CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	BLA
Application Number(s)	125,511
Priority or Standard	Standard
Submit Date(s)	October 23, 2013
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Division / Office	Division of Metabolism and Endocrinology Products (DMEP)/Office of Drug Evaluation II
Reviewer Name(s)	Naomi Lowy, M.D.
Review Completion Date	June 24, 2014
Established Name	Recombinant Human Parathyroid Hormone or (rhPTH[1-84])
(Proposed) Trade Name	Natpara®
Therapeutic Class	Parathyroid hormone
Applicant	NPS Pharmaceuticals
Formulation(s)	Lyophilized for reconstitution for injection
Dosing Regimen	Starting dose of 50 mcg once daily, with up-titration to 75 or 100 mcg daily or down-titration

	to 25 mcg daily
Indication(s)	Long-term treatment of hypoparathyroidism
Intended Population(s)	Adults with hypoparathyroidism

Template Version: March 6, 2009

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1 Recommendations/Risk Benefit Assessment

Natpara® (rhPTH[1-84]) for injection, a New Molecular Entity (NME), is being proposed as replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism. It is submitted as a biologic-device combination.

The active pharmaceutical ingredient, rhPTH(1-84) is identical to the full-length human 84-amino acid protein. Natpara® is supplied in a cartridge in 4 dosage strengths (25, 50, 75, or 100 µg) designed for use with a mixing device for product reconstitution and a reusable pen injector for drug delivery.

The recommended starting dose is 50 µg and, based on calcemic response, can be titrated at 2- to 4-week intervals upward to doses of 75 µg and then 100 µg. Down titration to 25 µg can occur at any time.

1.1 Recommendation on Regulatory Action

I recommend approval of Natpara® (rhPTH[1-84]) for injection for the treatment of hypoparathyroidism. The primary endpoint in the pivotal trial was met. While Natpara®, in the dosages studied, is not a complete parathyroid hormone replacement for the majority of patients, it can allow for a potentially clinically important decrease in the need of large and burdensome amounts of calcium and vitamin D supplements.

Unfortunately, the Applicant has not clearly demonstrated other clinically meaningful benefits that should theoretically be seen with replacement of parathyroid hormone. This includes correction of hypercalciuria that plagues patients with hypoparathyroidism.

Bone in hypoparathyroid patients is characterized by low bone turnover. Natpara's effect is evidenced by increases in the levels of bone turnover markers. However, the clinical relevance of these changes and whether they translate into a meaningful clinical benefit is unclear.

As of the completion of this Review, several important issues are still pending that could affect approvability of this product:

- Device-related questions: the Division and CDRH is awaiting more data regarding pen leakage problems as well as a summary of subjects and durations for those who used the to-be-marketed injector pen (Haselmeier)
- There were serious issues regarding conduct at one of the clinical sites. At the time this review was completed, inspection of the NPS's contract

research organization (CRO) was pending, and the findings of that inspection could have serious implications for this Application.
- This BLA will be presented at an Advisory Committee meeting in September 2014.

1.2 Risk Benefit Assessment

Hormone replacement therapy does not currently play a role in the treatment of hypoparathyroidism. The current standard of care involves large doses of calcium and vitamin D which are aimed at correcting hypocalcemia while minimizing hypercalciuria. This treatment also has no effect on defective bone metabolism resulting from PTH deficiency. Therefore, a true replacement for PTH—one that biochemically and clinically performs the role of endogenous PTH in patients with hypoparathyroidism--is lacking and would be an important milestone in the treatment of this patient population.

The Applicant conducted one pivotal trial and three supportive trials. The Applicant met the primary endpoint in the pivotal trial. Approximately 55% of subjects taking Natpara® reduced the amounts of calcium and vitamin D analogs by 50%, while maintaining a normal serum calcium level. While this relieves some of the burden of ingesting large amounts of supplements, other clinically important changes were not observed. A normalization of 24-hour urinary calcium was not observed, even in the long-term trial. Changes in bone turnover markers were observed. However, since reference ranges for these markers were established for the osteoporosis population, it is unclear if the changes translate into an important clinical benefit on bone.

From a safety perspective, Natpara® does not appear to be advantageous compared to the standard of care. In patients with hypoparathyroidism, serum calcium should ideally be kept in the lower end of the normal range (8 to 8.5 mg/dL) in order to minimize hypercalciuria. Although the mean serum calcium levels at Week 24 did show that Natpara-treated subjects approached this goal, other analyses (scatterplots in Section 7) suggest that overall, the ranges of serum calcium for Natpara-treated subjects were similar at baseline and at the end of the pivotal trial. The same analyses also suggest that both laboratory-confirmed hypocalcemia and hypercalcemia were more problematic in the Natpara group compared to placebo. There were two serious adverse events of hypercalcemia, and these were both in the Natpara group. Hypocalcemia was a particular problem when switching back from Natpara to the standard of care.

The immunogenicity program for Natpara was complicated. Nevertheless, the assays were validated and there is no apparent association of incidence of anti-drug antibodies with clinical adverse events.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

Not applicable to this Application.

1.4 Recommendations for Postmarket Requirements and Commitments

At the time this Review was completed, there were no PMRs or PMCs being discussed. However, reviews from all disciplines are not finalized.

