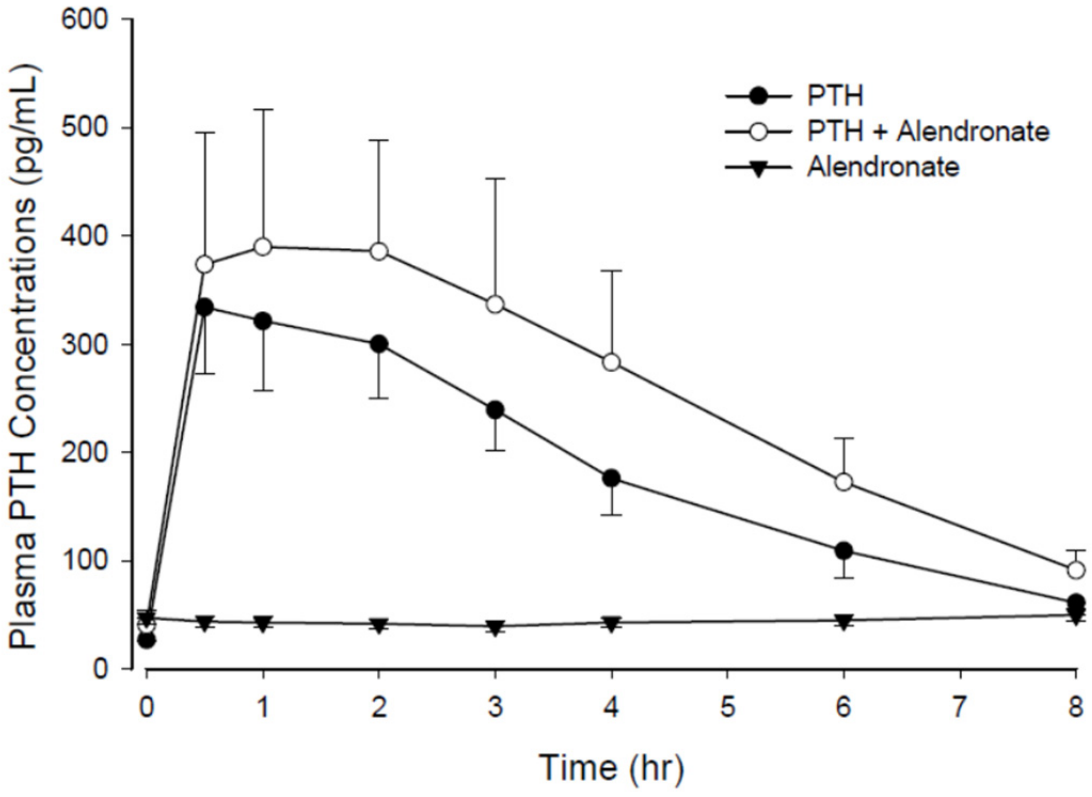


Figure 42 Mean (±SE) Plasma PTH(1-84) Concentration-time Profiles Following rhPTH(1-84), Alendronate, or rhPTH(1-84) Plus Alendronate at the Month 12 Visit of the ACR Substudy of PaTH

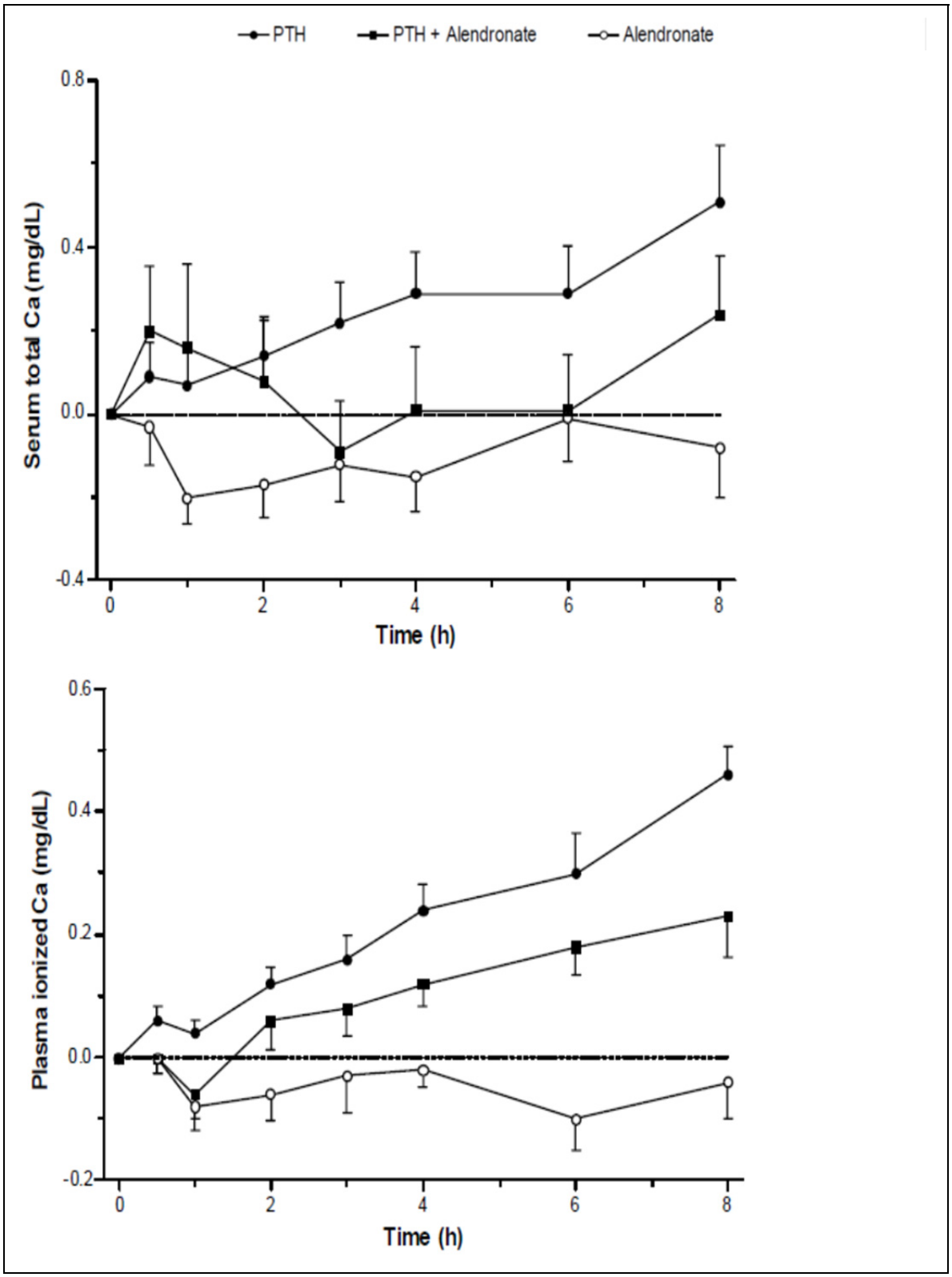


Figure 43 Serum total calcium and plasma ionized calcium by treatment

In absence of electronic data reviewer could not verify the sponsor's claim that alendronate co-administration did not alter the PK profile of PTH as is revealed in the Figure 42. The reviewer agrees with the sponsor that calcium response was reduced with alendronate co-administration. Although, the study did not capture the 24 hour calcium profile in serum or urine to adequately inform dosing recommendation, there is sufficient data to recommend that alendronate should not be co-administered with Natpara in hypoparathyroidism patients.

2.6 General Biopharmaceutics

2.6.1 Is bioequivalence established between the to-be-marketed formulation and the Phase 3 trial formulation and how does it relate to the overall product development?

The final to be marketed formulation was evaluated in Phase 3 trials (see Table 7 below). There was a BE study conducted for bridging the devices containing the same final formulation. Therefore, bioequivalence study was not considered pivotal for approval and thus Office of Scientific Investigation inspection was not requested for this study.

Table 7 Details of formulations utilized in various clinical trials

Formulation	Formulation Designation	Nominal Strength	rhPTH(1-84) Concentration[b]	Indication	Excipient Concentrations[b]	Container Closure System	Pen Injector	Primary Clinical Usage[c]
Single dose	A	(b) (4)		Osteoporosis	(b) (4)		N/A	Early studies in support of osteoporosis program
Multiple dose	B[c]	(b) (4)		Osteoporosis	(b) (4)			Pivotal Phase 3 studies for osteoporosis program
Multiple dose	B	100 mcg/dose	1.40 mg/mL	Hypopara-thyroidism	(b) (4) mg/mL NaCl; (b) (4) mM citrate buffer (pH (b) (4)); (b) (4) % w/v mannitol; (b) (4) % w/v m-cresol	Multiple dose dual-chamber cartridge/ stopper/ crimp cap	PREOS® Pen (Ypsomed)	Pivotal Phase 3 studies for hypopara-thyroidism program
		75 mcg/dose	1.05 mg/mL				Natpara® Reusable Pen (Haselmeier)	
		50 mcg/dose	0.70 mg/mL					
		25 mcg/dose	0.35 mg/mL					

N/A = not applicable; rhPTH(1-84) = recombinant human parathyroid hormone

(b) (4)

[b]Reconstituted solution concentration.

Mean Natpara concentrations from the two devices delivering the final formulation are presented in Figure 44 below.

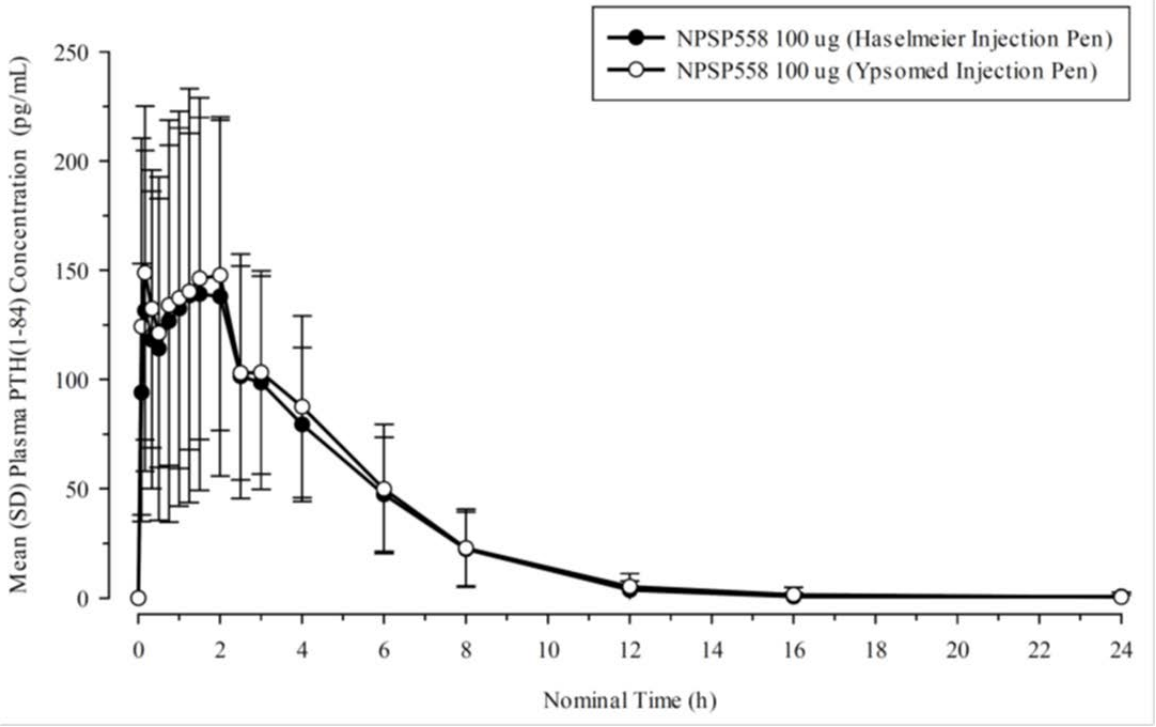


Figure 44 Mean (±SD) Baseline-adjusted Plasma Concentrations versus Time of rhPTH[1-84] Administered Subcutaneously with the Ypsomed and Haselmeier injection Pens

(Source: Figure 11-1 CSR PAR-C10-005 Page 54)

Table 8 Results of the ANOVA on Baseline-adjusted PK Parameters Following Administration of rhPTH[1-84] 100 µg SC in ITT Population

NPSP558 in Plasma
NPSP558 100 ug SC Haselmeier Injection Pen vs. NPSP558 100 ug SC Ypsomed Injection Pen

Baseline-adjusted PK Parameter (N = 50)	Haselmeier Pen Geometric LSM	Ypsomed Pen Geometric LSM	Ratio of Geometric LSM (90% CI)	Intra-subject CV (%)
AUC_{0-t} (pg•h/mL)	661.1[a]	688.41[a]	96.0 (88.48 – 104.23)	24.3
$AUC_{0-\infty}$ (pg•h/mL)	718.53[b]	742.34[b]	96.8 (88.5 – 105.86)	19.6
C_{max} (pg/mL)	170.29[a]	182.39[a]	93.4 (84.42 – 103.26)	30.0

AUC_{0-t} = area under the concentration-time curve from 0 to the last measurable concentration; $AUC_{0-\infty}$ = area under the concentration-time curve from 0 to infinity; CI = confidence interval; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; ITT = Intent-to-Treat; LSM = least square mean; N = number; PK = pharmacokinetic; SC = subcutaneous
[a] N = 48
[b] N = 28

(Source: Table 11-5 CSR PAR-C10-005 Page 60)

The ratios and 90% CIs of the geometric LS means of the ln-transformed baseline-adjusted PK parameters AUC0-t, AUC0-∞ and Cmax of NPSP558 between the Haselmeier and Ypsomed Injection Pens were contained within the 80 to 125% acceptance range.

2.7 Analytical

2.7.1 Are the analytical methods for Natpara appropriately validated?

(b) (4)

(b) (4)

sponsor selected the Scantibodies IRMA was selected for use in all subsequent studies in the osteoporosis and hypoparathyroidism programs.

The Scantibodies PTH(1-84) assay is a two-site IRMA using polyclonal antibodies. The capture antibody is immobilized onto plastic beads and binds the C-terminal (39-84) region of PTH(1-84); the second antibody binds the N-terminal (1-6) region of PTH(1-84), which confers specificity for full length PTH(1-84), and is radiolabeled with ^{125}I for detection. A sample containing PTH(1-84) is incubated simultaneously with both antibodies. Following incubation, the beads are washed and the radioactivity remaining bound to the beads is measured in a gamma scintillation counter. PTH(1-84) concentrations are determined by reference to an 6-point calibration curve.

The assay method is acceptable and adequately covers the concentration ranges observed in the clinical pharmacology studies.

Performance characteristics of the (b) (4) parathyroid hormone assay methods are summarized below in Tables 9 and 10.

Table 9 Summary of Validation Report for Scantibodies Whole Parathyroid Hormone (1-84) Assay (Scantibodies assay was used as the final method throughout)

Parameter	Description
Analyte	PTH(1-84)
Matrix	Human plasma
Assay method	Direct analysis using IRMA
Instrumentation	Packard Cobra II gamma counter
Standard curve concentrations, pg/mL	4.00 (anchor point), 10.0, 25.0, 50.0, 100, 200, 400, 800, 1600, and 2000
QC concentrations, pg/mL	LLOQ QC, endogenous (11.7), 29.7, 160, 1510, and ULOQ QC
QC intra-batch precision (% CV)	Range 1.2 to 18.0%
QC intra-batch accuracy (% bias)	Range −12.0 to 16.0%
QC inter-batch precision (% CV)	Range 2.7 to 11.6%
QC inter-batch accuracy (% bias)	Range −1.3 to 8.8%
Bench-top stability (hours)	Short-Term Stability: 24 hours in polypropylene tubes at ambient temperature under white light Cumulative Short-Term Stability: 39 hours in polypropylene tubes at ambient temperature under white light (total of all thaw cycles)
Stock stability (days)	Long-Term Stability for Stock Solutions (Stock): 132 days at approximately 100 µg/mL in phosphate-buffered saline/ 0.1% bovine serum albumin in polypropylene tubes at −20°C
Freeze-thaw stability (cycles)	Six freeze (−80°C) thaw (ambient temperature) cycles in polypropylene tubes under white light

Table 10 Performance characteristics of the (b) (4) parathyroid hormone assay methods (Scantibodies assay was used as the final method throughout)

	Scantibodies (Whole PTH)	(b) (4)
Standard Samples		
Number of curves	6	
Number of calibrators	6	
Assay range, pg/mL	6.10 to 2100	
CV, %	1.8 to 14.6	
RE, %	−8.1 to 11.0	
Quality control samples (N/level)	24	
Low concentration (pg/mL)	23.4	
CV, %	9.1	
RE, %	4.3	
Mid concentration (pg/mL)	173	
CV, %	4.8	
RE, %	6.4	
High concentration (pg/mL)	1503	
CV, %	3.9	
RE, %	−2.7	
LLOQ (pg/mL)	6.10	
Cross-reactivity, %		
PTH(1-84)	86	
PTH(3-84)	0.6	
PTH(7-84)	<0.1	

CV = coefficient of variation; LLOQ = lower limit of quantitation; N = number of samples; PTH = parathyroid hormone; RE = relative error;
[a]This immunofluorometric assay was used as a comparator in a validation study, not to analyze clinical samples. Scantibodies and (b) (4) used immunoradiometric assays.

3 Labeling Comments

Note: The labeling comments will be provided in a separate addendum at a later time-point.

4 Appendix

4.1 Summary of Individual Studies

(Based on the Sponsor's Summary of Clinical Pharmacology, Summary of Biopharmaceutics and Associated Bioanalytical Methods, Individual Study Synopses, as submitted, and Review of Individual Study Reports)

4.1.1 Single Rising Dose PK and PD in Patients with Hypoparathyroidism (C09-002)

Sponsor/Company Name: NPS Pharmaceuticals	
Name of Investigational Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	
Title of study: An Open-Label, Escalating, Single-Dose Study to Assess the Pharmacokinetics and Pharmacodynamics of NPSP558 Administered Subcutaneously to Subjects with Hypoparathyroidism	
Protocol No: C09-002	
Investigators: (b) (4)	
Study Center: Mayo Clinic, 200 1st Street SW, Rochester, MN 55905; Cetero Research, 5109 Medical Drive, San Antonio, TX 78229	
Publication (reference): None	
Study Period: **First Subject In:** 7 June 2010 (first subject, first visit) **Last Subject Out:** 24 April 2011 (last subject, last visit)	**Clinical Phase of Development:** Phase 1
Objectives: The primary objective of this study was to assess the pharmacokinetics (PK) of NPSP558 administered as single subcutaneous (SC) doses of 50 µg and 100 µg in subjects with hypoparathyroidism. The secondary objectives of this study were to assess the pharmacodynamics (PD), safety and tolerability of NPSP558 administration in this population.	
Methodology: This study was an open-label, escalating, single-dose, multi-center study in which a maximum of 8 subjects with a history of hypoparathyroidism were enrolled with the goal of having at least 6 subjects complete the study. These subjects were to receive a single SC dose of NPSP558 in the thigh. There were two periods to the study. During Treatment Period 1, each subject received a single SC injection of NPSP558 at 50 µg; during Treatment Period 2, each subject received a single SC injection of NPSP558 at 100 µg. There was at least a 7-day washout interval between doses. Blood samples were collected for 24 hours after dosing in each period (Day 1) to assess the PK of NPSP558 and the PD responses of serum calcium, albumin, albumin-corrected total calcium, magnesium, phosphate, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], and creatinine. Timed urine collections were also made during the 24 hours after dosing to assess the renal responses to NPSP558 administration. The blood and urine sampling schedules employed following NPSP558 administration on Day 1 in each period were also used during the 24-hours prior to each NPSP558 administration (Day -1) to assess the PD responses to the subject's habitual therapy, i.e., oral calcitriol, which was used to control the hypocalcemia resulting from their hypoparathyroidism. Calcitriol therapy was withheld on the days when NPSP558 was administered. Samples were analyzed using validated methodologies.	

Sponsor/Company Name: NPS Pharmaceuticals
Name of Investigational Product: NPSP558
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])
Number of Subjects (planned and analyzed): A maximum of 8 subjects with a history of hypoparathyroidism were enrolled with the goal of having at least 6 subjects complete the study. Number of Subjects Planned: 8 Number of Subjects Enrolled: 8 Number of Subjects Analyzed for Safety: 7 Number of Subjects Analyzed for Pharmacodynamics and Pharmacokinetics: 7
Diagnosis and Main Criteria for Inclusion: This study included male and female adult subjects 25 to 85 years of age with a diagnosis of hypoparathyroidism for ≥ 12 months defined by biochemical evidence of hypocalcemia with concomitant serum intact PTH concentrations below the lower limit of the laboratory normal range.
Investigational Product, Dose, Mode of Administration, and Batch Numbers: NPSP558, recombinant human parathyroid hormone (rhPTH[1-84]), is manufactured using a strain of *Escherichia coli* modified by recombinant deoxyribonucleic acid (DNA) technology and is identical to native human PTH, a single-chain polypeptide containing 84 amino acid residues. A single subcutaneous injection of NPSP558 was administered in the thigh using an injection pen device. During Period 1, six subjects received a single SC dose of 50 µg NPSP558 (batch numbers VVHB20D and Y08005). Subject 002-001 had a failed dose attempt on Day 1, Period 1 (50 µg) due to a user error of the injection pen of the injection pen. Following at least a 7-day washout interval subjects returned to the clinic and received a single SC dose of 100 µg NPSP558 (batch numbers P07003 and P10001D) preferably in the same thigh. Study drug was administered to the subject by trained personnel.
Duration of Treatment: The total duration of the study was approximately 5 weeks, inclusive of screening, with at least a 7-day washout interval between doses.
Reference Therapy, Dose, Mode of Administration, and Batch Numbers: Not Applicable
Criteria for Evaluation: Blood sampling for PK analysis of plasma PTH was performed in a total of 7 subjects. Six of the 7 subjects received NPSP558 in Period 1 and all 7 subjects received NPSP558 in Period 2 and were considered evaluable for this PK analysis. PD analysis was performed to assess the responses of serum total calcium, albumin, albumin-corrected total calcium, magnesium, phosphate, $1,25(OH)_2D$, and creatinine to NPSP558 administration. Urinary excretion of cyclic AMP, calcium, magnesium, phosphate, and creatinine were determined to assess the renal responses to NPSP558 administration. Subject 002-001 had a failed dose attempt on Day 1, Period 1 (50 µg) due to a user error of the injection pen; therefore, the derived PK and PD parameters were excluded from the summary statistics, but are presented for information purposes in the listings.
Safety: The safety variables of interest were vital signs, physical examinations, clinical laboratory tests, adverse events (AEs), and electrocardiograms (ECGs).
Statistical Methods: Plasma levels of NPSP558 (rhPTH[1-84]) and endogenous PTH; serum levels of total calcium, albumin, albumin-corrected total calcium, magnesium, phosphate, $1,25(OH)_2D$, and creatinine; were determined throughout each period and summarized at each time point using descriptive statistics. Plasma NPSP558 levels were used to calculate the PK variables C_{max}, T_{max}, $AUC_{0\text{-}last}$, $AUC_{0\text{-}\infty}$, CL/F, V_{ss}/F , and $t_{1/2}$. The PD variables $AUC_{0\text{-}24}$, E_{max}, E_{min}, T_{Emax} and T_{Emin} were derived using unadjusted serum levels of total

Sponsor/Company Name: NPS Pharmaceuticals
Name of Investigational Product: NPSP558
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])
calcium, albumin, albumin-corrected total calcium, magnesium, phosphate, $1,25(OH)_2D$, and creatinine. The PD variables AUC_{below}, AUC_{above}, AUC_{net}, E_{max}, E_{min}, T_{Emax} and T_{Emin} were derived using baseline-adjusted serum levels. All serum concentrations and PD variables were summarized using descriptive statistics. Urine levels of cyclic AMP, calcium, magnesium, phosphate, and creatinine were obtained during the 24 hours prior to NPSP558 administration and during the 24 hours following dosing. The excretion of each analyte was quantified in each urine sample and expressed relative to creatinine excretion; total and relative excretion over each 24-hours was also determined. The clearance and fractional excretion of calcium, magnesium and phosphate were also calculated in each sample. All urine excretion measures were summarized using descriptive statistics. Safety and tolerability data including clinical laboratory tests, physical exams, adverse events, ECG monitoring, and vital signs assessments were summarized by treatment and point of time of collection. Descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) were calculated for quantitative safety data as well as for the difference from baseline.
Pharmacokinetic Results: In general, the PK of PTH following SC administration of NPSP558 in the thigh of these hypoparathyroid subjects was consistent with that observed previously in normal postmenopausal women who received 100 µg of rhPTH(1-84) in the thigh (Study CL1-11-007). Following the SC injection in subjects with hypoparathyroidism, plasma PTH levels increased rapidly resulting in a double peak concentration profile similar to that seen previously; an initial peak occurred at 5 – 30 min and a second usually smaller peak at 1 – 2 hours after the injection. The baseline adjusted C_{max} was 174 and 233 pg/mL and the baseline adjusted mean $AUC_{0\text{-}last}$ was 572 and 924 pg·h/mL with the 50 µg and 100 µg doses, respectively. Plasma PTH levels declined from the peak with a $t_{1/2}$ of approximately 3 hours with both doses and returned to predose levels at 12 – 24 hours.
Pharmacodynamic Results: • The baseline-adjusted mean E_{max} for serum total calcium was 0.67 and 0.90 mg/dL with the 50 µg and 100 µg doses of NPSP558, respectively, and occurred at a median 12 hours postdose. The corresponding baseline adjusted mean AUC_{net} values were 2.4 and 10.3 mg·h/dL; the median baseline adjusted AUC_{net} values with the 50 µg and 100 µg doses of NPSP558 were 3.3 and 7.6 mg·h/dL, respectively. • Apart from a small increase during the overnight hours, there was little change in serum albumin levels in either period. • The mean E_{max} values for albumin-corrected, baseline-adjusted serum total calcium were 0.74 and 0.93 mg/dL, with the 50 µg and 100 µg doses of NPSP558, respectively, and occurred at a median 12 hours postdose. The corresponding mean AUC_{net} values were 6.07 and 11.4 mg·h/dL; the median AUC_{net} values with the 50 µg and 100 µg doses of NPSP558 were 5.5 and 9.3 mg·h/dL, respectively. • Neither mean serum total calcium, nor mean albumin-corrected serum total calcium had returned to predose levels by 24 hours after the administration of either dose of NPSP558. • The baseline-adjusted mean E_{max} for serum magnesium was 0.13 and 0.16 mg/dL with the 50 µg and 100 µg doses of NPSP558, respectively, and occurred at a median 8 – 9 hours postdose. The corresponding mean AUC_{net} values were 0.83 and 1.47 mg·h/dL; the median AUC_{net} values with the 50 µg and 100 µg doses of NPSP558 were 1.26 and 2.78 mg·h/dL, respectively. Predose mean serum magnesium had returned close to baseline levels by 24 hours after the administration of both doses of NPSP558. • NPSP558 had substantial effects on serum phosphate. Phosphate levels decreased by 1.5 – 1.6 mg/dL from near the upper limit to near the lower quartile of the normal range at a median 5 hours after NPSP558 administration. The baseline adjusted AUC_{net} values were -20.7 and -24.1 mg·h/dL with the 50 µg and 100 µg doses of NPSP558, respectively. The median baseline adjusted AUC_{net} values with the 50

µg and 100 µg doses of NPSP558 were -21.3 and -26.5 mg·h/dL, respectively. Mean serum phosphate remained 0.4 and 0.7 mg/dL below predose levels at 24 hours after administration of the 50 µg and 100 µg doses of NPSP558, respectively.

- The baseline-adjusted mean E_{max} for serum $1,25(OH)_2D$ was 27.2 and 19.6 pg/mL with the 50 µg and 100 µg doses of NPSP558, respectively, and occurred at a median 8 – 16 hours postdose. The mean AUC_{net} values with the 50 µg and 100 µg doses of NPSP558 were 232 and 199 mg·h/dL, respectively; the corresponding median AUC_{net} values were 276 and 101 pg·h/mL. Although serum $1,25(OH)_2D$ levels were highly variable both within and between subjects, serum $1,25(OH)_2D$ had not returned to baseline levels by 24 hours after the administration of either dose of NPSP558.
- Serum creatinine levels decreased following NPSP558 administration. The baseline-adjusted E_{min} was -0.15 – -0.17 mg/dL at a median 10 hours following both doses of NPSP558, but had returned close to predose levels by 24 hours.
- The increase in serum $1,25(OH)_2D$ levels following the oral administration of calcitriol at each subject's habitual dose on the day preceding NPSP558 administration in each period was similar to that observed with NPSP558 treatment, although the T_{Emax} occurred sooner with calcitriol. In general, calcitriol administration had similar or smaller effects on the PD parameters of serum total calcium and albumin-corrected serum total calcium than was observed with NPSP558. The PD parameters for serum magnesium were higher with both doses of NPSP558 than with calcitriol. In contrast, the PD parameters for serum phosphate following calcitriol administration were markedly different than was observed with NPSP558. An initial transient decrease in serum phosphate was followed by an increase above baseline levels resulting in mean AUC_{net} values of -20.7 and -24.1 mg·h/dL with the 50 µg and 100 µg doses of NPSP558, respectively.
- An exploratory analysis showed that creatinine clearance increased by approximately 30% following NPSP558 administration, but had returned to predose levels in the 16 – 24 hour urine collection.
- Urine cyclic AMP-to-creatinine ratio increased approximately 2.3 and 4.4 fold with the 50 µg and 100 µg doses of NPSP558, respectively. The maximum change occurred in the 0 – 3 hour sample and urinary cyclic AMP excretion had returned to predose levels in the 16 – 24 hour samples.
- The urinary fractional excretion of calcium (FE_{Ca}) decreased by approximately 65% to a nadir in the 3 – 6 hour sample with both doses of NPSP558. Thereafter, the FE_{Ca} increased slowly and achieved predose levels in the 10 – 16 hour and 16 – 24 hour samples with the 50 µg and 100 µg doses, respectively.
- The mean total amount of calcium excreted in urine over the 24 hours following the 50 µg and 100 µg doses of NPSP558 was 330 mg and 286 mg, respectively. By comparison, total urinary calcium was 380 mg and 373 mg on the day of calcitriol administration in Period 1 and Period 2, respectively.
- Urinary fractional excretion of magnesium (FE_{Mg}) decreased by approximately 68% to a nadir in the 3 – 6 hour sample with both doses of NPSP558. The FE_{Mg} then increased and was greater than predose levels in the 16 – 24 hour sample with both the 50 µg and 100 µg doses. There was no effect of NPSP558 on 24-hour urinary magnesium excretion.
- Urinary fractional excretion of phosphate (FE_P) increased by 2.6- and 3.3-fold with the 50 µg and 100 µg doses of NPSP558. The maximum FE_P level occurred in the 3 – 6 hour sample. The FE_P then decreased and had returned to predose levels in the 16 – 24 hour sample with both doses of NPSP558.
- The total amount of phosphate excreted in urine over the 24 hours following the 50 µg and 100 µg doses of NPSP558 was 942 mg and 1133 mg, respectively. By comparison, total urinary phosphate excretion was 624 mg and 707 mg on the day of calcitriol administration in Period 1 and Period 2, respectively.

Sponsor/Company Name: NPS Pharmaceuticals
Name of Investigational Product: NPSP558
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])
• In general, calcitriol administration had little overall effect on urinary cyclic AMP, calcium, magnesium, or phosphate excretion. Increases in calcium, magnesium and phosphate excretion were observed in the first 6 hours after dosing although these may be more related to consumption of calcium supplements and meals rather than to calcitriol itself.
Safety Results: • No deaths or serious AEs occurred and no subjects discontinued due to TEAEs. • There were no clinically significant changes from baseline in clinical laboratory parameters, vital signs, physical examinations, or ECGs. • There were no unexpected safety signals.

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. The agency's interpretation of urinary calcium excretion data from this study differed from the sponsor, and is presented in the main text of the review. There were no notable protocol violation and deviations. The bioanalytical method adequately supported the pharmacokinetic evaluation of the co-administered drug. However, the results from this study were not optimally utilized to inform the dosing/dosing regimen decision for the registration trial.

4.1.2 Multiple Dose PK and PD in Patients with Hypoparathyroidism (Mosekilde-IIT PKPD Study)

2 SYNOPSIS

Name of Sponsor/Company: Not applicable N/A	**(For National Authority Use Only)**
Name of Finished Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	
Title of study: Treatment of hypoparathyroidism with subcutaneous rhPTH(1-84) injections: effects on muscle function and quality of life. Amendment: A one-day study on diurnal variations in biochemical indices at the end of the 24-week study period.	
Primary principal investigator: Leif Mosekilde, MD, DMSci	
Study center(s): Århus University Hospital, Endocrinology Department C, Tage-Hansensgade 2, 8000 Århus C, Denmark	
Publication(s) (reference): Sikjaer T, Rejnmark L, Rolighed L, Heickendorff L, Mosekilde L, and the Hypoparathyroid Study Group. The effect of adding PTH(1-84) to conventional treatment of hypoparathyroidism: a randomized, placebo-controlled study. J Bone Miner Res 2011;26:2358–2370. Sikjaer T, Rejnmark L, Rolighed L, Mosekilde L. PTH(1-84) replacement therapy in hypoparathyroidism (HypoPT): a randomized controlled trial on pharmacokinetics and dynamic effects following 24 weeks of treatment. American Society for Bone and Mineral Research Annual Meeting, Sept 2011, San Diego, USA; Abstract 1098. Sikjaer T, Amstrup A, Rolighed L, Rejnmark L, Mosekilde L. PTH(1-84) replacement therapy in hypoparathyroidism (HypoPT): a randomized controlled trial on pharmacokinetics and dynamic effects following 24 weeks of treatment. European Congress on Osteoporosis and Osteoarthritis Annual Meeting, March 2012, Bordeaux, France; Abstract 2012. Sikjaer T, Rejnmark L, Thomsen JS, et al. Changes in 3-dimensional bone structure indices in hypoparathyroid patients treated with PTH(1-84): a randomized controlled study. J Bone Miner Res. 2012;27:781–788.	
Studied period (years): 05 September 2009 29 March 2010	
Objectives: The purpose of this 1-day amendment to this investigator initiated trial (IIT) was to determine diurnal variations in biochemical indices following subcutaneous (SC) administration of rhPTH(1-84) in subjects with hypoparathyroidism after 24 weeks of daily treatment with rhPTH(1-84).	
Methodology: This was a 1-day pharmacokinetic/pharmacodynamic (PK/PD) study, conducted on the last day of the 24-week, randomized, double-blind, placebo-controlled, parallel-group IIT in subjects with hypoparathyroidism receiving active or native vitamin D and calcium supplementation. Subjects fasted on the morning of their last study day of the IIT. Following a morning SC injection of 100 µg of rhPTH(1-84) or placebo in the thigh, blood sampling for determination of plasma rhPTH(1-84), total calcium, albumin, magnesium, and phosphate, as well as urine collection for total calcium, magnesium and phosphate were performed at specified intervals from baseline through 24 hours. This report presents analyses of specific elements of the amendment, namely, PK of rhPTH(1-84), correlations between PTH concentrations and certain PD parameters (calcium, magnesium, and phosphate), and safety.	

Name of Sponsor/Company: Not applicable N/A	**(For National Authority Use Only)**
Name of Finished Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	
Number of subjects (planned and analyzed): Thirty-nine of the 62 subjects who completed 24 weeks of treatment with daily rhPTH(1-84) or placebo in the 24-week IIT were invited to participate in this 1-day PK/PD study conducted according to the protocol amendment. All 39 subjects who received rhPTH(1-84) (n = 22) or placebo (n = 17) were included in the analyses and completed the study.	
Diagnosis and main criteria for inclusion: • Subjects with insufficient PTH production, resulting in low PTH and low circulating calcium concentrations, who completed the 24-week IIT conducted by Dr. L. Mosekilde were eligible for enrollment in the 1-day PK amendment. • Subjects were informed of the nature of the study and sign the Informed Consent Form prior to any screening procedures.	
Duration of treatment: 1 dose (for PK analysis)	
Test product, dose and mode of administration, batch number: rhPTH(1-84) 100 µg SC (PREOTACT®; Nycomed Danmark ApS, Denmark) Batch number not applicable	
Reference therapy, dose and mode of administration, batch number: Placebo SC Batch number not applicable	
Criteria for evaluation: **Pharmacokinetics:** The following PK parameters were calculated using raw data following administration of rhPTH(1-84): Area under the plasma concentration–time curve from time 0 (predose) to the time of the last quantifiable concentration and calculated by linear trapezoidal rule ($AUC_{0\text{-last}}$); maximum plasma concentration (C_{max}); and time to C_{max} (t_{max}). The following PK parameters were calculated using baseline-adjusted data: $AUC_{0\text{-last}}$, area under the plasma concentration–time curve from time 0 extrapolated to infinity and calculated by linear trapezoid rule ($AUC_{0\text{-}\infty}$), C_{max}, t_{max}, terminal rate constant estimated by regression of the terminal log-linear phase of the plasma concentration–time curve (λz), elimination half-life calculated as $0.693/\lambda z$ ($t_{½}$), apparent total body clearance, calculated as dose/$AUC_{0\text{-}\infty}$ (CL/F), and apparent volume of distribution, calculated as dose/$AUC_{0\text{-}\infty} \times \lambda z$ (Vz/F). **Pharmacodynamics:** Blood sample collection for rhPTH(1-84) and total serum calcium, albumin, magnesium, and phosphate concentrations were done at baseline, 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 20, and 24 hours. Urinalysis was conducted at 0-2, 2-4, 4-6, 6-8, 8-16, and 16-24 hours to determine total calcium, magnesium, and phosphate concentrations. **Safety:** Adverse events (AEs) were recorded during the study period. Blood pressure and heart rate were measured and 12-lead electrocardiograms (ECGs) were performed at baseline (predose) and at 1 and 10 hours postdose.	

Name of Sponsor/Company: Not applicable N/A	**(For National Authority Use Only)**
Name of Finished Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	

Statistical methods:

Pharmacokinetics: The PK parameters determined using raw data (listed above) were calculated in WinNonlin® using the Non-Compartmental Analysis (NCA) method. WinNonlin® using the NCA method was also used for calculation of the PK parameters that were determined using baseline-adjusted data. The predose rhPTH(1-84) plasma values measured at time 0 were used as baseline concentrations.

Pharmacodynamics: rhPTH(1-84) plasma concentrations and total serum calcium, albumin-corrected calcium, magnesium, and phosphate concentrations were analyzed.

At each urine collection, urine volume was measured, and urinary concentrations of total calcium, magnesium, and phosphate were analyzed. Correlations between these parameters and PTH concentrations were determined and concentration-time profiles calculated.

Results:

Pharmacokinetics:

rhPTH(1-84) was rapidly absorbed following SC administration of a 100-µg dose. C_{max} was observed less than 1 hour after administration of rhPTH(1-84). Starting at approximately 2 hours after injection, mean plasma rhPTH(1-84) concentration levels declined in an apparent mono-exponential fashion and returned close to baseline between 16 and 24 hours after administration. As expected, rhPTH(1-84) plasma concentrations remained low (close to zero) in the placebo group.

Median t_{max} was observed at 0.36 hours, indicating rapid absorption of rhPTH(1-84) from the SC depot site. Unadjusted and baseline-adjusted mean C_{max} concentrations of rhPTH(1-84) in plasma were relatively similar (228 pg/mL and 210 pg/mL, respectively). Drug exposure ($AUC_{0\text{-}last}$) derived from unadjusted and baseline-adjusted concentrations were 1311 pg•h/mL and 950 pg•h/mL, respectively.

CL/F, $t_{1/2}$, and Vz/F of rhPTH(1-84) were 89.0 L/h, 2.00 h, and 256 L, respectively.

Pharmacodynamics: In subjects receiving rhPTH(1-84), the plasma rhPTH(1-84) concentration peaked during the first hour after administration, and plasma concentrations of calcium, albumin-corrected calcium, and magnesium reached a peak at approximately 8 hours after rhPTH(1-84) administration then returned to approximately baseline levels at the 24-hour time point. Plasma phosphate concentration decreased in the first 2 hours after rhPTH(1-84) administration, then increased over the 24-hour period before returning to approximately baseline level at 24 hours, probably due to the ingestion of alphacalcidol during the PK/PD assessment day.

For placebo subjects, there was no clear correlation between plasma rhPTH(1-84) concentration and PD biomarkers. Plasma calcium, magnesium, and phosphate concentrations remained fairly stable.

Urinalysis conducted during the study did not produce meaningful results. Resulting figures are skewed due to the inclusion of data for a subject who took large amounts of oral supplementation throughout the analysis period and due to broad collection periods, which ranged from 2 hours to 8 hours.

Name of Sponsor/Company: Not applicable N/A	**(For National Authority Use Only)**
Name of Finished Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	
Safety and tolerability results: Two adverse events occurred during this study, both in the rhPTH(1-84) group. One subject had arterial thrombosis in the right femoral artery requiring hospitalization , and 1 subject had superficial thrombophlebitis. Both events were unrelated to treatment and resolved with appropriate treatment. There were no significant adverse effects of rhPTH(1-84) on heart rate, blood pressure, or ECG. **Conclusion:** The results of this 1-day IIT study confirmed findings of a sponsor-conducted PK/PD study (Study C09-002) with rhPTH(1-84) in subjects with hypoparathyroidism: the administration of 100 µg SC leads to rapid absorption and peak, followed by a return to baseline values within 16 to 24 hours. These comparisons indicate that this pattern is unchanged after 24 weeks of therapy with rhPTH(1-84).	
Date of the report: 14 September 2012	

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. The agency's interpretation of urinary calcium excretion data from this study differed from the sponsor, and is presented in the main text of the review.