2 Introduction and Regulatory Background

2.1 Product Information

The active ingredient in Natpara® is synthetic rhPTH(1-84) and is identical to the full-length human 84-amino acid protein. It is manufactured using a strain of *E. coli*. This biologic is a New Molecular Entity (NME) and is not approved in the United States for any indication. It is being proposed as replacement for endogenous parathyroid hormone (1-84) for the long-term treatment of hypoparathyroidism. The same product is approved in the European Union for the treatment of osteoporosis.

It is intended to be self-administered once daily by subcutaneous (SC) injection into alternating thighs. The recommended starting dose is 50 µg and can be titrated at 2- to 4- week intervals to a dose of 75 µg and subsequently 100 µg. Downward titration to a dose of 25 µg can occur at any time.

Natpara is supplied as a multiple dose, glass dual-chamber cartridge in 4 dosage strengths (25, 50, 75, or 100 µg) and is intended for daily subcutaneous injection. The disposable medication cartridge is designed for use with a reusable mixing device for product reconstitution and a reusable pen injector for drug delivery. Using the pen injector, each medication cartridge delivers 14 doses.

Although two drug delivery systems were used during the development program (the Ypsomed pen injector and the Haselmeier pen injector), the Applicant intends to market the Haselmeier system (renamed Natpara® Mixing Device and Natpara Q-Cliq™).

2.2 Tables of Currently Available Treatments for Proposed Indications

Hormone-replacement therapy does not currently play a role in the treatment of hypoparathyroidism. There are no formal guidelines for the management of hypoparathyroidism. However, the goals of therapy are symptom control, a serum albumin-corrected total calcium level at the lower end of the normal range (approximately 8.0 to 8.5 mg/dL), a 24-hour urinary calcium level well below 300 mg, and a calcium-phosphate product below 55.[1]

Standard treatment attempts to correct the hypocalcemia with oral calcium supplementation and vitamin D analogs. Large doses of calcium are given to augment intestinal calcium absorption. For example, to obtain 1000 mg of elemental calcium per day, a patient would need to ingest five 500 mg calcium carbonate tablets per day (40% elemental calcium by weight). This is also accompanied by large doses of vitamin D (to mimic the effects of the missing 1,25-dihydroxyvitamin D) or physiological doses of 1,25-dihydroxyvitamin D itself. The combined goal is to forcibly drive calcium transport across the intestinal epithelium in quantities sufficient to overwhelm the ability of the kidney to clear this intestinally derived calcium load, forcing the serum calcium to increase.

The standard treatment of calcium and vitamin D is less than optimal. This therapeutic model is rightfully compared to a tightrope walk and involves balancing forced intestinal calcium over-absorption, to maintain normocalcemia, with unavoidable increases in renal calcium excretion. Adjustment of serum calcium using calcium and vitamin D is imprecise and represents an inconvenience to patients. Episodes of both hyper- and hypocalcemia resulting from under or over treatment are commonplace. The kidney and urinary tract are particularly vulnerable to damage in patients with hypoparathyroidism. The filtered load of calcium increases proportionally with increases in serum calcium and in the absence of PTH's action to promote renal calcium reabsorption, calcium is excreted in excess amount in the urine and predisposes to nephrocalcinosis and kidney stones.

Finally, supplementation with calcium and vitamin D does not correct the defective bone metabolism resulting from PTH deficiency, which leads to chronically low bone turnover and brittle bone structure.

[1] Shoback D. Clinical Practice: Hypoparathyroidism. New England Journal of Medicine. 2008; 359: 391-403.

2.3 Availability of Proposed Active Ingredient in the United States

This biologic is an NME and is not approved in the US.

Preotact® (rhPTH[1-84]) was approved in the European Union (EU) in 2006 for the treatment of women with post-menopausal osteoporosis who are at high risk of fractures at a daily dose of 100 mcg . The most common adverse events seen with Preotact® in this population are hypercalcemia, hypercalciuria, and nausea.[2]

On March 21, 2014, the European Commission was notified by NPS of their decision to voluntarily withdraw the marketing authorization for Preotact® due to commercial reasons. On May 16, 2014, the European Commission issued a decision to withdraw the marketing authorization for Preotact®.[3]

2.4 Important Safety Issues With Consideration to Related Drugs

The Applicant originally developed rhPTH(1-84) for the treatment of osteoporosis in post-menopausal women at high risk of bone fracture. An NDA (21,847) for that indication was submitted on May 10, 2005 under the proprietary name Preos®. The Agency issued an approvable letter on March 9, 2006. Outstanding issues included safety concerns of hypercalcemia, particularly at the 100 µg dose, as well as reliability of the delivery device used in the clinical trials. The Applicant withdrew the NDA without prejudice on March 24, 2011. Although hypercalcemia was a major safety concern in that NDA, the patient population in the osteoporosis program was substantially different to the subjects studied in the current BLA. Specifically, the osteoporosis population is PTH-sufficient population, in contrast to the hypoparathyroid population, in which subjects are PTH-deficient. One would therefore expect a difference in the calcemic response in these two populations.