4.1.3 PKPD in Renal Impairment (CL1-11-010)

Name of Sponsor/Company: NPS Allelix Corporation	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
Name of Active Ingredient: ALX1-11, rhPTH(1-84)	Page:	
Title of Study: Pharmacokinetics of a single subcutaneous injection of 100 µg of ALX1-11 in subjects with mild-to-moderate renal impairment		
Protocol No: CL1-11-010		
Primary Principal Investigator: R. J. Noveck and L. A. Galitz		
Study centers: MDS Pharma Services, New Orleans, LA, and SFBC International, Inc., Miami, FL		
Publication(s) (reference): None at this time		
Studied period: 5 months First subject enrolled: 30 Sep 2003 Last subject completed: 03 Mar 2004	Phase of development: I	
Objectives: The primary objective of this study was to describe the pharmacokinetics (PK) of ALX1-11 administered as a single 100-µg subcutaneous injection in subjects, age 45 or older, with mild-to-moderately impaired renal function, and to compare the pharmacokinetic profile to that observed in subjects with normal renal function who are distributionally matched to the renally impaired subjects by gender and body mass index (BMI). The secondary objective of this study was to assess the safety and tolerability of ALX1-11 administered as a single 100-µg subcutaneous injection in subjects, age 45 or older, with mild-to-moderately impaired renal function.		
Methodology: This was an open-label, single-dose, multicenter study enrolling a total of 32 subjects. Subjects were to remain at the study center from the evening before ALX1-11 dosing until approximately 24 hours after dosing. Blood samples were obtained for analyses of ALX1-11 concentrations and serum total calcium. The study consisted of screening (Days –21 to –6), admission/baseline assessment (Day –1), dosing (Day 0), and end of study (Day 1). Eligible subjects were admitted to the clinical study unit on the evening of Day –1 when baseline laboratory and electrocardiogram (ECG) assessments were performed. Subjects meeting all continuation criteria were dosed on Day 0, and remained at the clinical center until discharge approximately 24 hours after dosing (Day 1). The following safety assessments were made: 12-lead ECG; physical examinations; vital signs; clinical laboratory evaluations (hematology, serum chemistry, urinalysis, pregnancy testing [for women of childbearing potential < 60 years of age], and testing for common drugs of abuse); and adverse events (AEs).		
Number of subjects (planned and analyzed): 32 planned; 31 analyzed for pharmacokinetics, 32 analyzed for safety.		
Diagnosis and main criteria for inclusion: Men and women, age 45 years or older, with BMI 18–45 kg/m^2 (inclusive) and either mild-to-moderate renal impairment or without impaired renal function. The subjects were divided into 2 groups of 16 subjects each. Those with an estimated creatinine clearance (CL_{cr}) of > 80 mL/min were assigned to group 1 (normal renal function), and those with CL_{cr} of 30–80 mL/min were assigned to group 2 (mild-to-moderate renal impairment). In group 2, no more than 12 subjects were to be of 1 gender, and at least 2 women and 2 men had to have moderate impairment (CL_{cr} 30–50 mL/min). Every attempt was to be made to match each renally impaired subject with a healthy subject by gender and BMI		

Name of Sponsor/Company: NPS Allelix Corporation	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
Name of Active Ingredient: ALX1-11, rhPTH(1-84)	Page:	

(± 15%) (Amendment 3 deleted the requirement to also match subjects by age). If individual matching of subjects was not practical, then renally impaired subjects were enrolled first, and healthy subjects enrolled afterwards and distributional matching was done.

Test product, dose and mode of administration, batch number:
Dosing was preceded by an overnight fast of at least 8 hours (water was allowed) and was performed in the morning to enable the drawing of all blood samples needed for pharmacokinetic analysis. All eligible subjects were to receive a single dose of 100 µg ALX1-11 via subcutaneous injection into the left lower quadrant of the abdomen.

Batch #239050/1 239052

Duration of treatment:
Dosing (sc injection) followed by observation for approximately 24 hours

Reference therapy, dose and mode of administration, batch number: NA

Criteria for evaluation:

Efficacy:
Efficacy was not assessed in this study.

Safety:
The following safety assessments were made: 12-lead ECG; physical examinations; vital signs; clinical laboratory evaluations (hematology, serum chemistry, urinalysis, pregnancy testing [for women of childbearing potential < 60 years of age], serum total calcium levels, and testing for common drugs of abuse); and adverse events.

Pharmacokinetic:
Blood samples for pharmacokinetic analysis were collected pre-dose (time=0, within 30 minutes before dosing), then at the following post-injection time points: 5, 10, 20, and 30 min; and 1, 1½, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hr. (b) (4)) determined plasma concentrations of ALX1-11 using a validated analytical procedure.

C_{max}: Maximum observed plasma concentration.
t_{max}: Time to maximum observed plasma concentration.
AUC_{0-last}: Area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration, calculated by the linear trapezoidal rule.
C_{base}: Baseline PTH concentration, calculated as the average of the PTH concentrations at pre-dose (eg, day -1, pre-dose -1 hour and pre-dose 0 hour) and 24-hour post-dose time points. Values below the assay limit of quantification will not be included in this calculation (ie, they will be treated as missing).
Baseline corrected C_{max}: Maximum observed baseline-corrected plasma concentration, where the baseline-corrected plasma concentrations are calculated as the observed plasma concentrations minus C_{base}.
Baseline corrected AUC_{0-last}: Area under the baseline-corrected plasma concentration-time curve from time 0 to time of last positive baseline-corrected plasma concentration, calculated by the linear trapezoidal rule. Baseline corrected plasma concentrations are calculated as the observed plasma concentrations minus C_{base}. Negative post-dose baseline-corrected plasma concentrations will be set to 0 along with all positive baseline-corrected plasma concentrations after the first negative value.

Name of Sponsor/Company: NPS Allelix Corporation	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
Name of Active Ingredient: ALX1-11, rhPTH(1-84)	Page:	

Statistical methods:
The study was conducted at 2 centers. Before pooling across centers, demographic, creatinine clearance, and selected pharmacokinetic data were summarized by center and reviewed. No interim analysis was performed in this study. Pharmacokinetic parameters were calculated from the concentration-time data using noncompartmental techniques. All statistical significance tests and confidence intervals are two-sided.

SUMMARY AND CONCLUSIONS

Pharmacokinetic results:
The mean maximum concentration (C_{max}) and mean baseline-corrected C_{max} of PTH following 100 µg ALX1-11 to subjects with mild-to-moderate renal impairment was approximately 22% and 23%, respectively, higher than that observed in subjects with normal renal function. The variability of C_{max} was high, with CV% estimates of 77% to 81%, for subjects with mild-to-moderate renal impairment and 63% to 67% for subjects with normal renal function.

Exposure to PTH as measured by AUC_{0-last} and baseline-corrected AUC_{0-last} was approximately 3.9% and 2.5%, respectively, higher than that observed for subjects with normal renal function. The variability of AUC_{0-last} was moderate to high, with CV% estimates of 35% to 49% for subjects with mild-to-moderate renal impairment and 54% to 79% for subjects with normal renal function.

The geometric mean ratios (%) for the comparison between treatment groups for C_{base}, C_{max} (uncorrected), and AUC_{0-last} (uncorrected and baseline-corrected) were 105.16, 125.63, 101.51, and 101.71, respectively. The 90% confidence intervals (CIs) were all within the range of 50% to 200%. For baseline-corrected C_{max}, the geometric mean ratio (%) was 127.45 and the upper range of 90% CI of the ratio was over 200%, which was slightly outside of the limits for concluding equivalence for the 2 treatment groups.

Safety results:
Overall, the administration of ALX1-11 was well tolerated. There were no deaths, no serious AEs, and no other significant AEs. A total of 4 AEs (nausea, vomiting, and injection site phlebitis) in 3 subjects (2 in the normal and 1 in the renally impaired group) were of mild to moderate severity. There were no laboratory abnormalities of clinical significance, and none were reported as AEs or required intervention. Similarly, none of the changes in vital signs and ECG from baseline were of clinical significance. Following subcutaneous administration of ALX1-11, changes in mean baseline-corrected serum total calcium concentrations in subjects with impaired renal function were within normal limits.

Conclusions:
Mild-to-moderate renal impairment did not have a clinically meaningful effect on the pharmacokinetics of PTH. A subcutaneous dose of 100 µg ALX1-11 was generally safe and well tolerated by subjects with mild-to-moderate renal impairment. No dosing adjustment is recommended for this group of subjects.

Date of the report: 01 Nov 2004

Reviewers Comments: The synopsis of this previously reviewed study[7] is presented for sake of completion. The Agency's additional interpretation of PD data is presented in the main review.

4.1.4 PK in Hepatic Impairment (CL1-11-009)

Name of Sponsor/Company: NPS Allelix Corporation	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
Name of Active Ingredient: ALX1-11, rhPTH(1-84)	Page:	
Title of Study: Pharmacokinetics of a single subcutaneous injection of 100 µg of ALX1-11 in subjects with moderate hepatic impairment		
Protocol No: CL1-11-009		
Primary Principal Investigator: Robert J. Noveck, MD		
Study Centers: Clinical Research Center, 2237 Poydras St., New Orleans, LA 70119-7561; SFBC International, Inc., 11190 Biscayne Blvd., Miami, FL 33181		
Publication(s) (reference): Not applicable		
Studied Period: First subject enrolled: 8 July 2003 Last subject completed: 25 Sep 2003	**Phase of Development:** I	
Objectives: The primary objective of this study was to describe and compare the pharmacokinetics of ALX1-11 from a single 100-µg subcutaneous injection dose in subjects, age 45 or older, with moderately impaired hepatic function, to subjects with normal hepatic function who were distributionally matched for age, gender, and body mass index (BMI). The secondary objective of this study was to describe and compare the safety and tolerability of ALX1-11 from a single 100-µg subcutaneous injection dose in subjects with moderately impaired hepatic function to subjects with normal hepatic function who were distributionally matched for age, gender, and BMI.		
Methodology: This was an open-label, single-dose study in 12 subjects (6 women and 6 men) with moderate hepatic impairment and 12 distributionally matched subjects with normal hepatic function. Each subject received a 100-µg dose of ALX1-11 administered subcutaneously into the abdomen. Blood samples were collected for 24 hours. Plasma PTH concentrations were determined to characterize the pharmacokinetics of ALX1-11. Serum total calcium, which changes as a pharmacodynamic response to PTH, was determined primarily as a safety measure in this study. The study consisted of screening (Days –21 to –2), admission/baseline assessment (Day –1), and dosing and follow-up (Days 0-1). Day 1 was the end-of-study/discharge day. Eligible subjects were admitted to the clinical study unit on Day –1. Clinical and laboratory assessments were performed on Day –1. Subjects meeting all continuation criteria were dosed on Day 0, and remained at the clinical site until discharge approximately 24 hours after dosing (Day 1). The following additional safety assessments were made: 12-lead electrocardiograms (ECGs); physical examinations; vital signs; clinical laboratory evaluations (hematology, serum chemistry, urinalysis); and adverse events (AEs).		
Number of Subjects (planned/analyzed): 24/24.		
Diagnosis and Main Criteria for Inclusion: A total of 24 subjects, age 45 or older, were dosed: 12 subjects (6 men and 6 women) with moderate hepatic impairment as defined by Child-Pugh classification of severity of liver disease (grade B), and 12 subjects comparable in age (±5 years), gender, and BMI (±15%), with normal hepatic function.		
Test Product, Dose and Mode of Administration, Batch Number: ALX1-11 for subcutaneous injection was provided as a lyophilized formulated powder that was reconstituted in a multi-dose, dual-chamber, 1-mL cartridge in an injection pen. The 2 batch numbers used in this study were 245059/2 245061, and 307010/2 307012. A single 100-µg dose was administered subcutaneously into the abdomen during the morning following an 8-hour overnight fast from food (not including water). The formulation and dose used in this study were the same as those used in the Phase III studies.		
Duration of Treatment: Single dose and evaluations for approximately 24 hours after dosing.		

Name of Sponsor/Company: NPS Allelix Corporation	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
Name of Active Ingredient: ALX1-11, rhPTH(1-84)	Page:	

Reference therapy, dose and mode of administration, batch number: Not applicable

Criteria for Evaluation:

Efficacy:

Efficacy was not assessed in this study.

Pharmacokinetics:

Blood samples for pharmacokinetic analysis were collected at the following times: predose (0 hr), 5, 10, 20, and 30 minutes, and 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 24 hours. Plasma concentrations of PTH were determined using a validated analytical procedure. For each subject, the following pharmacokinetic parameters were calculated from the concentration-time data using noncompartmental techniques:

- C_{base} – baseline PTH concentration defined as the average of the PTH concentrations at the 0-hour (predose) and the 24-hour time points
- C_{max} – maximum observed plasma concentration
- baseline-corrected C_{max} – maximum observed plasma concentration corrected for C_{base}
- $AUC_{0\text{-last}}$ – area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration
- baseline-corrected $AUC_{0\text{-last}}$ – area under the plasma concentration-time curve from time 0 to time of last measurable plasma concentration using plasma PTH concentrations corrected for C_{base}
- T_{max} – time of maximum observed plasma concentration time point

Safety:

Clinical evaluations (i.e., vital signs, physical examinations, ECGs, AE monitoring), and laboratory safety tests (i.e., hematology, serum chemistries, and urinalysis) were obtained prior to and after ALX1-11 administration.

Statistical Methods:

Pharmacokinetics:

Log-transformed C_{base}, C_{max}, baseline-corrected C_{max}, $AUC_{0\text{-last}}$, and baseline-corrected $AUC_{0\text{-last}}$ were each fit by an analysis of covariance model with hepatic impairment group as a factor, and age and BMI as covariates. The effect of hepatic impairment on the pharmacokinetics of ALX1-11 was assessed by examining the group ratio for each parameter, the 90% confidence intervals for the ratios, and box-plots of pharmacokinetic parameters by hepatic impairment group.

Safety:

All subjects dosed with ALX1-11 were included in the safety analysis. Descriptive statistics (e.g., mean, median, minimum, maximum) were used to summarize the safety parameters.

Summary and Conclusions:

Pharmacokinetic Results:

The mean baseline PTH concentrations (C_{base}) were similar between the hepatic function groups. Subjects with normal function had a mean value of 19.5 pg/mL and subjects with moderate impairment had a mean value of 18.3 pg/mL.

The mean and individual plasma PTH concentration-time profiles over the 24-hour sampling interval were comparable between the normal subjects and subjects with moderate hepatic impairment. The median time to reach maximum concentration was slightly shorter for subjects with moderate hepatic impairment.

Pharmacokinetic parameters were calculated with and without correction for endogenous levels of PTH. The mean C_{max} and baseline-corrected C_{max} values were 18% to 20% greater in the moderately impaired subjects than in those with normal function. The mean $AUC_{0\text{-last}}$ was similar between the groups, while the baseline-corrected $AUC_{0\text{-last}}$ was 20% greater in the moderately impaired group. Variability was high, with coefficient of variation values ranging from 40% to 91% for these exposure parameters.

Log-transformation of these data also indicated that moderate hepatic impairment had little effect on the

Name of Sponsor/Company: NPS Allelix Corporation	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
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pharmacokinetics of ALX1-11, with differences in the geometric means of 42% or less. However, the 90% confidence intervals of these mean parameter ratios were wide.
Mean serum total calcium concentrations increased slightly in response to increased PTH levels, but remained within the normal range. There were no apparent differences in the serum total calcium concentration-time profiles between the 2 hepatic function groups.

Safety results:
There were no serious AEs and no subjects withdrew from treatment for an AE. A total of 5 subjects reported 8 treatment-emergent AEs: headache (3 events), injection site erythema (2), nausea (2), and vomiting (1). All 5 of these subjects were in the group with normal hepatic function. All events were mild-to-moderate in intensity. In both groups, there were no clinically meaningful changes in laboratory values, vital sign measurements, or ECG parameters.

Conclusions:
Moderate hepatic impairment did not have a clinically meaningful effect on the pharmacokinetics of ALX1-11 or on serum calcium concentrations. A subcutaneous dose of 100 µg ALX1-11 was generally safe and well-tolerated by all subjects. No dosing adjustment is recommended for patients with moderately impaired hepatic function.

Date of the report: 06 May 2004

Reviewers Comments: The synopsis of this previously reviewed study[7] is presented for sake of completion. The Agency's additional interpretation of PD data is presented in the main review.

4.1.5 Relative BA (thigh versus abdomen in post-menopausal women) (CL-11-007)

Name of Sponsor/Company: NPS Allelix Corp.	**Individual Study Table Referring to Part of the Dossier:**	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
Name of Active Ingredient: ALX1-11, rhPTH(1-84)	Page:	
Title of Study: A phase I, randomized, three-way crossover bioavailability study of ALX1-11 in normal healthy postmenopausal women		
Protocol No: CL1-11-007		
Primary Investigator: James D. Carlson, Pharm.D.		
Study center: PRACS Research Institute, Ltd 4801 Amber Valley Parkway Fargo, ND 58104 701-239-4750 (Office Telephone No.)		
Publication(s) (reference): Not applicable		
Studied period: 2 months First subject enrolled: 15 October 2002 Last subject completed: 17 December 2002	Phase of development: I	
Objectives: To evaluate the comparative bioavailability of subcutaneous injection of ALX1-11 to an abdominal site and to the upper thigh in normal healthy postmenopausal women To assess the intra-subject variation of pharmacokinetic parameters for ALX1-11 following subcutaneous injection to an abdominal site in normal healthy postmenopausal women To continue to evaluate the safety of a subcutaneous injection of 100 µg of ALX1-11 in normal healthy postmenopausal women		
Methodology: Potential subjects were screened to assess their eligibility within 8 days to 2 days prior to study entry. Subjects were randomized to one of three treatment sequences. Subjects in Sequence I sequentially received treatment A followed by treatment A, and finally treatment B. Subjects in Sequence II sequentially received treatment B followed by treatment A, and finally treatment A. Subjects in Sequence III sequentially received treatment A followed by treatment B, and finally treatment A.		
Number of subjects (planned and analyzed): 18		
Diagnosis and main criteria for inclusion: Normal healthy postmenopausal subjects. Subjects had to have been postmenopausal for at least one year and had to be within ±15% of their ideal body weight for height and frame.		
Test product, dose and mode of administration, batch number: The treatments administered in this study were as follows: Treatment A: Single 100 µg dose of ALX1-11 administered subcutaneously into the abdomen. Lot number 150019/2 150021. Treatment B: Single 100 µg dose of ALX1-11 administered subcutaneously in the upper thigh. Lot number 150019/2 150021.		
Duration of treatment: 20 days; single dose of study drug on day 1 of each of 3 treatment periods		

Name of Sponsor/Company: NPS Allelix Corp.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
Name of Active Ingredient: ALX1-11, rhPTH(1-84)	Page:	

Reference therapy, dose and mode of administration, batch number:

Treatment A: Single 100 µg dose of ALX1-11 administered subcutaneously into the abdomen. Lot number DR02113. Note: Subjects received treatment A on two separate occasions.

Criteria for evaluation:

Safety: All subjects who received at least one dose of ALX1-11 were included in the safety analysis. Safety evaluations were performed during each period as described in the protocol. Descriptive statistics (e.g., mean, median, min, max) were used to summarize the safety parameters. No formal statistical analyses were planned.

Pharmacokinetic: Subjects who received at least one dose of ALX1-11 and had plasma concentrations post-dose were included in the pharmacokinetic analysis. The evaluable pharmacokinetic population included subjects who received treatment A and treatment B, and who had sufficient plasma concentration data for evaluation of C_{max} and baseline-corrected AUC_{0-t} following each treatment.

For each subject, the following pharmacokinetic parameters were calculated, whenever possible, based on the plasma concentrations of PTH, according to the model-independent approach for each treatment using WinNonlin Enterprise (Version 4.0.1), Pharsight.

C_{max} Maximum observed plasma concentration over the sampling interval.

T_{max} Time to maximum plasma concentration.

AUC_{0-t} Area under the plasma concentration-time curve from Time 0 to time of last measurable plasma concentration, calculated by the linear trapezoidal rule.

To understand the effects of subcutaneous administration, AUC and C_{max} were baseline corrected for endogenous levels of PTH that were already present. Concentrations of PTH at the 0 and 24-hour timepoints were used to make these corrections as it is assumed that the levels of PTH are back to endogenous baseline concentrations by the 24 hour timepoint. The following additional parameters were determined:

Baseline PTH concentration, defined as the average of the endogenous PTH concentrations at the 0 (pre-dose) hour and 24 hour timepoints.

Baseline corrected AUC_{0-t} calculated as (AUC_{0-t} - baseline AUC_{0-t}) where baseline AUC_{0-t} is the AUC_{0-t} calculated from the 0-hour and 24-hour timepoints.

Baseline-corrected C_{max}; calculated as the observed (C_{max} - the baseline PTH concentration).

Statistical methods:

Treatment classifications of the statistical analysis included A1 (Period 1 of sequence I or II, or Period 2 of sequence II) and A2 (Period 2 of sequence I or Period 3 of sequence II or III). Relative bioavailability of treatment B compared to A1 and A2, and of A1 compared to A2, intra-subject variability for treatment A, and the difference in intra-subject variability between treatments B and A were evaluated based on C_{max} and baseline-corrected AUC_{0-t}, of the pharmacokinetic evaluable population. Data for C_{max} and baseline corrected AUC_{0-t} were natural log (ln) transformed prior to analysis. The SAS Mixed Procedure was used to fit a model for the effects of study sequence, subject (random), period, and treatment effect. Bioavailability ratios and the 90% confidence intervals were reported for A1/A2, B/A1, and B/A2 comparisons of C_{max}, and baseline corrected AUC_{0-t}. Any evident ($p<0.15$) sequence or period effect was described and the relevant mean summaries presented.

Name of Sponsor/Company: NPS Allelix Corp.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
Name of Finished Product: Parathyroid hormone (PTH)	Volume:	
Name of Active Ingredient: ALX1-11, rhPTH(1-84)	Page:	

Summary and Conclusions:

Pharmacokinetic results:

Endogenous PTH concentrations were measurable in all study subjects prior to each study period, and ranged from 14.84 pg/mL to 38.67 pg/mL. The endogenous PTH concentrations present prior to dosing and at the 24-hour timepoint were averaged to determine a baseline PTH concentration. The mean baseline PTH concentrations were similar across all treatments. Among all subjects, the mean ± SD baseline PTH concentrations were 25.13 ± 5.88 pg/mL, 23.95 ± 5.56 pg/mL and 24.04 ± 7.10 pg/mL for treatments A1, A2, and B, respectively. There was low variability for the baseline PTH concentrations as evidenced by CV% values of less than 30% for all treatments. Also the geometric mean baseline PTH concentrations were similar across period ranging between 22 pg/mL and 24 pg/mL among all subjects.

The endogenous PTH concentrations measured at 0 and 24 hours were used to correct AUC estimates for endogenous PTH levels. Since the $T_{1/2}$ of subcutaneously administered PTH is estimated at 2 hours, it was expected that PTH levels at 0 and 24 hr represent endogenous PTH. PTH concentrations were slightly lower at the 24-hour timepoint when compared to the 0-hour timepoint suggesting that there may have been some negative feedback due to the slightly elevated levels of serum calcium resulting from ALX1-11 administration. In an attempt to better estimate the effect of ALX1-11 on PTH levels, the endogenous PTH concentrations at the 0-hour and 24-hour timepoint were used to baseline-correct the AUC estimates. In addition, the PTH concentrations for two subjects did not increase above baseline following ALX1-11 administration. Plasma PTH concentrations for subject 0003 did not increase above endogenous levels measured in this subject for treatments B and A2, and the concentrations of PTH did not increase above endogenous levels for subject 0008 for treatment B. Therefore, these subjects were excluded from the treatment comparisons.

The mean maximum concentration, C_{max}, was similar for treatments A1 and A2, but was substantially lower following treatment B. Among all subjects the mean C_{max} ± SD estimates were 553.05 ± 223.54 pg/mL, 459.42 ± 189.97 pg/mL and 293.54 ±. 133.92 pg/mL for treatment A1, A2 and B, respectively. The variability of C_{max} was comparable between treatments as evidenced by a CV% range of 40.42% to 45.62%. Excluding subjects 0003 and 0008, the CV% of C_{max} following treatment A1 was unchanged, 40.42% to 40.54%, but the CV% following treatments A2 and B appeared to be reduced, respectively from 41.35% to 31.93% and from 45.62% to 30.68%.

T_{max} was similar for all treatments with median values of 1.00 hr, 1.27 hr and 0.84 hr for treatments A1, A2 and B, respectively. Excluding subjects 0003 and 0008 the median T_{max}following treatment B was 0.17 hr which was lower than what was observed for treatments A1 and A2.

Exposure to PTH, as measured by AUC_{0-t} values was similar for treatments A1 and A2, and was slightly lower for treatment B as evidenced by mean ± SD values of 2129.07 ± 581.94 pg*hr/mL, 2015.05 ± 602.86 pg*hr/mL, and 1771.50 ± 555.29 pg*hr/mL for treatments A1, A2 and B, respectively, evaluated among all subjects. When AUC_{0-t} was corrected for baseline, the treatment ratios were similar to the uncorrected ratios. The baseline-corrected AUC_{0-t} values were 1526.99 ± 574.66 pg*hr/mL, 1442.16 ± 560.40 pg*hr/mL, and 1199.48 ± 570.93 pg*hr/mL for treatments A1, A2, and B, respectively, evaluated among all subjects. The variability in AUC_{0-t} (%CV = 27.33% to 31.35%) was slightly lower than that observed for the baseline-corrected AUC_{0-t} (%CV = 37.63% to 47.60%). Excluding subjects 0003 and 0008, the CV% of baseline-corrected AUC_{0-t} following treatment A1 was unchanged, 37.63% to 37.93%, but the CV% following treatment A2 and B appeared to be reduced, respectively from 38.86% to 30.82% and from 47.60% to 29.02%.

Excluding subjects 0003 and 0008, comparisons of B:A1 or B:A2 had C_{max} ratios (90% confidence intervals) of 66% (54% to 80%) or 58% (48% to 70%) and each had baseline-corrected AUC_{0-t} ratios of 88% (78% to 99%). Confidence intervals for the two B:A baseline-corrected AUC_{0-t} ratios were very similar and each

Name of Sponsor/Company: NPS Allelix Corp.	Individual Study Table Referring to Part of the Dossier:	(For National Authority Use Only)
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90% confidence interval was only slightly below the standard interval (80% to 125%) for rejecting a hypothesis of non-equivalence.

The A1:A2 comparison among the sample excluding subjects 0003 and 0008 had a C_{max} ratio [90% confidence interval] of 88% [71% to 111%] and a baseline-corrected AUC_{0-t} ratio of 100% [87% to 115%].

Safety results:

Adverse Events: In general, adverse events were reported more frequently with the abdominal injections than with the thigh injections. There was no increase in incidence of adverse events with the second abdominal injection in comparison with the first abdominal injection. All reported adverse events were determined to be mild by the investigator and primarily associated with study drug.

Laboratory Data: The majority of the abnormal laboratory values were minimally outside of the corresponding normal range. There were no meaningful changes among laboratory results measured at screening or at study completion either for an individual subject or overall.

Serum Calcium Samples: Elevated calcium levels were reported slightly more frequently with the thigh injection than with the abdominal injection; the numbers, however, are too small to make any conclusions. Mean serum total calcium concentrations were within the normal range. Frank hypercalcemia, defined in the Investigator's Brochure as serum total calcium above 11.5 mg/dL, was not observed for any subject. No subject was withdrawn due to elevated calcium concentrations.

Vital Signs: No changes were observed in individual subject data or overall mean changes by treatment or intervals other than what would be considered acceptable variability for vital sign and weight parameters.

Electrocardiograms: Across all subjects, the mean heart rate and electrocardiogram intervals were within normal limits and not notably different among injection sites or intervals. There was no difference observed in the mean change over the intervals measured.

Conclusions:

Overall, ALX1-11 was safe and well-tolerated when administered as a 100 µg subcutaneous injection to the abdomen or the thigh. The relative bioavailability of PTH, as measured by overall exposure (AUC), was only slightly lower following the administration of ALX1-11 to the thigh when compared to the abdomen. However, the peak exposure (C_{max}) of PTH following thigh injection was considerably lower than that of abdominal injection. In addition, a second administration of ALX1-11 to the abdomen resulted in comparable bioavailability estimates. Intrasubject variability among all injections was calculated as 18% for AUC or 30% for C_{max}. This degree of variability is not unexpected for a subcutaneously administered drug.

Date of the report: 10 May 2004

Figure 1 below summarizes PK and PD results from this study

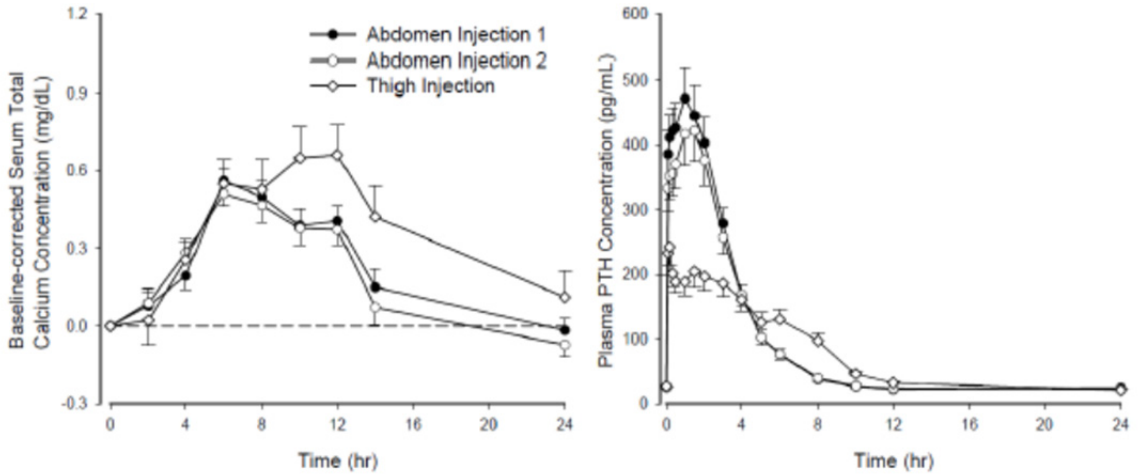


Figure 1. Mean (± SE) Change in Serum Total Calcium Concentrations (left panel) and Plasma PTH(1-84) Concentrations (right panel) Following Subcutaneous Administration of 100 μg rhPTH(1-84) to the Abdomen or Thigh of Healthy Postmenopausal Women – Study CL1-11-007

(Source: Figure 2-10 2.7.2 Summary of Clinical Pharmacology Studies)

Reviewers Comments: The results of this study indicated the dependence of serum calcium response on duration of exposure rather than magnitude of exposure. The sponsor's assessments and conclusions from this study are acceptable. The data was collected in post-menopausal women with normal parathyroid function. However, this information was not optimally utilized in designing the product or dosage-regimen for use in patients with hypoparathyroidism.

4.1.6 BE Study (Comparison of two pen injectors: PAR-C10-005)

Study Synopsis:

Name of Sponsor/Company: NPS Pharmaceuticals, Inc.	**(For National Authority Use Only)**
Name of Finished Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	
Title of study: 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	
Protocol no: PAR-C10-005	
Primary principal investigator: Douglas Logan, MD	
Study center(s): Medpace Clinical Pharmacology Unit; 4685 Forest Avenue, Suite B; Cincinnati, Ohio 45212	
Publication(s) (reference): There have been no publications based on this study.	
Studied period (years): 16 June 2011 (first subject, first visit) 30 July 2011 (last subject, last visit)	**Phase of development:** 1
Objectives: The primary objective of this study was to assess the comparative in-vivo bioequivalence of NPSP558, recombinant human parathyroid hormone (rhPTH[1-84]), administered as single subcutaneous (SC) doses of 100 µg delivered by the clinically tested Ypsomed and to-be-marketed Haselmeier pen injection devices in healthy volunteers. The secondary objective of this study was to assess safety (including measurement of calcium and phosphate levels) and tolerability of a 100-µg SC injection of NPSP558 administered by the Ypsomed and Haselmeier pen injection devices in healthy volunteers.	
Methodology: This study was designed as a randomized, open-label, single-dose, two-treatment, two-period, crossover, single-center study in which approximately 50 healthy volunteers were to be randomized to one of two treatment sequences, beginning with one of two pen injection devices. Following a screening period of up to approximately 30 days, subjects who met eligibility criteria were domiciled on the check-in day (Day -1) and randomized in a 1:1 ratio to a pen lot number that corresponded to either the Ypsomed or Haselmeier injection pen. Subjects received a single 100-µg SC injection of NPSP558 administered with the designated pen on Day 1. A single 100-µg SC injection of NPSP558 was administered with the opposite injection pen on Day 4. There was a 3-day washout interval between doses, including the day of the first morning injection. Following each injection, blood samples were collected at multiple time points. Both NPSP558 injections were administered in the mid-thigh, approximately 15 cm above the patella, but in alternating thighs. Haselmeier and Ypsomed pen injections were administered by trained study personnel. A subject was to be administered both injections by the same trained study personnel.	
Number of subjects (planned and analyzed): Fifty healthy volunteer subjects were enrolled in the study at one investigational site, with the goal of having at least 46 subjects complete the study. This sample size was based on the variability of C_{max} following drug administration in the abdomen from earlier pharmacokinetic (PK) studies. Female and male subjects were to be enrolled in an approximate 1:1 ratio. Fifty subjects completed the study and the data from 50 subjects were analyzed.	

Name of Sponsor/Company: NPS Pharmaceuticals, Inc.	**(For National Authority Use Only)**
Name of Finished Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	

Diagnosis and main criteria for inclusion:

- Adult males or females age 18 to 55 years, inclusive, at the time of signing the informed consent form
- Agreement to abstain from sexual activity during the domiciled treatment period
- Absence of clinical evidence or history (including that from medical and medication history, physical examination, laboratory, electrocardiogram and any other available test results such as those from medical imaging studies) of significant cardiovascular, respiratory, renal, gastrointestinal, hematologic, neurologic, or psychiatric disorder or of any disease that may interfere with the objectives of the study or with the subject successfully completing the study
- No history of abnormalities of calcium homeostasis including hyperparathyroidism, hypoparathyroidism, hyperthyroidism, Cushing's syndrome, hypercalcemia, hypocalcemia, or any other calcium disorder
- Total serum calcium $\leq$ upper limit of normal (ULN) at screening or check-in
- Serum PTH levels $\leq$ ULN at screening
- Body mass index ≤ 30 kg/m^2
- Not presently taking prescription or over the counter medication (including vitamins, herbs, or dietary supplements) which cannot be discontinued. The administration of any concomitant medication during the study was prohibited without prior approval by the sponsor, unless its use was deemed necessary in a medical emergency or would not affect the integrity of the study, such as a nonsteroidal analgesic agent, excluding aspirin. All medications were discontinued at least 1 week prior to check-in, unless otherwise noted. (Note: oral, implantable, vaginal rings, transdermal patch and injectable contraceptives, and/or hormone replacement therapy were allowed.)

Duration of treatment: Following a screening period of up to approximately 30 days, the duration of the domiciled part of the study for each subject was 6 days.

Test product, dose and mode of administration, batch number:

NPSP558, recombinant human parathyroid hormone (rhPTH[1-84]), is manufactured using a strain of *Escherichia coli* modified by recombinant deoxyribonucleic acid (DNA) technology and is identical to native human PTH. NPSP558 is a single-chain polypeptide containing 84 amino acid residues.

Single SC injections of NPSP558 100 µg were administered into the mid-thigh, approximately 15 cm above the patella utilizing the following NPSP558 lot numbers:

Study Drug for use with Haselmeier injection pen: P10001D
Lot number of Haselmeier injection pens: 14865

If the Ypsomed pen injector was used for the first administration, the administration with the Haselmeier pen injector was done on the opposite thigh.

Name of Sponsor/Company: NPS Pharmaceuticals, Inc.	**(For National Authority Use Only)**
Name of Finished Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	

Reference therapy, dose and mode of administration, batch number:

Single injections of NPSP558 100 µg SC were administered into the mid-thigh, approximately 15 cm above the patella utilizing the following NPSP558 lot numbers:

Study Drug for use with Ypsomed injection pen: P10001D
Lot number of Ypsomed injection pens: H051

If the Haselmeier pen injector was used for the first administration, the administration with the Ypsomed pen injector was done on the opposite thigh.

Criteria for evaluation:

Pharmacokinetics: Blood samples were collected for the determination of NPSP558 in plasma at multiple time points until 24 hours post-dose on Days 1 and 4. Plasma samples were analyzed using a validated immunoradiometric assay. The following PK parameters of NPSP558 were calculated, with and without baseline correction, using non-compartmental methods: area under the concentration time curve from 0 to the last measurable concentration and from 0 to infinity, maximum observed concentration, time to maximum observed concentration, elimination half-life, apparent total body clearance, apparent volume of distribution (AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, t_{max}, $t_{1/2}$, CL/F, and V_z/F, respectively).

Statistical methods:

Pharmacokinetics: Individual plasma concentrations and PK parameters of NPSP558 on Days 1 and 4 were summarized by treatment using descriptive statistics. Individual and mean concentration-time profiles were presented on semi-log and linear scales.

Analyses of variance (ANOVA) were performed on the *ln*-transformed unadjusted PK parameters (AUC_{0-t} and C_{max}) and baseline-adjusted PK parameters (AUC_{0-t}, $AUC_{0-\infty}$, and C_{max}) of NPSP558 following 100-µg SC administration using the Ypsomed and the to-be-marketed Haselmeier pen injection devices. A linear mixed-effects ANOVA model was used that included treatment (SC administration from different pen injectors), sequence, and day of drug administration (Day 1 and Day 4) as fixed effects and subject nested within sequence as a random effect. The ANOVA model included the calculations of least-squares means (LS means), differences between treatment LS means, and the standard error associated with these differences. Bioequivalence between the Haselmeier pen and Ypsomed pen was concluded if the ratios of geometric LS means and 90% confidence intervals (CIs) of the *ln*-transformed baseline-adjusted PK parameters AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} were contained within an interval of 80% to 125%. The two one-sided test method for bioequivalence was used (Schuirmann,1987).

In addition, nonparametric analysis was performed on the PK parameter of t_{max} of NPSP558. The Hodges-Lehmann estimator associated with Wilcoxon's signed rank statistic for the median of the difference in t_{max} values observed after drug administration with the Haselmeier and Ypsomed pen and the 90% distribution-free CI based on Wilcoxon's signed rank test.

Name of Sponsor/Company:	(For National Authority Use Only)
NPS Pharmaceuticals, Inc.	
Name of Finished Product:	
NPSP558	
Name of Active Ingredient:	
Recombinant human parathyroid hormone (rhPTH[1-84])	

Results:

Pharmacokinetic results: Parameter estimation analyses were performed on the PK Per Protocol population, which included subjects who completed both periods of the study. These results, with and without baseline adjustment, are presented in the following tables. There were several subjects for which the unadjusted PK parameter $AUC_{0-\infty}$ could not be estimated since the terminal elimination phase could not be characterized in the unadjusted (35 for Haselmeier and 34 for Ypsomed) and baseline-adjusted (10 for Haselmeier and 12 for Ypsomed) datasets.

Table 1: Unadjusted Pharmacokinetic Parameters

NPSP558 in Plasma		
Geometric Mean (CV% Geometric Mean)		
PK Parameter (N = 50)	**NPSP558 100 µg SC (Haselmeier Injection Pen)**	**NPSP558 100 µg SC (Ypsomed Injection Pen)**
AUC_{0-t} (pg•h/mL)	1091.8 (26.7)	1119.2 (28.1)
$AUC_{0-\infty}$ (pg•h/mL)	1308.3 (19.7)[b]	1491.0 (42.3)[c]
C_{max} (pg/mL)	188.7 (41.0)	203.1 (43.2)
t_{max} (h)[a]	0.425 (0.00, 4.00)	0.417 (0.0833, 4.00)

AUC_{0-t} = area under the concentration time curve (AUC) from 0 to the last measurable concentration; $AUC_{0-\infty}$ = AUC from 0 to infinity; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; Min = minimum; Max = maximum; N = number; PK = pharmacokinetic; SC = subcutaneous; t_{max} = time to C_{max}

[a] Median (Min, Max)
[b] N = 15
[c] N = 16

Source: End-of-Text Tables 14.2.1.1.5 and 14.2.1.1.6

The pre-dose concentration for Subject 5555-0028 (Haselmeier) was the C_{max} for this subject, therefore the baseline-adjusted post-dose values were zero. The pre-dose sample for Subject 5555-0079 (Ypsomed) was missing, therefore the baseline adjusted post-dose values for this subject could not be derived. As a result, no baseline-adjusted PK parameters could be estimated for these two subjects.