A related product is teriperatide (Forteo®, Eli Lilly and Company), which is recombinant human parathyroid hormone analog (1-34) and is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture, increase of bone mass in men with primary of hypogonadal osteoporosis at high risk for fracture, and treatment of men and women with osteoporosis associated with sustained systemic glucocorticoid therapy at high risk for fracture.[4] Forteo contains the N-terminal region of endogenous PTH but does not contain the C-

[2] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000659/human_med_000984.jsp&mid=WC0b01ac058001d124

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2014/07/WC500169775.pdf

[4] Forteo Full Prescribing Information, Revised 3/2012

terminal region. The Package Insert (PI) for Forteo includes a boxed warning for the potential risk of osteosarcoma, which is based on findings in rats. The PI also includes the following statements: "The safety and efficacy of Forteo have not been evaluated beyond 2 years of treatment. Consequently, use of the drug for more than 2 years during a patient's lifetime is not recommended." As discussed further in this Review, the non-clinical findings regarding osteosarcoma in rats in the Forteo program are identical to those observed in the Preos®/Natpara program. This has potential important safety implications, particularly when used chronically.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

As discussed in Section 2.4, the Agency issued an approvable letter for Preos® for the osteoporosis indication. The Applicant then decided to pursue the development of the drug along with the development of a new pen injector system for the treatment of hypoparathyroidism. For this indication, rhPTH(1-84) was designated as NPSP558, which is referred to often and interchangeably with rhPTH(1-84) and Natpara in this Review.

In 2007, the Agency granted Orphan Drug Designation for NSPSP558 for hypoparathyroidism. A pre-IND meeting was held on December 17, 2007. The Applicant submitted IND 76,514 on September 19, 2008 with the initiation of the Phase 3 pivotal trial CL1-11040 for the hypoparathyroidism indication.

A Type C meeting was held on September 26, 2011. During this meeting, the following was discussed:

- The Division explained that pooling data from the osteoporosis program was not appropriate.
- The Division inquired why a 25 µg dose was not studied in the pivotal trial. The Applicant explained that midway through the pivotal trial, a subject had an elevated calcium level (≥11.9 mg/dL) at the first dosing tier. In anticipation that patients could potentially need the 25 µg dose, the Applicant initiated a clinical trial (PAR-C10)-007). The 25 µg dose was then also introduced into the open-label extension PAR-C10-008.
- The Division agreed the proposed exposure—12 months in hypoparathyroid subjects (N=73, with 49 having 2-year exposure)--was acceptable, with the condition that the pivotal trial had a positive outcome.
- The Applicant explained that case reports forms (CRFs) from Dr. Bilezikian's trials were not generated, but rather the subjects' medical records served as source documents.

- The Division stated that Dr. Mosekilde's trial from the literature would be considered purely supportive to the BLA.

Another Type C meeting was held on July 6, 2010 to discuss the drug-device combination, since the device used in the clinical trials (Ypsomed) is different than the intended US commercial mixing deice and pen injector. The Applicant stated that the bridging program for these devices was added to Study PAR-C10-008.

On November 7, 2011, the proprietary name Natpara® was accepted.
On December 23, 2011, the Agency confirmed that rhPTH(1-84) be designated as a biologic and that the applications would be a BLA for a biologic-device combination.

A pre-BLA meeting was held on May 15, 2012.

(b) (4)

2.6 Other Relevant Background Information

Because this is a biologic-device, this Application is also being reviewed by Center for Devices and Radiologic Health (CDRH). The development program was complicated by a switch in the injector pen mid-way through the long-term trial, as mentioned in 2.5 above. The pen was switched to the Haselmeier, which is the to-be-marketed pen. The data are reviewed under Safety, but as of the completion of this Review, the Division is awaiting further data from the Applicant.

3 Ethics and Good Clinical Practices

This application had serious issues discovered upon inspection of the clinical sites. Because of these issues, the Division chose to eliminate efficacy and safety data from one site. This is discussed in detail below.

[5] (b) (4)

3.1 Submission Quality and Integrity

The Applicant's initial submission was adequately organized and information was generally easily retrievable. Multiple information requests were sent to the Applicant, and responses were generally submitted promptly and thoroughly.

Issues related to the integrity of the submission are discussed in 3.2.

3.2 Compliance with Good Clinical Practices

Inspections of the 3 clinical sites were completed. One of the sites chosen was 1002, Primary Investigator Dr. John Bilezikian (Columbia University, New York). This site was chosen for inspection as he is one of two lead Investigators of this clinical program. In addition, he had one of the highest enrolling sites.

The clinical inspection revealed the following pertaining to Trials 040, 007, and 008.

- Forging of Dr. Bilezikian's signature by the Study Coordinator on Form 1572, two SAE reports, and 2 protocol agreements
- Forged prescriptions for test article using the sub-investigator's name and Dr. Bilezikian's name. Between 2009 and 2011there were 150 prescriptions: the study coordinator forged 127 with the sub-investigator's name and 2 with Dr. Bilezikian's name.

The following were findings pertaining only to Trial 040 (pivotal trial):

- SAEs were not reported within 24 hours, as required by protocol
- Not following protocol-required procedures, such as laboratory tests and 24-hour urine testing
- For one subject, Dr. Bilezikian signed off on inclusion/exclusion criteria on a date that was a university holiday.
- Inclusion/exclusion criteria signed off by PI and sub-PI after subjects had already been randomized and began taking study drug (in 2 subjects)
- In one subject, 24-hour urine collection took place before subject signed Informed Consent.

The following were findings pertaining to Trial 007:

- Inclusion/exclusion criteria for 2 subjects were signed off by PI/sub-PI after subjects had completed the trial.
- Inclusion/exclusion criteria for one subject were signed off by PI/sub-PI after subject had already been randomized and taking study drug.

The following were findings pertaining to Trial 008:

- Forged Form 1572 and Investigator Agreement

The study coordinator admitted to forging signatures and was terminated from Columbia University in April 2014. The forgery had been reported to OSI in 2013 from a former employee of NPS.

Overall, as per the Summary of Inspectional Findings, Dr. Bilezikian had little involvement in the trials. Documents show that he refused to review any data in the electronic data system and most charts were signed by the sub-Investigator.

Because of these issues that questioned the integrity and reliability of all data coming from this site, the Division decided to re-analyze all efficacy and safety data excluding Site 1002. The Company provided revised tables, figures, listings, and all Information Requests for all trials in which Site 1002 was involved (all trials except 009, which enrolled Hungarian patients only). This review only discusses the re-analyzed data, except where otherwise noted.

At the time this review was completed, inspection of the NPS's contract research organization (CRO) was pending.

3.3 Financial Disclosures

The Applicant provided Financial Disclosure forms for the following studies: C09-002, CL1-11-040, PAR-C10-005, PAR-C10-007, PAR-C10-008, PAR-C10-009, and the HEXT Study (also known as the Bilezikian ITT).

The only investigator with disclosable information is Dr. (b) (6). He was an investigator in Studies PAR-C10-007, PAR-C10-008, and CL1-11-040. (b) (6) His services, along with his compensation, are summarized below. He has received a total of approximately $46,000 from NPS.

Date	Amount	Nature of Disclosure	Reported for Trial
(b) (6)	$7300	(b) (6)	008
	$6436.65		008
	$7500		040, 008, 007
	$7500		040, 007
	$4485.60		040, 007

(b) (6)	$12742.80	(b) (6)	040, 007

Applicant's Response to Information Request, June 6, 2014

The Applicant lists the following steps that were taken to minimize potential bias of clinical study results: 1) randomized, double-blind, placebo-controlled pivotal trial 2) the company's fair market value review of Dr. (b) (6) compensation for consulting services 3) the Company's contract with Dr. (b) (6) that states that his "judgment with respect to the advice and care of each patient will not be affected by the compensation" that he receives".

(b) (6)

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Refer to Dr. Su Tran's review for complete details.

4.2 Clinical Microbiology

The Microbiology Reviewer, Dr. Jessica Cole, recommends approval. This is an (b) (4) filled drug product. One compartment of the cartridge is filled, lyophilized, and stoppered before the diluent is filled into the second chamber. The drug cartridge is later loaded in to the pen and packaged with the mixing device.

4.3 Preclinical Pharmacology/Toxicology

Refer to Dr. Robert Maher's review for complete details.

4.4 Clinical Pharmacology

Refer to complete review by Dr. Manoj Khurana.

4.4.1 Mechanism of Action

PTH is necessary for the regulation of serum calcium and phosphate. It does this by the following actions:

- stimulates calcium reabsorption at the proximal tubule in the kidney
- stimulates 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)
- stimulates urinary excretion of phosphate

4.4.2 Pharmacodynamics

Initial review of Natpara showed a dose-dependent increase in serum calcium up to 100 µg and a similar decrease in serum phosphate up to 100 µg.

4.4.3 Pharmacokinetics

Natpara has fairly rapid absorption, with T_{max} approximately 0.1-0.3 hour. The half-life is approximately 3 hours. The absolute bioavailability is 55%. There is also some evidence of time-dependent PK. This biologic is metabolized hepatically.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The clinical development program includes 5 safety and efficacy trials and 12 clinical pharmacology studies. As part of the BLA, the Applicant also submitted data from 7 studies in osteoporosis.

Trials that are relevant to the efficacy and safety of rhPTH(1-84) for the treatment of hypoparathyroidism included in the BLA submission are summarized below. Study CL1-11-040 is the primary study and the others are considered supportive. The Applicant obtained the right of reference to the Investigator (Bilezikian) trial. Subjects were allowed to participate in more than one trial. Overall, there were 226 unique subjects in the Efficacy and Safety studies. There were 161 subjects in the 4 NPS-sponsored studies below (132 treated with rhPTH(1-84) and 44 treated with placebo) and 79 in the Bilezikian Investigator-initiated trial (referred to as IIT).