Name of Sponsor/Company:	(For National Authority Use Only)
NPS Pharmaceuticals, Inc.	
Name of Finished Product:	
NPSP558	
Name of Active Ingredient:	
Recombinant human parathyroid hormone (rhPTH[1-84])	

Table 2: Baseline-adjusted Pharmacokinetic Parameters

	NPSP558 in Plasma	
	Geometric Mean (CV% Geometric Mean)	
PK Parameter	**NPSP558 100 µg SC (Haselmeier Injection Pen) (N = 49)[b]**	**NPSP558 100 µg SC (Ypsomed Injection Pen) (N = 49)[c]**
AUC_{0-t} (pg•h/mL)	661.8 (43.9)	698.1 (45.3)
$AUC_{0-\infty}$ (pg•h/mL)	689.4 (39.7)[d]	758.5 (36.4)[e]
C_{max} (pg/mL)	169.4 (47.2)	182.6 (48.6)
t_{max} (h)[a]	0.500 (0.0833, 4.00)	0.500 (0.0833, 4.00)
$t_{1/2}$ (h)	1.877 (54.9)[d]	1.898 (56.7)[e]
CL/F (L/h)	145.05 (39.7)[d]	131.83 (36.4)[e]
V_z/F (L)	392.8 (73.5)[d]	361.0 (84.5)[e]

AUC_{0-t} = area under the concentration time curve (AUC) from 0 to the last measurable concentration; $AUC_{0-\infty}$ = AUC from 0 to infinity; CL/F = apparent total body clearance; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; Min = minimum; Max = maximum; N = number; PK = pharmacokinetic; SC = subcutaneous; t_{max} = time to C_{max}; $t_{1/2}$ = elimination half-life, V_z/F apparent volume of distribution

[a] Median (Min, Max)
[b] PK parameters could not be derived for Subject 0028
[c] PK parameters could not be derived for Subject 0079
[d] N = 39
[e] N = 37
Source: End-of-Text Tables 14.2.1.1.7 and 14.2.1.1.8

The assessment of bioequivalence was performed on the baseline-adjusted and unadjusted PK parameters in the Intent-to-Treat (ITT) population. These results are presented in the following tables. Since PK parameters could not be estimated for Subjects 5555-0028 and 5555-0079 in one of the two periods, these subjects were therefore excluded from the ANOVA. The ANOVA was performed on the 48 subjects with a comparison of interest. Since there were some subjects for which the terminal elimination phase could not be characterized in one of the two periods, there are 28 subjects with a comparison of interest for the baseline-adjusted PK parameter $AUC_{0-\infty}$.

Name of Sponsor/Company:	(For National Authority Use Only)
NPS Pharmaceuticals, Inc.	
Name of Finished Product:	
NPSP558	
Name of Active Ingredient:	
Recombinant human parathyroid hormone (rhPTH[1-84])	

Table 3: ANOVA of Baseline-adjusted PTH Concentration - Intent-to-Treat Population

NPSP558 in Plasma NPSP558 100 µg SC Haselmeier Injection Pen vs. NPSP558 100 µg SC Ypsomed Injection Pen				
PK Parameter (N = 50)	**Haselmeier Pen Geometric LSM**	**Ypsomed Pen Geometric LSM**	**Ratio of Geometric LSM (90% CI)**	**Intra-subject CV (%)**
AUC_{0-t} (pg•h/mL)	661.1[a]	688.41[a]	96.0 (88.48 to 104.23)	24.3
$AUC_{0-\infty}$ (pg•h/mL)	718.53[b]	742.34[b]	96.8 (88.5 to 105.86)	19.6
C_{max} (pg/L)	170.29[a]	182.39[a]	93.4 (84.42 to 103.26)	30.0

AUC_{0-t} = area under the concentration time curve (AUC) from 0 to the last measurable concentration; $AUC_{0-\infty}$ = AUC from 0 to infinity; CI = confidence interval; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; h = hour; LSM = least square mean; N = number; PK = pharmacokinetic; SC = subcutaneous

[a] N = 48
[b] N = 28
Source: End-of-Text Table 14.2.1.1.11

Unadjusted PK parameter $AUC_{0-\infty}$ could not be compared since most of the subjects' terminal elimination phase could not be characterized for both periods.

Table 4: ANOVA of Unadjusted PTH Concentration - Intent-to-Treat Population

NPSP558 in Plasma NPSP558 100 µg SC Haselmeier Injection Pen vs. NPSP558 100 µg SC Ypsomed Injection Pen				
PK Parameter (N = 50)	**Haselmeier Pen Geometric LSM**	**Ypsomed Pen Geometric LSM**	**Ratio of Geometric LSM (90% CI)**	**Intra-subject CV (%)**
AUC_{0-t} (pg•h/mL)	1091.76[a]	1119.20[a]	97.6 (93.55 to 101.72)	12.5
C_{max} (pg/L)	188.69[a]	203.12[a]	92.9 (85.03 to 101.49)	26.9

AUC_{0-t} = area under the concentration time curve (AUC) from 0 to the last measurable concentration; CI = confidence interval; C_{max} = maximum observed concentration; CV% = percent coefficient of variation; h = hour; LSM = least square mean; N = number; PK = pharmacokinetic; SC = subcutaneous

[a] N = 48
Source: End-of-Text Table 14.2.1.1.9

Name of Sponsor/Company: NPS Pharmaceuticals, Inc.	(For National Authority Use Only)
Name of Finished Product: NPSP558	
Name of Active Ingredient: Recombinant human parathyroid hormone (rhPTH[1-84])	

The t_{max} of NPSP558 is characterized in the Table 5 below.

Table 5: Results of the Non-Parametric Analysis on t_{max} of NPSP558

NPSP558 100 µg SC Haselmeier Injection Pen vs. NPSP558 100 µg SC Ypsomed Injection Pen (N = 48)				
Median Values (hours)			90% Confidence Interval[b]	
Haselmeier Pen Test	Ypsomed Pen Reference	Hodges-Lehmann Estimator[a] for B – A	Lower	Upper
0.625	0.417	0.0917	0.00	0.25

N = number; SC = subcutaneous; t_{max} = time to maximum concentration in plasma
Treatment A: Ypsomed Injection Pen
Treatment B: Haselmeier Injection Pen
[a]An estimator associated with Wilcoxon's Signed Rank statistic.
[b]A distribution-free confidence interval based on Wilcoxon's signed rank test

Source: End-of-Text Table 14.2.1.1.13

Safety and tolerability results: A total of 20/50 (40.0%) subjects reported a total of 44 TEAEs. The most frequently reported TEAEs were nausea (14/50 subjects; 28.0%), headache (6/50 subjects;12.0%), dizziness (4/50 subjects; 8.0%), and hyperhidrosis (2/50 subjects; 4.0%). There were no TEAEs due to hypercalcemia. Most TEAEs were mild in severity. No subjects had severe TEAEs. No deaths or SAEs occurred during the study and no subjects discontinued due to TEAEs. There were no clinically significant changes from baseline in clinical laboratory parameters, vital signs, physical examinations, or ECGs.

Conclusion:

Based on the protocol, the primary PK analysis was performed on those subjects who completed both periods. The ratios and 90% CIs of the geometric LS means on the *ln*-transformed baseline-adjusted PK parameters AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were contained within the 80 to 125% acceptance range. Based on these results, the Haselmeier and Ypsomed injection pens are considered as bioequivalent. The NPSP558 injections were well tolerated and no unexpected safety signals were observed.

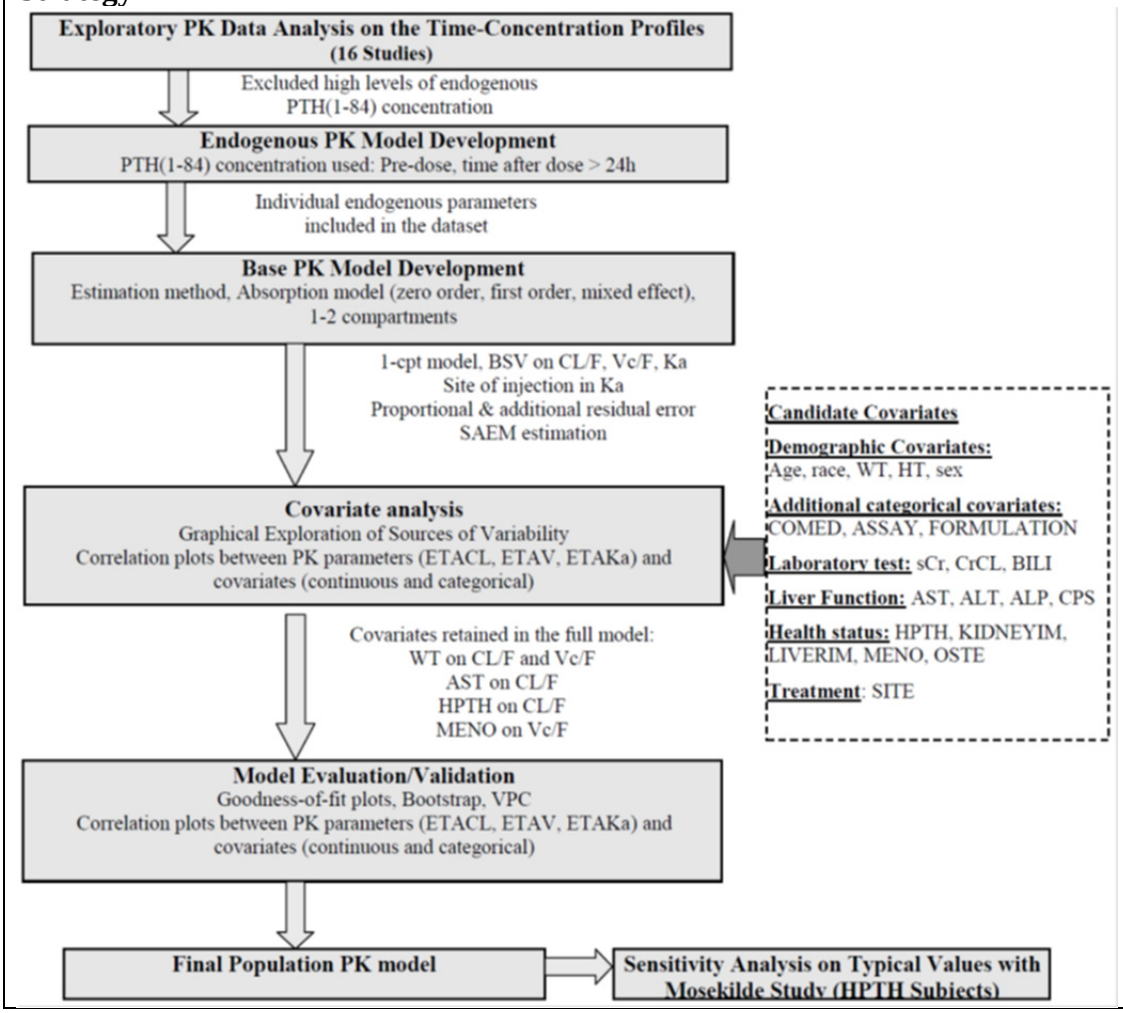
Date of the report: 19 April 2012

Reviewers Comments: The sponsor's assessments and conclusions from this study are acceptable. There were no notable protocol violation and deviations. The bioanalytical method ((b) (4) Study AA96673-01) adequately supported the pharmacokinetic evaluation of rhPTH[1-84].

4.2 Supplemental Information on Pharmacometrics Review

4.2.1. Population Pharmacokinetic Analysis

Agency's review focused on the Population PK analysis study report **NPSP-PCS-101**, which included PK data from subjects with and without hypoparathyroidism. The main highlights of the population PK analysis are mentioned below:

Data	16 studies from Phase I, II, and III clinical studies as well as PK data collected from an Investigator-Initiated study (i.e., Mosekilde study). A total of 11 studies were performed in non-hypoparathyroidism subjects, 4 studies in hypoparathyroidism subjects (C09-002, Phase III clinical studies: CL1-11-040 and PAR-C10-007, and Mosekilde-IIT study], and 2 other studies in special populations (hepatic and renal impaired subjects).
Platform	NONMEM Version 7.2 (ICON Development Solutions, Ellicott City, Maryland, USA) with Intel Visual Fortran Compiler for applications running on IA-32, Version 10.1. Perl-Speak-NONMEM (PsN) Version 3.5.3 was used to evaluate/validate the population PK model with a bootstrap re-sampling approach and predictive checks.
Strategy	

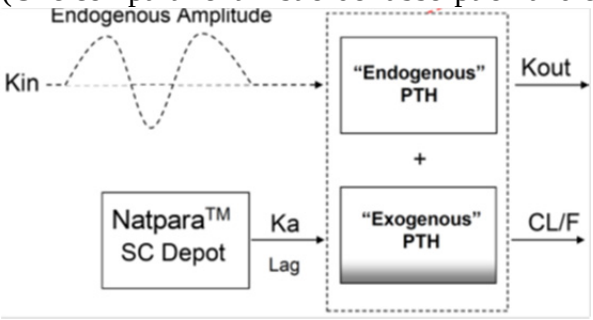
NONMEM Dataset	NPSALLSTUDIES.csv (sponsor submitted this data file named as NPSACTIVE20JUN2012.CSV)
Bioanalysis	Immuno-radiometric assay (IRMA) from Scantibodies Laboratories (Whole PTH IRMA)
Structural Model	Endogenous (circadian model with a cosine function) + Exogenous PTH (One compartment first order absorption and elimination):  ENDO = MU+ALPHA*COS(2*π/24*(Tclock – Tmax)); where ALPHA = amplitude of endogenous PTH(1-84) variation; ENDO = endogenous PTH(1-84) concentration; MU = rhythm-adjusted mean of PTH(1-84) endogenous level; Tclock = relative time clock; Tmax = relative time clock with maximum endogenous PTH(1-84) concentration.
Random Effects	$\theta_i = \theta_{Typical} \cdot e^{\eta_i}$ or $\theta_i = \theta_{Typical} + \cdot\eta_i$
Residual Error	Proportional and additive: $y_{ij} = \hat{y}_{ij} \cdot (1+\varepsilon_{1ij}) + \varepsilon_{2ij}$

Table 11 Summary of Continuous and Categorical Demographic data

Covariates	Mean (CV %)		
	Overall N = 1546	Without History of Hypoparathyroidism N = 1410	With History of Hypoparathyroidism N = 136
Age (years)	59.9 (20.8)	61.1 (19.2)	46.7 (26.4)
Height (cm)	160 (5.62)	160 (5.49)	167 (5.34)
Body Weight (kg)	66.7 (20.6)	65.2 (18.2)	82.4 (24.7)
BMI (kg/m^2)	25.9 (17.8)	25.6 (16.6)	29.6 (21.8)
sCr (µmol/L)	82.7 (18.3)	82.4 (17.7)	85.7 (22.8)
CrCL (mL/min)	70.6 (34.3)	67.7 (31.3)	100 (32.2)
ALB (g/L)	42.5 (7.27)	42.3 (7.32)	44 (5.75)
ALT (U/L)	19.9 (69.7)	19.6 (68.1)	23.5 (78.4)
AST (U/L)	21.9 (57.1)	21.8 (58.7)	23.0 (37.7)
BILI (µmol/L)	9.88 (43.8)	10 (43.4)	8.61 (46.4)
ALP (U/L)	103 (48.6)	106 (47.6)	66.7 (30.0)

ALB = total albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BILI = bilirubin; BMI = body mass index; CrCL = creatinine clearance; CV = coefficient of variation; N = number of subjects; sCr = serum creatinine

Covariates	Category	N (%)
Hypoparathyroidism	Yes	136 (8.8%)
	No	1410 (91.2%)
Sex	Female	1417 (91.7%)
	Male	129 (8.3%)
Race	Asian	17 (1.1%)
	Black/African American	60 (3.9%)
	Caucasian	1442 (93.3%)
	Missing	18 (1.2%)
	Native Hawaiian/Pacific Islander	2 (0.1%)
	Other	7 (0.5%)
Menopausal Status	Premenopausal women	81 (5.2%)
	Postmenopausal women	1336 (86.4%)
Osteoporosis	Non-osteoporosis	385 (24.9%)
	Osteoporosis	1153 (74.6%)
	Not Available	8 (0.5%)

N = number of subjects

(Source: Sponsor's Tables 5.2:1 and 5.2:2 from NPSP-PCS-101, Page 31)

Highlights of the results from final model:

Table 12 Typical Values and Relative Standard Error of Endogenous PTH(1-84)

Endogenous Parameters	Typical Values (RSE%)	Between-Subject Variability (RSE%)
MU (pg/mL)	25.3 (1.8%)	34.2% (2.9%)
ALPHA (pg/mL)	3.29 (14.0%)	0 FIX
Tmax (h)	22.0 (1.9%)	332% (7.05%)
Proportional Error	26.6% (2.3%)	

ALPHA = amplitude of endogenous PTH(1-84) variation; MU = rhythm-adjusted mean of PTH(1-84) endogenous level; Tmax = relative time clock with maximum endogenous PTH(1-84) concentration; RSE = relative standard error

(Source: Sponsor's Table 5.3:1 from NPSP-PCS-101, Page 32)

As expected, hypoparathyroidism subjects displayed lower rhythm-adjusted means as compared to non-hypoparathyroidism subjects (mean values of 15.3 and 27.9 pg/mL, respectively, $p < 0.001$) (Figure 45). However, actual mean baseline values of PTH(1-84) (endogenous levels) were expected to be even lower for hypoparathyroidism subjects as compared to those estimated with the model due to the substantial numbers of samples with BLQ concentrations which were not considered in the model.

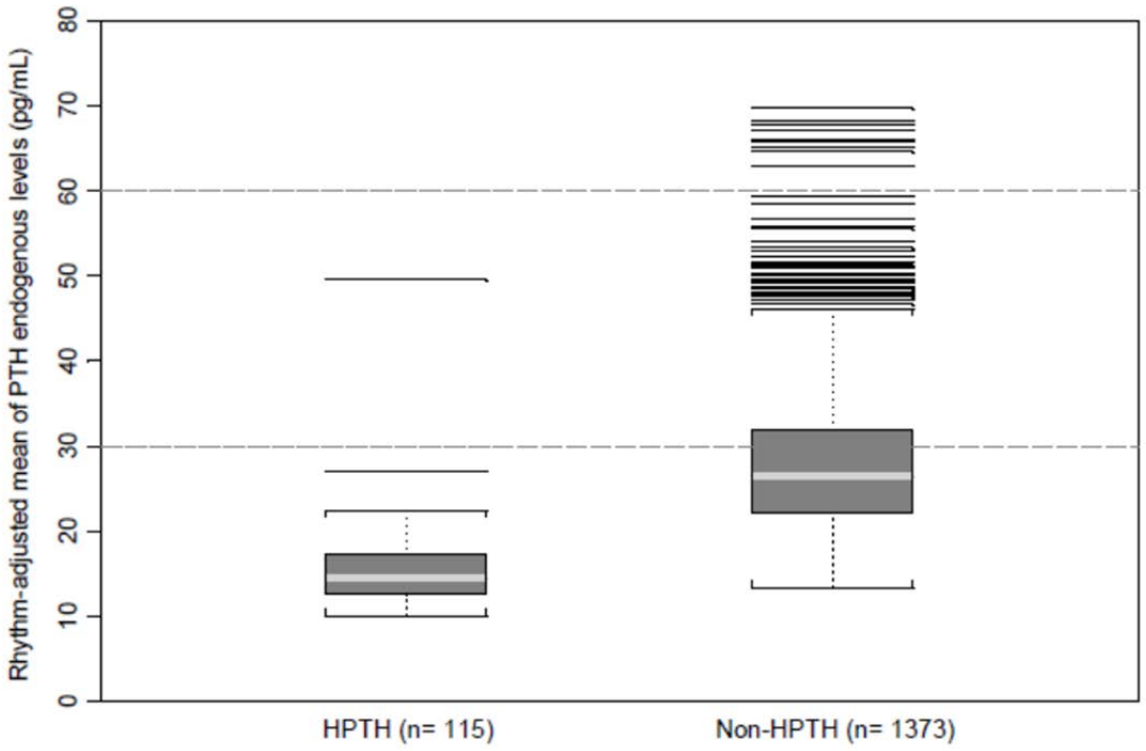


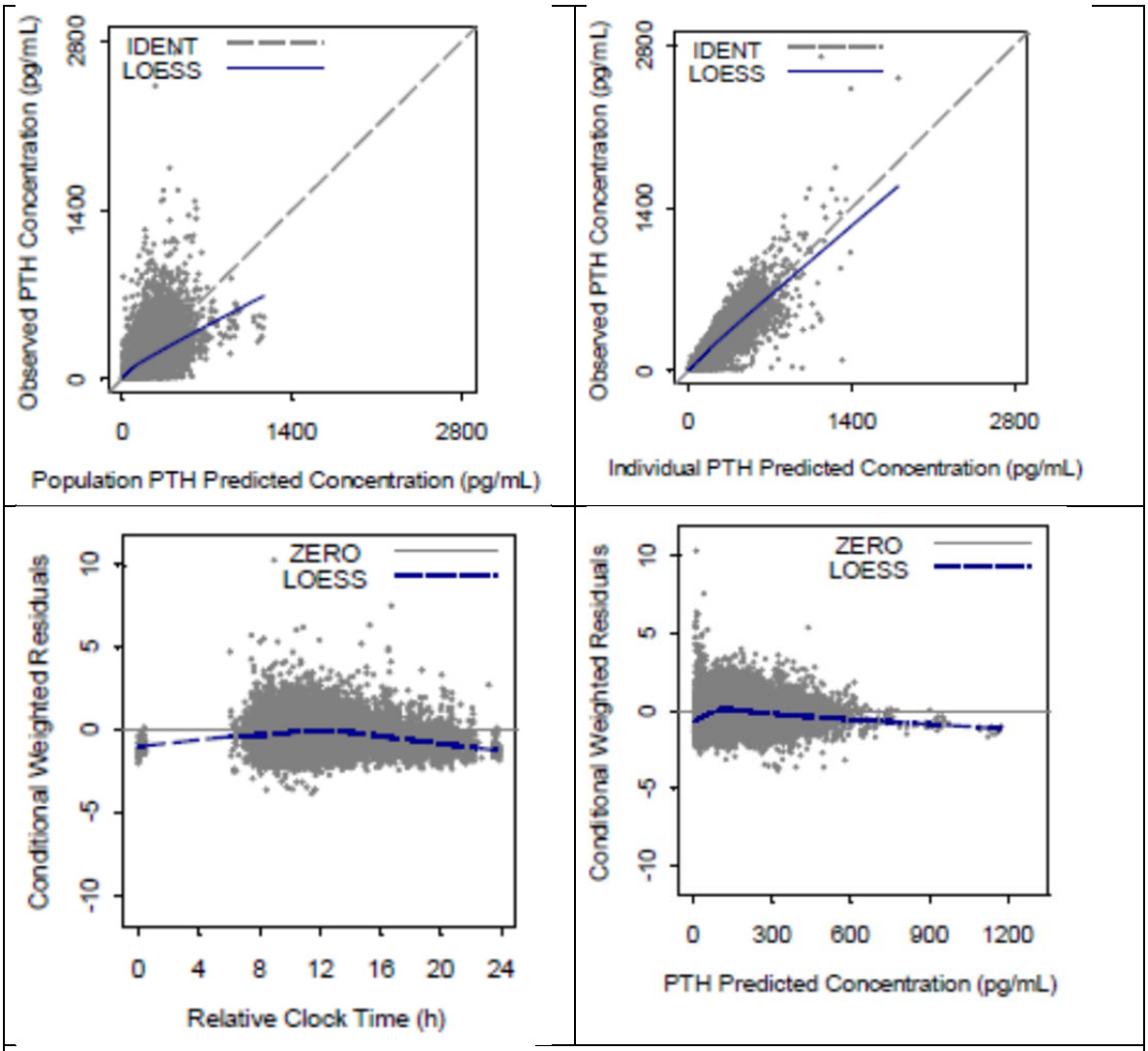
Figure 45 Individual Rhythm-Adjusted Means for Hypoparathyroidism and Non-Hypoparathyroidism Subjects

(Source: Sponsor's Figure 5.3:1 from NPSP-PCS-101, Page 33)

Sponsor tested various elimination (one, two-compartment) and absorption (first-, zero-order rate of absorption, with and without lag-time, effects of injection sites) models. The mixed-order absorption model was tested (since concentration-time profiles of PTH(1-84) were characterized by double absorption peaks) but did not achieve successful convergence when testing the sites of injection.