Table 1 Efficacy and Safety Studies in Hypoparathyroidism

Study	Objectives	Design/Control	Dose[a]	# Subjects	Duration
NPS-Sponsored Efficacy and Safety Studies in Hypoparathyroidism					
CL1-11-040 (REPLACE)	Efficacy and safety	Randomized, double-blind, placebo-controlled	50, 75, and 100 µg (flexible doses) or placebo	rhPTH(1-84), 90; placebo, 44	24 weeks
PAR-C10-007 (RELAY)	Efficacy and tolerability	Randomized, dose-blinded	25 or 50 µg (fixed doses)	25 µg, 23; 50 µg, 24	8 weeks
PAR-C10-008 (RACE)	Safety and tolerability	Open-label	25, 50, 75, and 100 µg (flexible doses)	53	52 weeks + extension ONGOING
PAR-C10-009 (REPEAT)	Safety and tolerability	Open-label	50, 75, and 100 µg (flexible doses)	24	24 weeks
Investigator-initiated Trial (IIT) in Hypoparathyroidism					
Bilezikian IIT	Safety and efficacy	Open-label study, prospective	25, 50, 75, and 100 µg (flexible doses)	79	6 month pilot, 2-year study with multiple 1-year extensions

[a] All doses of rhPTH(1-84) in the NPS-sponsored trials were daily SC injections in the thighs. Dosing in the Bilezikian IIT was either daily or less than daily.

In addition, the Applicant submits the following:

- placebo-controlled IIT in hypoparathyroidism that was published in 2 peer-reviewed publications (referred to as “Mosekilde IIT”); 62 subjects were treated (32 treated with rhPTH(1-84) and 30 treated with placebo)
- NPS-sponsored Pharmacokinetic/Pharmacodynamic (PK/PD) Study in Hypoparathyroidism[6] (Study C09-002)

The clinical development program also included a total of 12 Clinical Pharmacology Studies: 6 Comparative Bioavailability and Bioequivalence Studies, 2 Healthy Subject PK and Initial Tolerability Studies, 2 Patient PK and Initial Tolerability Studies in subjects with hypoparathyroidism, and 2 intrinsic-factor PK studies in subjects with hepatic and renal impairment.

6 The Applicant obtained right of reference to data in a PK/PD substudy, referred to in the submission as “Mosekilde IIT PK/PD Substudy”.

Clinical data from osteoporosis indication were previously reviewed under NDA 21,847 (Preos®) which received an approvable letter on March 9, 2006, due to concerns with hypercalcemia and issues related to the reliability of the device. This was discussed above. A detailed review from these older data was not done. However, this Review makes mention of the data when specifically relevant to the hypoparathyroidism indication.

5.2 Review Strategy

The "pivotal trial" CL1-11-040 (referred to as REPLACE) was the basis for the analysis of safety and efficacy for this application. This trial was the largest and the only double-blinded. Data from the long-term trial 008 is also discussed. Also, since REPLACE only used doses of 50, 75, and 100 µg, and the Applicant believed that a 25 µg dose may be appropriate for some patients, the trial PAR-C10-007 (also referred to as RELAY), which compared doses of 25 µg and 50 µg, was useful in assessing this lower dose and is discussed particularly under Efficacy.

The other open-label (Hungary only) trial 009 is reviewed in the Appendix.

Because of the issues at his clinical site and the exclusion of data from his site, Dr. Bilezikian's data is not discussed.

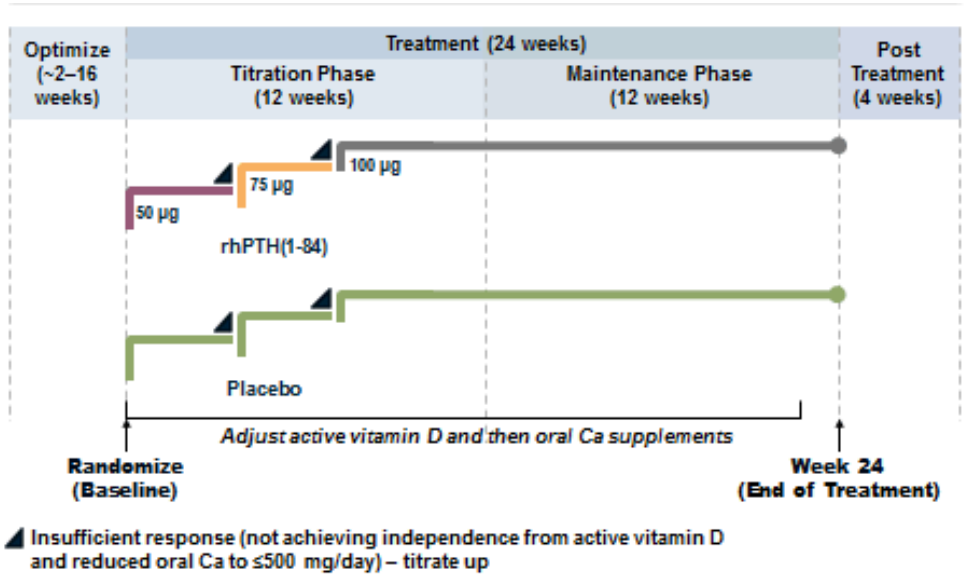
5.3 Discussion of Individual Studies/Clinical Trials

One "pivotal" trial was planned for this program. Because of this and other major differences in trial design, data from this development program are not pooled. Although emphasis is placed on the REPLACE trial, all clinical trials are introduced in this section with results following in Section 6.

CL1-11-040 (REPLACE, referred to as Trial 040 or "pivotal trial")
This was a randomized, double-blind, placebo-controlled Phase 3 study. It consisted of a screening and stabilization period, collectively referred to as the optimization period, of 2 to16 weeks, to ensure a common baseline for all subjects. This period was followed by a 24-week treatment period during which patients were randomized 2:1 to either once daily (qd) subcutaneous (SQ) NPSP558 or placebo.