The SAEM estimation method was used since goodness-of-fit was better to that derived with the FOCE method. A one-compartment model with linear elimination, a first-order rate constant of absorption (Ka) and effect of injection site (i.e., thigh, abdomen, unknown) was used as a final structural model to describe the mono-exponential elimination of PTH(1-84) following administration of Natpara. The BSV of PK parameters was explained using a log-normal distribution and residual variability in plasma concentrations of PTH(1-84) fitted using a proportional and an additive error model.

The goodness-of-fit plots, form the final model, are presented below in Figure 46:



Source: Sponsor's Figure 5.6:1 and 5.6:2 from NPSP-PCS-101, Pages 43 and 44

Figure 46 Goodness-of-fit plots from the final model

The estimates for PK parameters and between subject variability from the initial and final model are presented below:

Table 13 Typical Values of the Structural Population PK Model of Exogenous PTH(1-84)

Population PK Parameters		Typical Values	BSV (%)
Ka (h^{-1})	Abdomen	19.1	257.3%
	Thigh	7.68	
	Unknown	6.81	
CL/F (L/h)		109	69.8%
Vc/F (L)		253	76.3%
Error Model			
Additive Error (pg/mL)		2.36	
Proportional Error (%)		33.0%	

ALPHA = amplitude of endogenous PTH(1-84) variation; BSV = between-subject variability; CL/F = apparent clearance of PTH(1-84); Ka = first-order constant absorption rate; MU = rhythm-adjusted mean of PTH(1-84) endogenous level; PK = pharmacokinetic; Tmax = relative time clock with maximum endogenous PTH(1-84) concentration; Vc/F = apparent central volume of distribution of PTH(1-84)
Note: The individual parameters of the endogenous model (MU, ALPHA and Tmax) were used as a baseline variation.

(**Source: Sponsor's Table 5.4.1 from NPSP-PCS-101, Page 34**)

Table 14 Typical Values of the Final Population PK Model of Exogenous PTH(1-84)

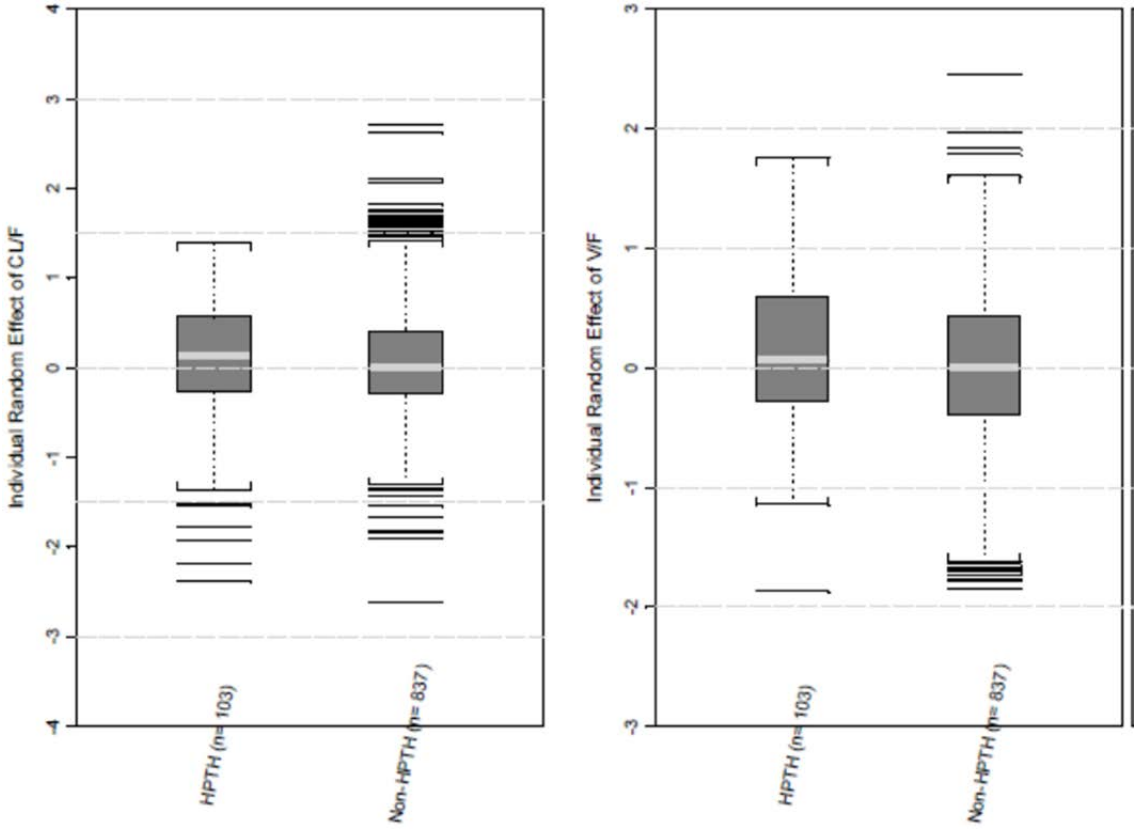
Population PK Parameters		Typical Values	BSV (%)
Ka (h^{-1})	Abdomen	19.4	254%
	Thigh	7.5	
	Unknown	3.68	
CL/F (L/h)	Non-Hypoparathyroidism	$111 \cdot (WT/65)^{0.851} \cdot (AST/20)^{-0.0315}$	69.1%
	Hypoparathyroidism	$93.2 \cdot (WT/65)^{0.851} \cdot (AST/20)^{-0.0315}$	
Vc/F (L)	Postmenopausal Women	$242 \cdot (WT/65)^{1.51}$	68.3%
	Premenopausal Women	$380 \cdot (WT/65)^{1.51}$	
	Men	$178 \cdot (WT/65)^{1.51}$	
Error Model			
Additive Error (pg/mL)		2.35	
Proportional Error (%)		33.0%	

ALPHA = amplitude of endogenous PTH(1-84) variation; AST = aspartate aminotransferase (U/L); BSV = between-subject variability; CL/F = apparent clearance of PTH(1-84); HPTH = hypoparathyroidism; Ka = first-order constant absorption rate; PK = pharmacokinetic; Vc/F = apparent central volume of distribution of PTH(1-84); WT = body weight (kg)
Note: The individual parameters of the endogenous model (MU, ALPHA and Tmax) were used as a baseline variation

(**Source: Sponsor's Table 5.6.1 from NPSP-PCS-101, Page 45**)

Result of the sponsor's NONMEM analysis was confirmed and accepted as is with the exception of body weight assessment as explained below.

While body weight was identified by the sponsor as most significant covariate, the review team considers that the inclusion of this covariate seems to have only a statistical basis, as the inclusion of this covariate only explained 0.7% and 8% of the variability (BSV in Tables above) in apparent clearance and volume of distribution of rhPTH[1-84], respectively. In the Agency's analysis, a modest slope was apparent for inter-individual variability (ETA) for CL/F and Vc/F versus body weight (see QBR). None of the other tested covariates reached to the level of significance to consider any dose-adjustment.



(**Source: Sponsor's Figure 5.5:3 from NPSP-PCS-101, Page 40**)

Figure 47 BSV in PK Parameters of PTH(1-84) versus Hypoparathyroidism Status from the Structural Model

Sponsor in an addendum to the NPSP-PCS-101 report provided the assessment of impact of antibody formation on apparent clearance and volume of distribution (Figures are respectively, sourced from Figure 4-1 and 4-2 in 2.7.2 Summary of Clinical Pharmacology Studies Pages 94 and 95).

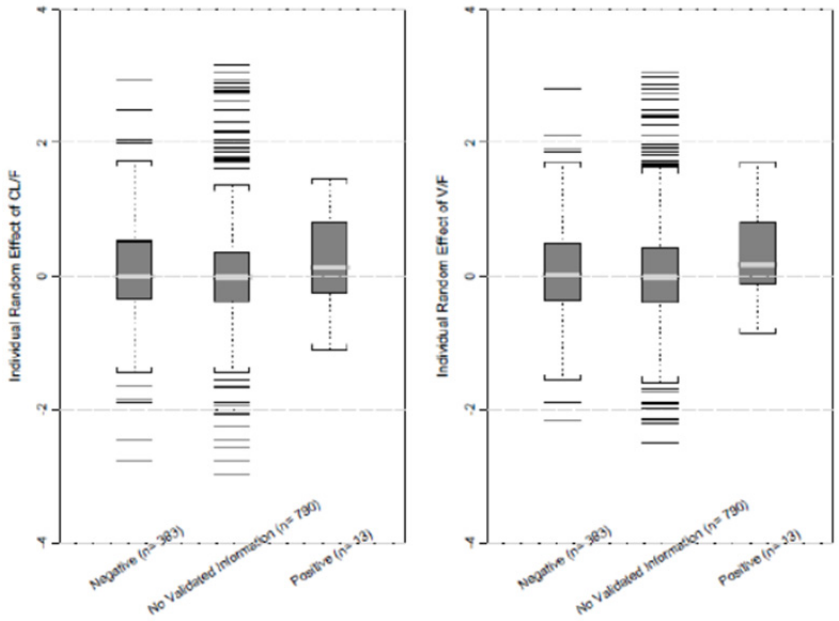


Figure 48 BSV in PK Parameters of PTH(1-84) versus Immunogenicity Results

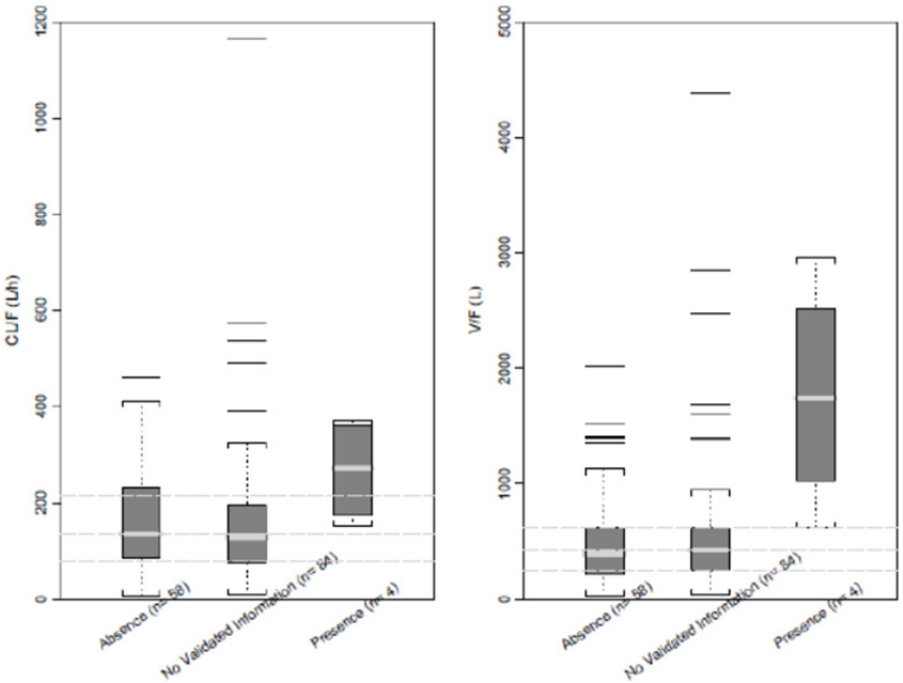


Figure 49 PK Parameters of PTH(1-84) versus Immunogenicity Results in Patients with Hypoparathyroidism (C09-002, PAR-C10-007, CL1-11-040, and PAR-C10-008)

The presence of antibody indicated a higher apparent volume of distribution and clearance (higher t1/2) in these subjects, although the low number of subjects (n=4) with specific antibodies did not allow robust statistical comparison among the groups (Figure 49).

4.2.2. Modeling and Simulations Using a Calcium Homeostasis Model

Calcium Homeostasis Model:

We used a publically available version of the base model [as published in M.C. Peterson and M.M. Riggs. Bone, 46 (2010) 49–63], implemented using open source R and modified the model code to include the following:

1. Describe rhPTH(1-84) pharmacokinetics – Model was based on PTH(1-34) PK and therefore, the code was supplied with rhPTH(1-84) specific CL/F and Vd/F from the Natpara PK studies.
2. Allow the exogenous calcitriol (Vitamin-D) input and describe calcitriol PK, in addition to built-in feature to describe calcitriol systemic levels – A depot compartment was added to account for first order input of calcitriol.
3. Generate 24-hour urinary calcium excretion data – Model included a flux parameter describing loss of calcium in urine and code was modified to compute cumulative excretion over 24-hour.

Model Evaluation Using Sponsor's PKPD study C09-002 study:

Assumptions:

- PTH treatments (single doses of 50 and 100 µg) were administered at steady-state of Hypoparathyroidism induction in the model (snapshot of last 4 days of 6 month treatment simulation).
- 60% reduction in PT gland pool and 50% reduction in max capacity.
- Calcium (2600 mg/day) continued throughout.
- Vitamin D as calcitriol (0.5 µg QD) initiated after 2 months and continued throughout.

Model Evaluation Using Mosekilde-IIT study data:

Assumptions:

Mosekilde-IIT PKPD sub-study in Hypoparathyroidism tested QD dose of 100 mcg rh-PTH on for 6 months versus placebo. Based on the publication[24] from this study, Placebo mean oral calcium intake was 1200 (range 800–3200) mg/day, Vitamin D as alphacalcidiol was [1.6 (0.25–3.5)] or calciferol was [33 (10–60)] µg/day. In the rhPTH arm oral calcium intake was 1600 (400–22,500) mg/day, Vitamin D as alphacalcidiol was [2.0 (0.25–42)] or calciferol was [20 (5–92)] µg/day.

Assumptions:

- 50% reduction in PT gland pool and 50% reduction in max capacity for steady-state of Hypoparathyroidism induction in the model (snapshot of last day of 6 month treatment simulation).
- Placebo - Calcium (2600 mg/day) and Vitamin D as calcitriol (0.5 mcg/day) continued throughout
- 100 mcg PTH - initiated after 1 month and continued throughout over 6 months and oral calcium (2200 mg/day) and Vitamin D as calcitriol (1.5 mcg/day)

[24] Sikjaer et al. Journal of Bone and Mineral Research, Vol. 26, No. 10, October 2011, pp 2358–2370

Assumptions for Simulations of Alternate Dosing Regimen Scenarios:

- 50% or 90% reduction in PT gland pool and 50% reduction in max capacity for steady-state of Hypoparathyroidism induction in the model (snapshot of last day of 6 month treatment simulation).
- High-dose Calcium (2000 mg/day) and Vitamin D as calcitriol (1.5 mcg/day) or Low-dose Calcium (1000 mg/day) and Vitamin D as calcitriol (0.5 mcg/day) continued throughout
- 100 mcg PTH - initiated after 1 month and continued throughout over 6 months and oral calcium (2200 mg/day) and Vitamin D as calcitriol (1.5 mcg/day)

A typical output from the total of 7 month simulation based on the modified model for a typical patient with hypoparathyroidism and assumed to have lost 99% of the PTH gland pool for select variables is shown in the Figure 50 below.

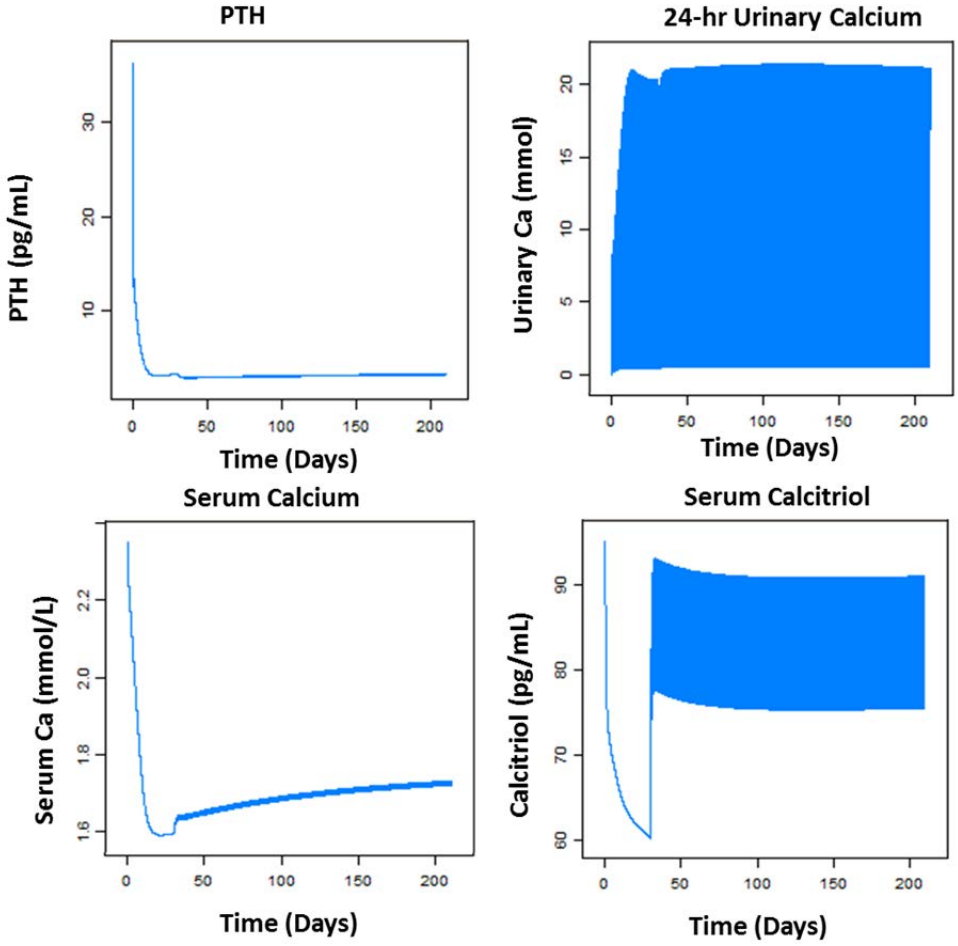


Figure 50 Model predictions for a typical patient with 99% reduction PTH production and taking 1000 mg calcium and 0.5 µg calcitriol / day from Day 30.