The initial NPSP558 dosage was 50 µg daily and the dosage cold be up-titrated, first to 75 µg daily and then to 100 µg daily. Upon discontinuation of study drug, subjects entered a 4-week post-treatment follow-up period. All subjects who received at least one dose of drug were followed during this period as patients returned to baseline oral supplementation. The overall study scheme is depicted here:

Figure 1 Scheme for Trial 040



From Sponsor's Clinical Study Report

During the optimization period, both oral calcium and vitamin D doses were adjusted towards a goal of albumin-corrected total serum calcium within the target range of 8.0 to 9.0 mg/dL. Subjects were optimized on calcium citrate (or carbonate in some cases[7]) and either calcitriol or alfacalcidol. Subjects who were taking other forms of calcium prior to the study were switched to these sponsor-provided supplements. Also, Investigators aimed to achieve normal serum 25-hydroxyvitamin (OH) D levels. Those with below normal levels were supplemented with Vitamin D_3 (2,000 IU/day) until normal. Those with normal levels received Vitamin D_3 (400 IU/day), and those with above-normal levels received no supplementation during this period. Once 25(OH) vitamin D levels were normal levels (30 ng/mL considered lower limit of normal), subjects received 400 IU of native vitamin D daily for the entire treatment period. Levels were monitored during treatment.

Also, subjects could not be randomized with abnormal magnesium levels. Therefore, supplementation was provided to achieve normal levels by the end of the optimization period.

7 Two subjects used calcium carbonate as calcium supplementation. The first subject switched from citrate to carbonate 15 days after randomization because of gastrointestinal intolerance. They continued on calcium carbonate for the remainder of the trial. The use of calcium carbonate was listed as a protocol deviation. The second subject was taking Gaviscon liquid which contains calcium carbonate along calcium citrate supplements during optimization and treatment period. The subject withdrew on Day 58 due to multiple adverse events. The use of Gaviscon was listed as a protocol deviation.

During optimization, subjects taking thiazide diuretics for hypertension were to be changed to and stabilized on an alternate antihypertensive agent that was neutral on calcium metabolism.

Finally, prior to randomization all subjects were to have BMD assessment by DXA. Subjects were to withhold calcium supplementation for the 24-hour period prior to the scan. If the subjects could not tolerate this, DXA was to be performed 2 hours after ingestion of the last calcium pill.

Subjects were ready for randomization when:

a) Their daily dose of calcium citrate was 1,000 mg or greater and the daily dose of calcitriol was 0.25 µg greater, or the daily alfacalcidol dose was 0.50 µg or greater (relative potency of calcitriol thought to be approximately double compared to alfacalcidol);
b) 2 successive study visits separated by a 2-week interval were characterized by:
    a. No more than a 25% change in the daily doses of both calcium, citrate and active vitamin D metabolite/analog and
    b. The second of 2 serial albumin-corrected total serum calcium concentrations 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 ULN.

Following screening, a subject had up to 8 biweekly visits to demonstrate the above-outlined criteria.

Following randomization, subjects underwent staged reductions in calcium and active vitamin D metabolite/analog supplementation (according to an Applicant-recommended titration algorithm that started with vitamin D reductions) while maintaining or normalizing their pre-dose, albumin-corrected total serum calcium concentrations. Study drug/placebo was introduced at Week 1/Day 1 with a concomitant 50% drop in vitamin D analog. Dose escalation of NPSP558 to 75 µg occurred at Week 2 (in both groups to maintain blind), if subjects had not achieved independence from active vitamin D metabolite/analogs and reduced oral calcium supplementation to 500 mg/day or less on the initial 50 µg dose of NPSP558. Further up-titration was conducted at Week 4 (Visit 9), if subjects had not achieved independence from active vitamin D metabolite/analogs and reduced oral calcium supplementation to 500 mg/day or less on the 75 µg dose. This was the final intra-subjects dose escalation (to 100 µg). One additional week was allowed at each up-titration interval if a patient required time to clinically adapt to treatment changes, and 2 additional window days were allowed for each visit thereby allowing for a maximum titration timeline of close to 8 weeks.

Up-titration of study drug occurred in conjunction with measurements of serum calcium and urine calcium. Occurrences of hypercalcemia, hypercalciuria, and hypocalcemia were managed by incremental alterations in vitamin D metabolite/analog dose and/or oral calcium supplementation, followed by retesting of serum and urine biochemistry. Hypercalcemia was also addressed by down-titration of study drug if no further supplements were left to down-titrate. This could be done at any time during the trial.

In the post-titration phase, if the serum calcium level decreased to below the subject's baseline value, or increased above 9.0 mg/dL, then the supplemental calcium and vitamin D was to be checked and the drug administration technique revised. Oral calcium was then to be increased or decreased incrementally until an albumin-corrected serum calcium level was either maintained compared to baseline or fell within the targeted range of 8.0-9.0 mg/dL.

Down-titration could occur under certain circumstances. If the pre-dose serum calcium remained above 9.0 mg/dL for 2 or more safety assessments on normal dietary intake and study drug alone, the Investigator could return the subject to the previous lower dose level and adjust supplementary oral calcium and/or active vitamin D metabolite/analog requirements to obtain a pre-dose serum calcium of 8.0-9.0 mg/dL. A subject could be discontinued if the level remained above the ULN for 2 or more assessments at the lowest drug level, following withdrawal of all supplementary calcium and vitamin D.