Mathematically introduced, 99% loss of endogenous parathyroid gland production of PTH, translated into sustained hypocalcemia (serum Ca << 2.0 mmol/L) and hypercalciuria (24-hr urinary calcium > 7.3 mmol/day) with a daily treatment of 25 mmol

(1000 mg) oral calcium and 0.5 µg Calcitriol), which was introduced on Day 30 in the simulation.

For the same typical patient, the model simulated profile of the 6 month rhPTH(1-84) treatment using 50 µg b.i.d. dose based on the modified model for select variables is shown in the Figure 51 below.

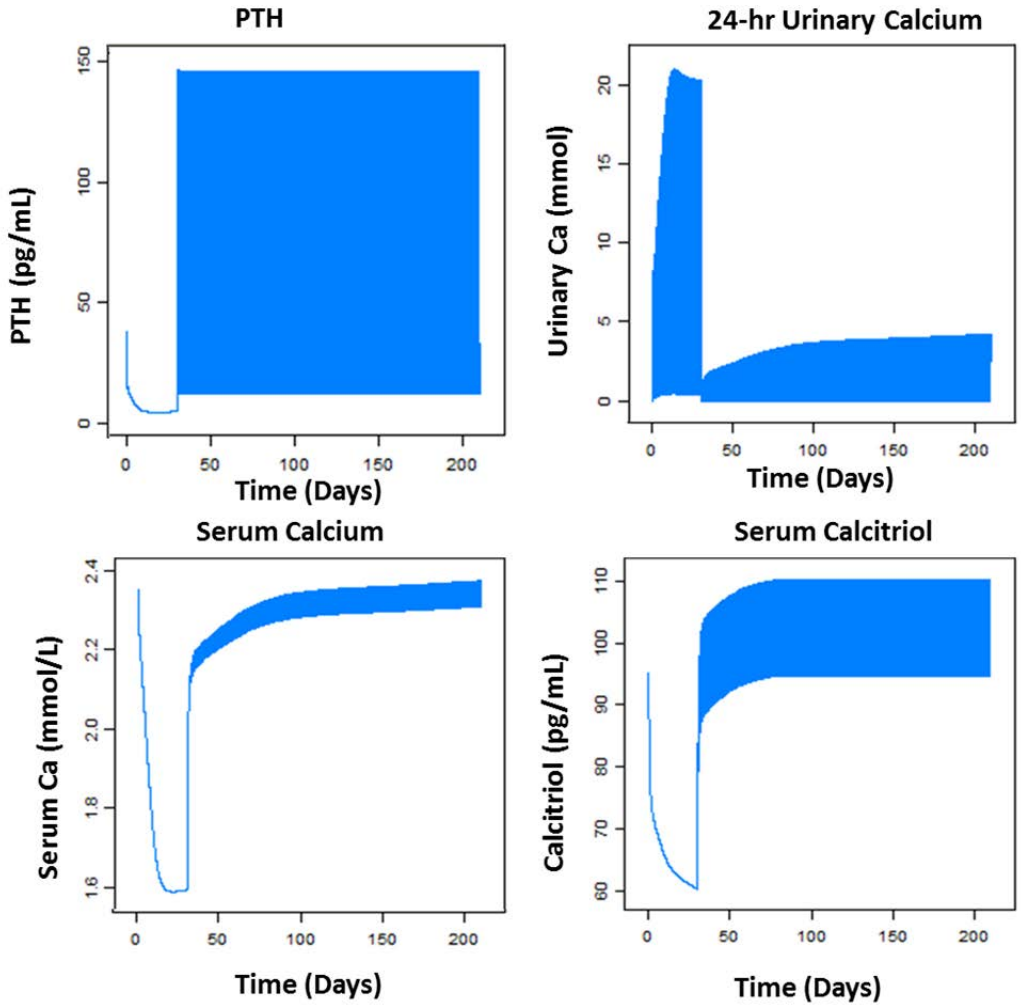


Figure 51 Model predictions for a typical patient with 99% reduction PTH production on 50 µg b.i.d rhPTH(1-84) treatment and taking 1000 mg calcium and 0.5 µg calcitriol / day from Day 30.

In this typical patient, with 99% loss of endogenous parathyroid gland production of PTH, with more frequent 50 µg b.i.d. dose model predicted normocalcemia (serum Ca between 2.0 – 2.65 mmol/L) and normocalciuria (24-hr urinary calcium < 7.3 mmol/day) on a background daily treatment of 25 mmol (1000 mg) oral calcium and 0.5 µg Calcitriol), which was introduced on Day 30 in the simulation.

The overview of results from model projections for several scenarios is summarized in Table 15 below. Simulations demonstrate that conceptually with an alternate dosing regimen there are situations where both normocalcemia and normocalciuira is achievable.

Table 15 Overview of the results from projection scenarios using the mechanistic calcium homeostasis model

Scenario #	Assumption of 50% loss in PTH gland pool (Similar to Mosekilde-IIT Population) 6 month treatment simulation			Assumption of 99% loss in PTH gland pool (Extreme Clinically Realistic Scenario) 6 month treatment simulation		
	PTH µg Dose (Frequency)	Oral Ca (mmol/d)	Oral Calcitriol (µg)/Duration (d)	PTH µg Dose (Frequency)	Oral Ca (mmol/d)	Oral Calcitriol (µg)/Duration(d)
1	0 QD	50	1.5	0 QD	50	1.5
2	0 QD	25	1.5	0 QD	25	1.5
3	0 QD	50	0.5	0 QD	50	0.5
4	0 QD	25	0.5	0 QD	25	0.5
5	100 QD	50	1.5	100 QD*	50	1.5
6	100 QD	25	1.5	100 QD*	25	1.5
7	100 QD	50	1.5 / 120 d	100 QD*	50	1.5 / 120 d
8	100 QD#	25	0.5	100 QD*	25	0.5
9	50 QD**	25	0.5	50 QD*	25	0.5
10	50 BID#	50	1.5	50 BID*	50	1.5
11	-			50 BID**	50	1.5 / 120 d
12	-			50 BID**	25	1.5 / 120 d
13	50 BID**	25	0.5	50 BID**	25	0.5
Assuming a different slow release PTH PK profile (1/10th absorption rate constant than current)						
14	-			100 QD*	50	1.5 / 120 d
15	100 QD	25	0.5	100 QD#	25	0.5
16	100 QD	25	0.5 / 120 d	100 QD#	25	0.5 / 120 d
17	50 QD**	25	0.5	50 QD**	25	0.5

d=days

Orange shades (*) indicate scenarios that projected decrease in calciuria but >ULN with/without normocalcemia. Green shades (**) indicate scenarios that projected normocalcemia and normocalciuria. Blue shades (#) indicate scenarios that projected calcium and calciuria in the proximity but below ULN. Remaining scenarios were projected as hypocalcemic/hypercaciuric.

4.3 OCP Filing Memo

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	BLA 125511	Brand Name	Natpara
OCP Division (I, II, III, IV, V)	II	Generic Name	rhPTH(1-84) [human parathyroid hormone rDNA origin]
Medical Division	DMEP	Drug Class	Endocrine hormone
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	Treatment of hypoparathyroidism
OCP Team Leader	Immo Zadezensky, Ph.D.	Dosage Form Strengths	Lyophilized powder for injection 25, 50, 75, and 100 mcg
Pharmacometrics Reviewer	-	Dosing Regimen	Individualized
Date of Submission	10/24/2013	Route of Administration	Sub-cutaneous injection
Estimated Due Date of OCP Review	08/24/2014	Sponsor	NPS Pharmaceuticals
Medical Division Due Date		Priority Classification	Orphan Drug Designation/ Standard
PDUFA Due Date	10/24/2014	Relevant IND	

Clinical Pharmacology and Biopharmaceutics Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA_BLA or Supplement

15 Pages Have Been Withheld As A Duplicate Copy Of The "OCP NDA Filing and Review Form" dated 05/20/2014 Which Is Located In This Clinical Pharmacology Review Section Of This NDA Approval Package

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MANOJ KHURANA
09/09/2014

PING JI
09/09/2014

NITIN MEHROTRA
09/09/2014

IMMO ZADEZENSKY
09/09/2014

CHANDRAHAS G SAHAJWALLA
09/09/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	BLA 125511	Brand Name	Natpara
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Medical Division	DMEP	Drug Class	Endocrine hormone
OCP Reviewer	Manoj Khurana, Ph.D.	Indication(s)	Treatment of hypoparathyroidism
OCP Team Leader	Immo Zadezensky, Ph.D.	Dosage Form Strengths	Lyophilized powder for injection 25, 50, 75, and 100 mcg
Pharmacometrics Reviewer	-	Dosing Regimen	Individualized
Date of Submission	10/24/2013	Route of Administration	Sub-cutaneous injection
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	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Study Nos./Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Human Biomaterials:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I)				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				

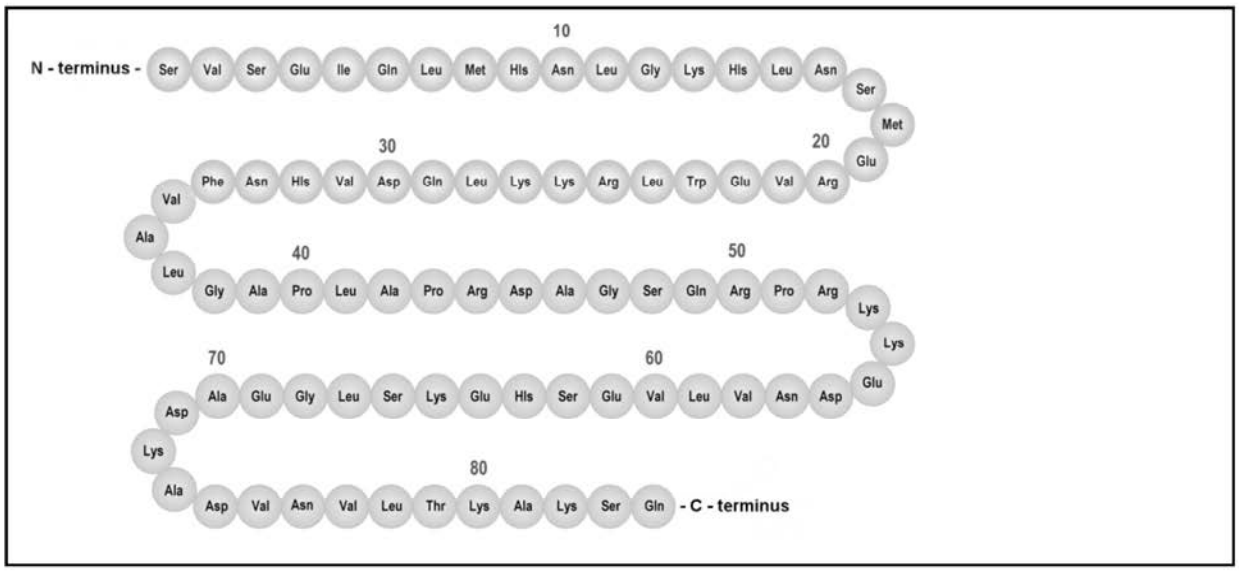
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
in-vivo effects on primary drug:				
in-vivo effects of primary drug:				
in-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		CL1-11-009
hepatic impairment:	**X**	**1**		CL1-11-010
PD -				
Phase 1:				
Phase 2:				
Phase 3:	**X**	**2**		CL1-11-040, PAR-C10-007
PK/PD -				
Phase 1 and/or 2, proof of concept:	**X**	**3**	**2**	C09-002, Mosekilede-IIT PKPD Sub-study, CL1-11-017
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	**X**	**2**	**1**	NPSP-PCS-101 (Overall), ALX1-11-93001 (Osteoporosis population)
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability	**X**	**1**		CL1-11-013
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	**X**	**2**		CL1-11-007, PAR-C10-005
Bioequivalence studies -				
traditional design; single / multi dose:	**X**	**2**		CL1-11-012, SH-PTH-0001
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**14**		

Summary of the submission:

NPS Pharmaceuticals (NPS, the sponsor) has submitted this Biologic License Application (BLA) for NATPARA™ (rhPTH[1-84]). NATPARA™ (rhPTH[1-84]) for subcutaneous injection is proposed as a replacement for endogenous parathyroid hormone (full 1-84 amino acid peptide).

rhPTH(1-84) (Figure 1) is manufactured using a strain of Escherichia coli modified by recombinant deoxyribonucleic acid (rDNA) technology.

Figure 1 Amino Acid Sequence of rhPTH(1-84)



Molecular Formula: $C_{408}H_{674}N_{126}O_{126}S_2$ **Molecular Weight:** 9425 Daltons.

Parathyroid hormone is an 84-amino acid protein that is secreted by the parathyroid glands. Parathyroid hormone has a variety of important physiological functions that are outlined below to explain the effects of absent or deficient PTH levels. Parathyroid hormone regulates bone metabolism and serum levels of calcium and phosphate: if the serum calcium is low, the parathyroid glands increase PTH secretion, when the serum calcium is high the parathyroid glands reduce PTH secretion.

Hypoparathyroidism is a rare disease caused by low or absent PTH(1-84), characterized by hypocalcemia and leading to hyperphosphatemia and hypercalciuria. Signs and symptoms of the disease may include tetany, paresthesia/numbness, mental status changes (mood, memory), and seizures. Patients have reduced bone turnover, increased bone mineral density (BMD), and abnormal bone microstructure. The current approach to treating these patients is limited to symptomatic management with high doses of calcium and active vitamin D because parathyroid hormone replacement therapy is currently not available. Long-term complications with the current approach can include soft tissue calcifications (kidney stones, basal ganglia) and end-organ damage (kidney, eye, and central nervous system).

During the years of initial development, rhPTH(1-84) was also designated in documents as PTH, PTH(1-84), hPTH, hPTH(1-84), rhPTH, rhPTH(1-84), rPTH, and rPTH(1-84). For the osteoporosis development program the proprietary name in the United States (US) is Preos™ (NDA for Osteoporosis (b) (4) was not approved and was withdrawn by the sponsor) and in Europe, Preotact®. Only 2 drug delivery systems have been used throughout the hypoparathyroidism program, the Ypsomed pen injector and the Haselmeier pen injector. The Haselmeier system (renamed Natpara® Mixing Device and Natpara Q-Cliq™) was developed specifically for rhPTH(1-84) and was used in the ongoing study, PAR-C10-008.

The details on the submission as presented during the filing are mentioned in the slides below:

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BLA 125511 Filing Meeting
Clinical Pharmacology Perspective

rhPTH(1-84) for injection
(human parathyroid hormone, r-DNA origin)
NATPARA™ (Proposed)
Sponsor: NPS Pharmaceuticals
Submitted: 10/24/2013

Manoj Khurana, PhD
Division of Metabolism and Endocrinology Products
Office of Clinical Pharmacology

OCP Review Team:

Clin. Pharm. and Pharmacometrics Reviewer:	Manoj Khurana, PhD
Clin. Pharm. Team Leader :	Immo Zadezensky, PhD
Pharmacometrics Team Leader:	Nitin Mehrotra, PhD

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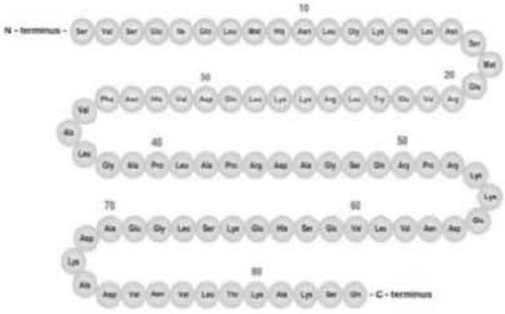
rhPTH(1-84) is a new molecular entity



Amino acid sequence of rhPTH(1-84)

- **Class:**
  - Endocrine hormone
- **Proposed Indication:**
  - Replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism.
- **Formulation:**
  - Lyophilized powder for reconstitution and SC injection
  - Multiple dose glass dual-chamber cartridge available in 4 nominal
  - Dosage strengths (25, 50, 75, and 100 mcg/dose)
- **Proposed dose:**
  - Starting dose of 50 mcg QD.
  - Based on calcemic response, titrate at 2 to 4 week intervals upward to doses of 75 mcg and then 100 mcg.
  - Downward titration to a minimum dose of 25 mcg can occur at any time.

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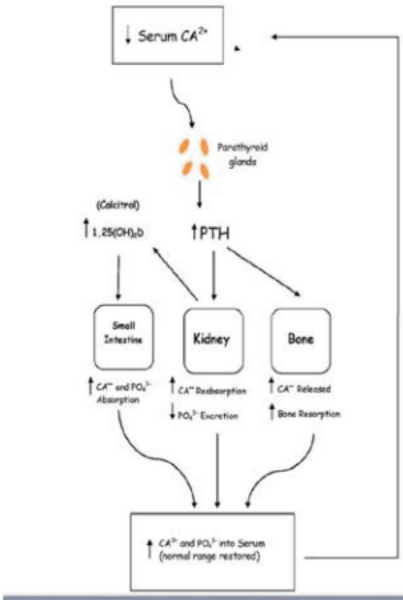
Hypoparathyrodism



Role of PTH in Ca and PO Regulation

- **Main Effects of PTH – normal health:**
  - Precise regulation of serum calcium and phosphate
  - stimulates calcium reabsorption at the proximal tubule
  - stimulates the $25(OH)D_3$-1-α-hydroxylase that converts 25(OH) vitamin D into 1,25-dihydroxyvitamin D ($1,25(OH)_2$ vitamin D, calcitriol)
  - Stimulate urinary excretion of phosphate
  - Bone regulation
- **Rare disorder:**
  - hypocalcemia leading to hyperphosphatemia and hypercalciuria
  - Signs and symptoms of the disease may include tetany, paresthesia/numbness, mental status changes (mood, memory), and seizures.
  - Patients have reduced bone turnover, increased bone mineral density (BMD), and abnormal bone microstructure.
  - No approved replacement therapy
- **Current treatment options:**
  - high doses of calcium and active vitamin D
- **Products under development:**
  - Synthetic hPTH1-34 (NIH)

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Formulation/Devices Used

- Modified (b) (4) pen (b) (4)) with a (b) (4) needle delivered the B formulation in the osteoporosis development program from 1999 to 2002
- Modified (b) (4) pen (b) (4) with a (b) (4) needle delivered the B and (b) (4) formulations in the osteoporosis development program from May 2002 to October 2005
- Ypsomed pen (Ypsomed, Burgdorf, Switzerland) with a 31-G, 8 mm needle delivered the B formulation in the hypoparathyroidism development program from 2007 to March 2012
- Haselmeier pen (Haselmeier, Stuttgart, Germany) with a 31-G, 8 mm needle delivered the B formulation in the hypoparathyroidism development program beginning in March 2012.

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Overview of Clinical Pharmacology

Study	Objective	Key Design Features	Dose / Route
PBR 930811	Safety, tolerability, MTD, and PK profile	R, DB, SAD, N=32, PMW	0.02, 0.05, 0.1, 0.2, 0.5, 1, 1.5, 2, 2.5, 3, 4, and 5 µg/kg SC (thigh), 3 single doses
PBR 930812	Safety, tolerability, MTD, and PK profile	R, DB, MAD, N=48, PMW	0.5, 1, 1.5, 2, 2.5, and 3 µg/kg SC (thigh), 7-day repeat dose
C09-002	PK and PD	OL, N=7, HPTH PT	50 µg SC (thigh) SD; washout ≥ 7 days, 100 µg SC (thigh), SD
Mosekilde IIT PK/PD sub-study	PK PD – diurnal variation in biochemical indices	R, DB, PRL, PBO, N=39, HPTH PT	100 µg SC (thigh), QD for 24 wk, PK/PD performed on the last day of treatment
CL1-11-009	PK, effect of hepatic impairment	OL, M&F, HLTH=12, Mod-HI=12	100 µg SC (abdomen)
CL1-11-010	PK, effect of renal impairment	OL, M&F, HLTH=12, Mild to Mod-RI=16	100 µg SC (abdomen)

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Overview of Clinical Pharmacology

Study	Objective	Key Design Features	Dose/Route
ALX1-11-93001	Pop-PK in a subset from Efficacy safety trial	R, DB, PBO, PRL, PMW with Osteoporosis	100 µg SC (abdomen or Thigh), QD for 18 months
NPSP-PCS-101 Overall Pop PK and PK/PD Report and Addendum	Population PK and PK/PD PK modeling, PK/PD Correlation analysis and Specific Antibody effects on PK	16 Studies: Hypoparathyroidism: 136 Others: 1410	SC in the thigh or abdomen QD, single dose or multiple doses up to 18 months
CL1-11-040 (REPLACE)	Efficacy and safety (Phase III)	R, DB, HPTH PT, N=134	50 µg, 75 µg, or 100 µg, QD flexible dosing, SC thigh, 24 wk
PAR-C10-007 (RELAY)	Efficacy and safety (Phase III)	R, Dose-B, HPTH PT, N=46	25 or 50 µg SC in the thigh, QD for 8 weeks
PAR-C10-008 (RACE) Ongoing	Efficacy and safety (Phase III)	OL, HPTH PT, N=53	25 to 100 µg SC (thigh), QD for 12 months + Extension

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Other Studies

Study	Objective	Key Design Features	Dose/Route
CL1-11-006	Develop Pop-PK model in the TOP population (Study ALX1-11-93001)	R, DB, PBO, PRL, N=238, PMW with Osteoporosis	100 µg SC (abdomen or Thigh), QD for 18 months
CL1-11-008	Primary: BMD with/without calcium supplementation Secondary: PK and serum total calcium PD as part of an acute calcemic response substudy	R, DB, PBO, PRL, N=106, PMW with Osteoporosis	100 µg SC (abdomen or Thigh), QD for 6 months
N01-AR-9-2245 NIAMS-045 [ACR substudy	Efficacy and safety in combination with alendronate Serum calcium response during 8 hours after injection of rhPTH(1-84) in a subset	R, DB, PBO, PRL, N=106, PMW with Osteoporosis	100 µg SC (abdomen or Thigh), QD for 12 months. ACR substudy performed on a single day at the Month 12 visit.