If down-titration was not needed, subjects continued on their final dose through Week 24. There was a follow-up period from Week 24 to Week 28.

For analysis, the Applicant considered the titration period to include the 5-weeek period of up-titration through the end of Week 12, since most study drug and calcium/vitamin D titration was done during this period. Weeks 12 through 24 were considered the stable period.

An important time point in the primary efficacy endpoint definition was Week 24, which coincided with the scheduled end of treatment (EOT). If a subject completed Week 24 efficacy assessments, the EOT would use the Week 24 data. If a subject dropped out early or did not have Week 24 assessments, then the last efficacy assessment would be carried forward to EOT. The EOT data was used for all efficacy analyses using the ITT population.

Based on certain observations made from an internal audit, NPS made the decision to unlock the CL1-11-040 database. Specifically, it was noted that some non-serious adverse events were not recorded from the source documents into the database.

The database was unlocked on March 16, 2012 for the following five sites, after 11 sites were re-monitored: 1009 (Meek), 1003 (Clarke), 1004 (Peacock), 1010 (Vokes), and 1080 (Warren). The database was re-locked on April 5, 2012. Initially, additional adverse events were discovered upon an internal audit of the Vokes site. Based on this finding, 10 additional sites were audited to verify source documents versus the database. From the total 11 sites, 5 sties had data query findings. Of the 5 sites, 28 additional AEs from 4 sites were not entered into the original database. Three of the sites were updated on medical history and one of the sites was updated on concomitant medications. At all 11 sites, there were no findings regarding the efficacy data.

The Applicant chartered an independent Data Safety Monitoring Board (DSMB) comprised of 3 physicians and an independent statistician. The Applicant states that they were individuals free of "significant" conflicts of interest and none of the members were NPS employees. They had access to unblinded data. Some of the issues the DSMB were involved were as follows:

- Episodes of hypocalcemia: At a July 2010 meeting, in a review of the post-treatment study period, following withdrawal of study drug and return to oral calcium and vitamin D at Visit 16, it was noted that 3 of 38 NPSP558-treated subjects required intravenous calcium gluconate treatment in order to correct symptomatic hypocalcemia. Although no change was made to the protocol, 2 letters were sent to all sites reminding them of the need to closely monitor patients during this period. According to the Applicant, the incidence of such occurrences subsequently dropped from 31% to 11%.
- Pen complaints: At the July 2010 meeting, the DSMB discussed complaints of the injection pen by 26 subjects. Curiously, there were no AEs associated with those pen complaints. The Board made recommendations, including establishing a complaint reporting system, tracking product complaints, a retraining program, and implementing additional training materials. The Applicant states that these led to a reduction in the pen complaints and no further action was taken by the DSMB.

The daily doses of calcium and vitamin D were computed based on both investigator-prescribed data and subject-diary data. Use of the investigator-prescribed data was considered the primary method for all efficacy analysis endpoints.

The daily dose of calcium and vitamin D based on investigator prescription was determined using the latest prescribed dose prior to the assessment date of albumin-corrected total serum calcium, for each analysis visit.

The average daily dose of calcium and vitamin D based on subject diaries was calculated as the average daily dose over a 14-day interval. If the number of days from the previous albumin-corrected total serum calcium date to the current assessment date was less than 14, the actual number of days during the 2 analysis visits was used to calculate the average daily dose. If the number of days was less than 9, the average daily dose was not calculated and was classified as missing.

Missing daily dose from subject diaries was not imputed and a minimum of non-missing data from intervals was required, otherwise the interval was classified as missing. Additional explanation of handling of missing data is included in the statistical review.

The analyses for the primary endpoint were performed using both datasets. For all efficacy analysis endpoints the investigator data were considered the primary method and subject diary data were considered supportive. There was no discrepancy in the results of these analyses using both data sets.

Number of Subjects: It was planned that 110 male and females with hypothyroidism would be randomized (2:1) to NPSP558 or placebo at approximately 30 international sites with 84 expected to complete the trial. A total of 196 subjects were screened, and 134 eligible subjects were randomized to NPSP558 (90 subjects) and placebo (44 subjects). All 134 subjects were included in the Intent-to-Treat (ITT) and safety analyses. From this, 115 subjects (78, NPSP558 and 37, placebo) were included in the Per Protocol analysis.

Key Inclusion Criteria were:

1) Male and female adults ages 18 to 85 years
2) History of hypoparathyroidism for ≥18 months, including historical biochemical evidence of hypocalcemia and concomitant serum intact PTH concentrations below the lower limit of normal of 2 test dates at least 21 days apart within 12 months prior to randomization
3) Requirement for vitamin D metabolite/analog therapy with calcitriol ≥0.25 µg per day or alfacalcidol ≥0.50 µg per day prior to randomization.
4) Requirement for supplemental oral calcium treatment ≥1000 mg per day over and above normal dietary calcium intake
5) Normal thyroid function tests. For subjects on thyroid replacement therapy, the dose must have been stable for at least 3 months prior to screening.
6) Normal serum magnesium levels at the end of optimization period
7) Serum 25-hydroxyvitamin D level ≤1.5-fold the laboratory ULN at the end of the optimization period. Subjects with low levels at screening underwent supplementation with vitamin D during the optimization period. Subjects with levels above the ULN had vitamin D supplements withdrawn during

the optimization period. Normal levels were confirmed by the end of the optimization period.