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Overview of Clinical Pharmacology

Study	Objective	Key Design Features	Route for 100 µg dose	Formulation
PAR-C10-005	BE –Ypsomed and Haselmeier injection pens	R, OL, SD, 2way-CO, 3-d washout, N=50, HV	SC (alt. thighs)	B
CL1-11-013	PK after IV and absolute BA after SC	R, OL, 2way-CO, 1-wk washout, N=12, PMW	IV (15 min inf.) SC (abdomen)	B / IV infusion, (b) (4) pen
CL1-11-007	PK and BA at 2 SC inj. sites and assess ISV variability	R, OL, 3way-CO, 5-d washout, N=18, PMW	SC (abdomen and thigh)	B / (b) (4) pen for SC inj.
CL1-11-012	BE without (Formulation B) and with (Formulation (b) (4)	R, OL, 2way-CO, 1-wk washout, N=64, PMW	SC (abdomen)	B vs (b) (4) / (b) (4) pen for SC inj.
SH-PTH-0001	BE/PK of Formulation B vs. Phase 2 Formulation A	R, OL, 2way-CO, 1-28d washout, N=43, HM	SC (abdomen)	A & B / (b) (4) pen
CL1-11-017	PKPD ID vs SC	R, OL, 3way-CO, 1-wk washout, N=22, PMW	ID (abdomen) SC (abdomen)	B / (b) (4) pen for SC inj.

Formulation A: (b) (4) **Formulation** (b) (4) (intended commercial); **Formulation** (b) (4) same as B with the addition of (b) (4) (not developed further).

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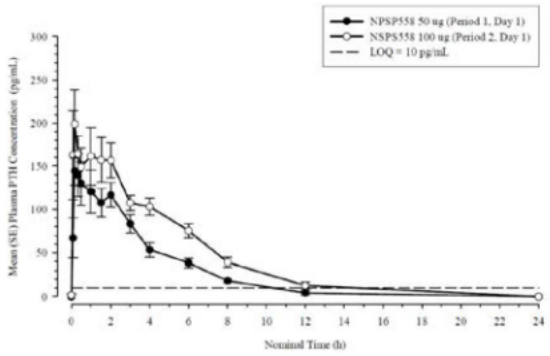
rh-PTH ADME

PK Profile – SD in HPTH (Trial C09-002)



- Fairly rapid absorption (t_{MAX} ~ 0.1 -0.3 hr)
- T1/2 ~3 hr (R_{accum} ~ 1 QD)
- Absolute BA – 55% (36-92%)
- Some evidence of time dependent PK
- Metabolism:
  - Hepatic (non-specific protease/cathepsins)
- No CYP based DDI potential
- No PB based DDI potential
- No DDI observed with alandronate in PMW

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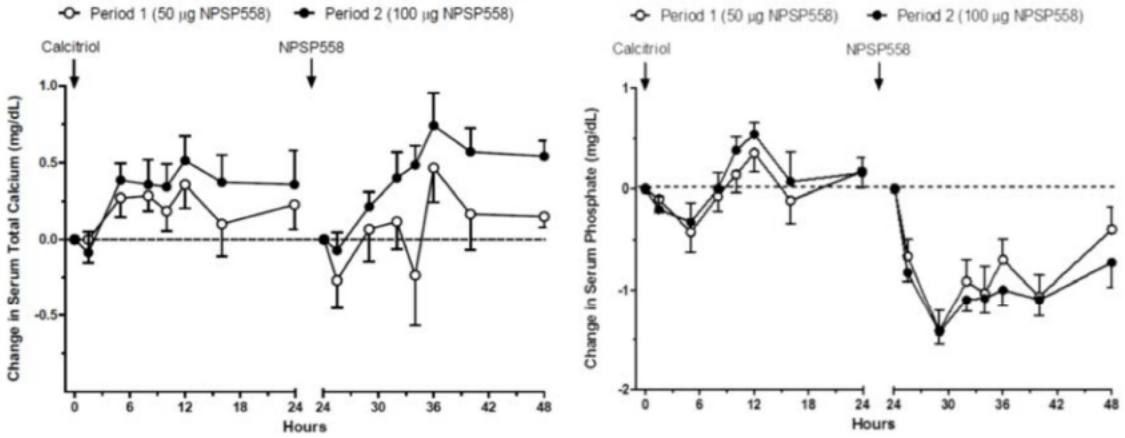
rh-PTH (1-84) Pharmacodynamics

PD Profile – SD in HPTH (Trial C09-002)



Period 1: N = 7 (0 - 24hours); N = 6 (24 - 48 hours)
Period 2: N = 7 (0 - 48 hours)

Note: Baseline resets to zero at 24 hours in each period
Period 1: N = 7 (0 – 18 hours); N = 6 (24 - 48 hours)
Period 2: N = 7 (0 - 48 hours)

- **Dose dependent increase in serum calcium up to 100 mcg**
- **Similar decrease in serum phosphate up to 100 mcg**

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Clin. Pharm. Review Questions

- **Review Questions:**
  - What are the PK and PD characteristics of rh-PTH?
  - Do they support or explain dose-efficacy relationship?
- **Filing Issues:**
  - Did sponsor submit all the information for review? **– Yes**

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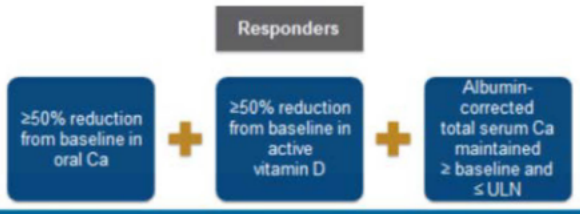
Efficacy from Pivotal Trials

- Pimary registration study, CL1-11-040, was randomized, double-blind and placebo-controlled.
- During pre-randomization optimization period subjects' oral calcium and active vitamin D doses were adjusted towards a goal of an albumin-corrected total serum calcium concentration within the target range (8.0 to 9.0 mg/dL). Thereafter, subjects were randomly assigned to receive 24 weeks of treatment with either rhPTH(1-84) or placebo.
- Starting dose was 50 µg SC 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.

Primary End-point in Trial CL1-11-040
Responder Rate By Week 24



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rh-PTH Efficacy in Hypoparathyroidism

Analysis of Responder Rate at End of Treatment Based on Investigator-prescribed Data (Primary Endpoint) – ITT Population – Study CL1-11-040

Status	Placebo (N= 44) n (%)	Placebo (95% CI)[a]	rhPTH(1-84) (N= 90) n (%)	rhPTH(1-84) (95% CI)[a]	Treatment Difference (95% CI)[b]	p-value[c]
Responder	1 (2.3)	(0.1, 12.0)	48 (53.3)	(42.5, 63.9)	51.1 (39.9, 62.3)	< 0.001
Non-Responder	43 (97.7)		42 (46.7)			

CI = confidence interval; ITT = intent-to-treat; N, n = number of subjects
Note: Percentages are based on the number of ITT subjects in each treatment arm.
[a] Based on exact 95% CI for the responder rate.
[b] Treatment difference is calculated as responder rate of rhPTH(1-84) minus the responder rate of placebo, the 2-sided asymptotic 95% CI is based on normal approximation.

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Clin. Pharm. Review Questions

- **Review Questions:**
  - What is the dose-response, systemic exposure-response relationship for rh-PTH (1-84) for efficacy?
    - Does exposure-response information support the adequacy of the proposed titration based dosage regimen?
  - What is the dose-response, systemic exposure-response relationship for rh-PTH (1-84) for safety?
    - Does exposure-safety information support the proposed titration based dosage regimen?
- **Filing Issues:**
  - Did sponsor submit all the information for review? **– Yes**

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Intrinsic Factors on PK

Typical Values of the Final Population PK Model of Exogenous rhPTH(1-84) [NPSP-PCS-101]

Population PK Parameters		Typical Values	BSV (%)
Ka (h^{-1})	Abdomen	19.4	254%
	Thigh	7.5	
	Unknown	3.68	
CL/F (L/hr)	Non-hypoparathyroidism	$111 \cdot (WT/65)^{0.851} \cdot (AST/20)^{-0.0315}$	69.1%
	Hypoparathyroidism	$93.2 \cdot (WT/65)^{0.851} \cdot (AST/20)^{-0.0315}$	
Vc/F (L)	Postmenopausal Women	$242 \cdot (WT/65)^{1.51}$	68.3%
	Premenopausal Women	$380 \cdot (WT/65)^{1.51}$	
	Men	$178 \cdot (WT/65)^{1.51}$	
Error Model			
Additive Error (pg/mL)		2.35	
Proportional Error (%)		33.0%	

- **Sponsor:**
  - *No dose adjustment for body weight, sex, and age based on the results of population PK analysis.*
  - *None of these covariates had clinically relevant effect on PK of rh-PTH (1-84)*
- **Review Questions:**
  - What is the impact of covariates on PK of rh-PTH (1-84)?
  - Is sponsor's proposed language in the label acceptable?
- **Filing Issues:**
  - Did sponsor submit all the information for review? **– No, the input data and NONMEM model files are not submitted**

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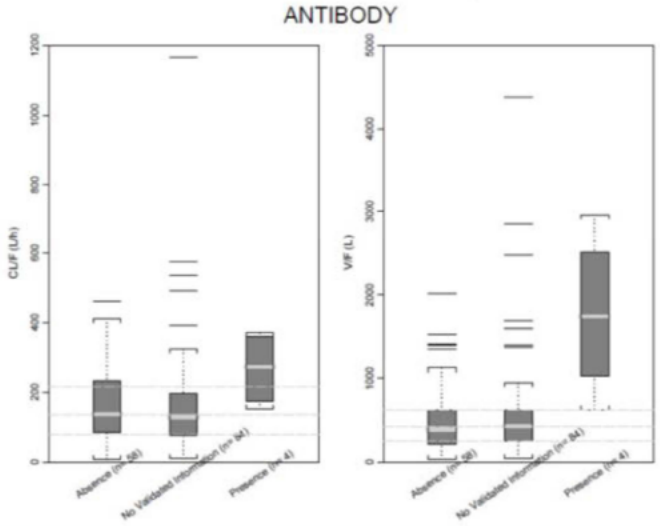
Intrinsic Factors on PK

Exploratory Correlation Between Individual Values of CL/F and V/F and Immunogenicity Results for Subjects with Hypoparathyroidism (Studies C09-002, PAR C10-007, CL1-11-040 and PAR C10-008)



- **Sponsor:**
  - *No major immunogenicity concern*
- **Review Questions:**
  - Is sponsor's claim acceptable?

Filing Issues:

- Did sponsor submit all the information for review? **– No, the input data and NONMEM model files are not submitted**

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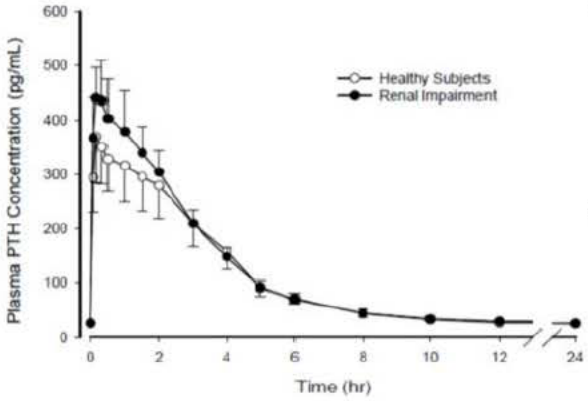
Specific Populations – Renal Impairment



~27% higher Cmax, 2% higher AUC

SC dose was administered in abdomen

- **Sponsor:**
  - *No dose adjustment in mild to moderate RI*
  - *Not studied use in severe RI and ESRD*
- **Review Questions:**
  - What is the impact of renal impairment on PK of rh-PTH (1-84)?
  - Is sponsor's proposed language in the label acceptable?
- **Filing Issues:**
  - Did sponsor submit all the information for review? – **Yes**

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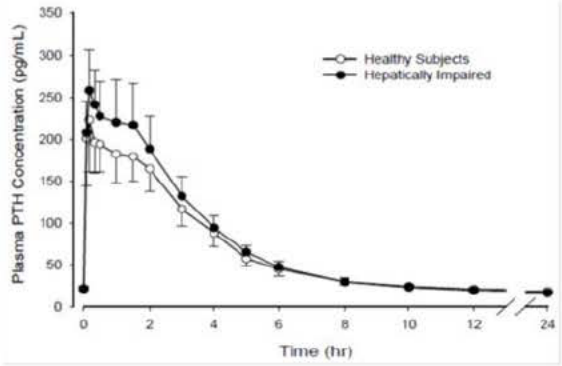
Specific Populations – Hepatic Impairment



~20% higher Cmax and AUC

SC dose was administered in abdomen

- **Sponsor:**
  - *No dose adjustment in mild, to moderate HI*
  - *Not studied in severe HI*
- **Review Questions:**
  - What is the impact of hepatic impairment on PK of rh-PTH (1-84)?
  - Is sponsor's proposed language in the label acceptable?
- **Filing Issues:**
  - Did sponsor submit all the information for review? – **Yes**

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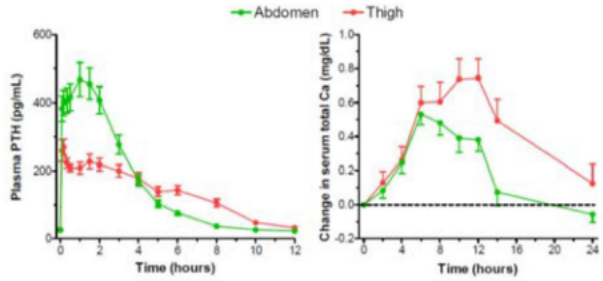
Abdomen versus Thigh – PKPD is Different

Figure 3-2 **Thigh Versus Abdomen Injection Sites - Study CL1-11-007 (Single-dose Crossover Study of 100 µg Natpara Injected SC in the Thigh or Abdomen)**



SE = Standard Error, PTH = Parathyroid hormone
Source: CL1-11-007, serum total calcium recalculated from Table 14-20, PTH recalculated from Table 14-19.

- **Sponsor:**
  - *Thigh was selected as the preferred site- desired PKPD*
- **Review Questions:**
  - What is the impact of injection site on PKPD?
  - Does it support the proposed route of administration?
- **Filing Issues:**
  - Did sponsor submit all the information for review? – **Yes**

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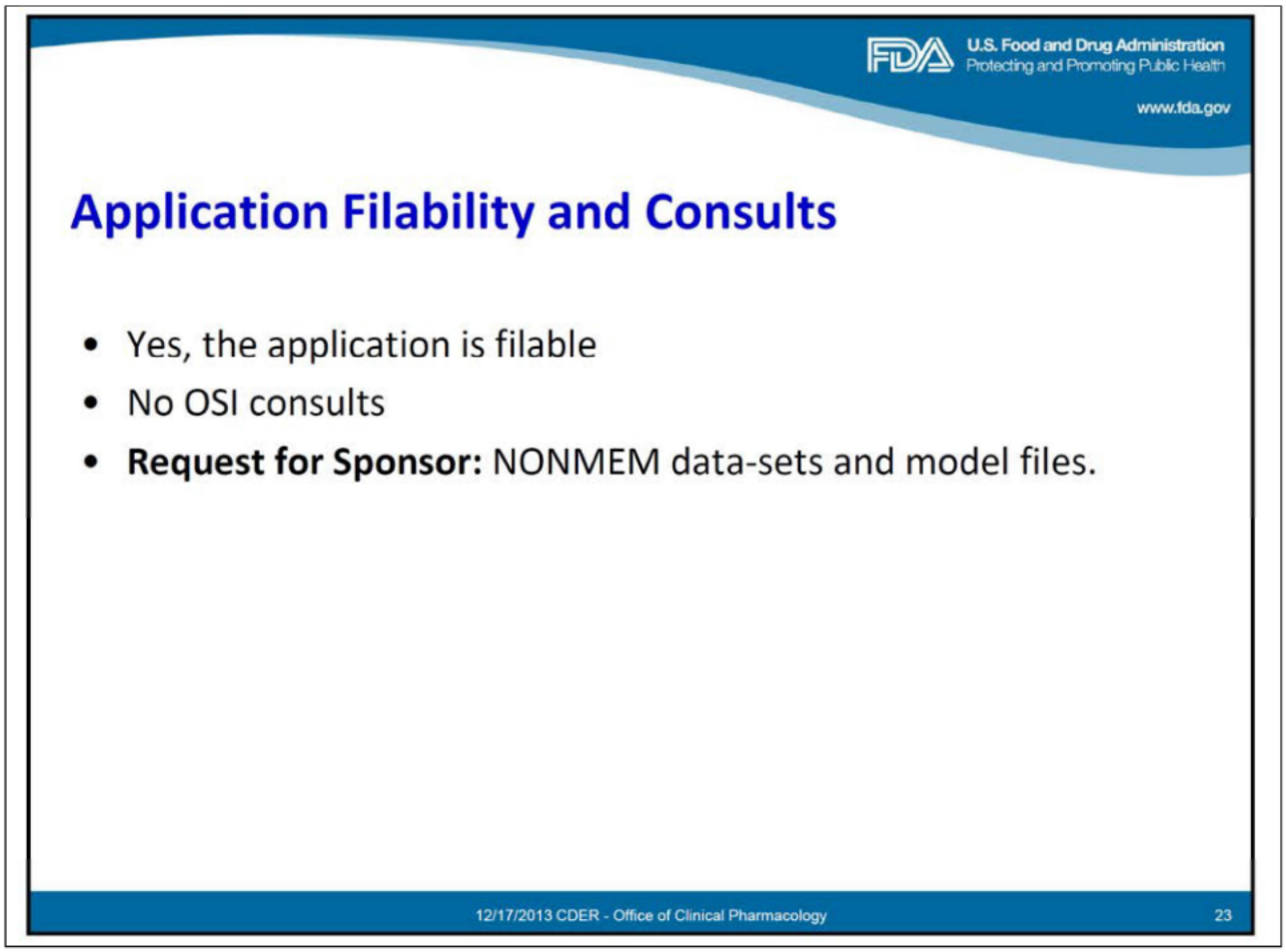
PK Comparability of Different Formulations

- **Sponsor:**
  - *The NPS Sponsored Efficacy and Safety Studies in Hypoparathyroidism and Clinical Pharmacology Study PAR-C10-005 used the to-be-marketed rhPTH(1-84) formulation administered with the to-be-marketed Natpara® Pen or the Ypsomed pen*
  - *Phase 2 and Intended commercial Formulations are marginally bioequivalent for PK (11-17% higher exposure)*
  - *100 µg administered SC using the Haselmeier pen is bioequivalent to the same formulation administered SC using the Ypsomed pen*
- **Review Questions:**
  - Are sponsor's claims acceptable?
- **Filing Issues:**
  - Did sponsor submit all the information for review? – **Yes**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Application Filability and Consults
• Yes, the application is filable
• No OSI consults
• Request for Sponsor: NONMEM data-sets and model files.
12/17/2013 CDER - Office of Clinical Pharmacology
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On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	
2	Has the applicant provided metabolism and drug-drug interaction information?			X	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?		X		
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X		X	

15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Comment to Sponsor (Have been Communicated): "Please submit the NONMEM data sets and model files associated with the Population PK reports ALX1-11-93001-POP-PK, NPSP-PCS-101-POP-PK, and NPSP-PCS-101-Exploratory PKPD Analysis. All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt). In addition, include a model development decision tree and/or table which gives an overview of modeling steps or indicate the location, in case you have included such information in the existing reports. In case you have submitted these data sets in the requested format, indicate its location."

Manoj Khurana

Reviewing Clinical Pharmacologist Date

Immo Zadezensky

Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MANOJ KHURANA
05/19/2014

IMMO ZADEZENSKY
05/20/2014