8) Creatinine clearance >30 mL/min on 2 separate measurements OR creatinine clearance >60 mL/min and serum creatinine <1.5 mg/dL by the end of the optimization period
9) Women were required to either be post-menopausal or have a negative pregnancy test and use 2 medically acceptable methods of contraception with a pregnancy test scheduled at each visit.

Key Exclusion Criteria were:

1) Known history of hypoparathyroidism resulting from an activating mutation in the *CaSR* gene or impaired responsiveness to PTH (pseudohypoparathyroidism)
2) Any disease that may affect calcium metabolism or calcium-phosphate homeostasis, including active hyperthyroidism, Paget's disease, Type 1 and poorly controlled Type 2 diabetes mellitus (HbA1c>8%), severe and chronic cardiac, liver or renal disease, Cushing's syndrome, neuromuscular disease, myeloma, pancreatitis, malnutrition, rickets, recent prolonged immobility, active malignancy, primary or secondary hyperparathyroidism, a history of parathyroid carcinoma, hypopituitarism, acromegaly, or multiple endocrine neoplasia types I and II
3) Subjects with a history of thyroid cancer must have been documented to disease-free for a period of at least 5 years
4) Dependent on regular parenteral calcium infusions to maintain calcium homeostasis
5) Subjects who have undergone gastric resection or have active peptic ulcer disease requiring medical therapy
6) Use of prohibited medication such as loop and thiazide diuretics, raloxifene hydrochloride, lithium, estrogens and progestins for replacement therapy, methotrexate, or systemic corticosteroids within respective prohibited period.
7) Use of other drugs known to influence calcium and bone metabolism, such as calcitonin, fluoride tablets, or cinacalcet hydrochloride within the prohibited period
8) Use of oral bisphosphonates within the previous 6 months or IV bisphosphonate preparations within the previous 12 months prior to screening
9) Previous treatment with PTH-like drugs, including PTH(1-84), PTH(1-34) or other N-terminal fragments or analogs of PTH or PTH-related protein within 6 months prior to screening
10) Seizure disorder/epilepsy with a history of seizure within the previous 6 months prior to screening
11) Presence of open epiphyses
12) Radiotherapy within 5 years

13) Serum 25-hydroxyvitamin D levels greater than 1.5-fold the ULN prior to randomization
14) Pregnant or lactating women
15) Clinical history of renal stones within the past 12 months
16) History of gout
17) Diseases that adversely affect gastrointestinal absorption, including short bowel syndrome, bowel resection, tropical sprue, celiac disease, ulcerative colitis, and Crohn's disease
18) Chronic/severe cardiac disease
19) History of cerebrovascular accident

Schedule of Evaluations: The schedule is included in the Appendix.

Efficacy Measurements:
Primary efficacy endpoint was the percentage of responders at Week 24, based on investigator-prescribed data relating to a composite endpoint of 3 components. A subject was considered a responder if he/she achieved:

- At least a 50% reduction from the baseline oral calcium supplementation dose and
- At least a 50% reduction from the baseline active vitamin D metabolite/analog dose and
- An albumin-corrected total serum calcium concentration that as maintained or normalized compared to the baseline value (≥7.5 mg/dL) and did not exceed the upper limit of normal

The albumin-corrected total serum calcium goal was defined in Protocol Amendment 7. Prior to this, this parameter was defined as a clinically stable serum calcium level established at baseline and normalized by Week 24. The Applicant states that there were nine subjects deemed responders prior to the specification of this criterion.

Secondary efficacy endpoints included a comparison of NPSP558 vs placebo group on the following assessments:

- percent reductions in calcium supplementation dose at Week 24
- proportion of subjects who achieved independence from supplemental active vitamin D metabolite/analog usage and a calcium supplementation dose of ≤500 mg/day by Week 24
- the frequency of clinical symptoms of hypocalcemia (including paresthesia, muscle cramping, tetany, seizures) during Week 16 to Week 24

Exploratory endpoints which will be discussed in the Review are:

- change from baseline in 24-hour urine calcium excretion at Week 24

- proportion of patients that maintain a calcium –phosphate product in the normal range of 35-55 mg^2/dL^2 at Week 24 in the NPSP558 treatment group vs placebo
- change in bone mineral density (BMD) as measured by DXA at Week 24
- change in bone turnover markers at Week 24
- change in QoL score from baseline to Week 24

The Original Protocol included the following as secondary endpoints: 'maintenance of calcium-phosphorus product in the normal range' and 'proportion of patients who achieve a 24 hour urinary calcium level below 300 mg at Week 24 in the NPSP558 treatment group vs. placebo'. Both endpoints were changed to exploratory endpoints before unblinding.

Safety Measurements: These included monitoring of AEs, clinical evaluations (vital signs, physical exams, and EKGs), and laboratory tests (hematology, chemistry, creatinine clearance, urinary biochemistry, immunology, urinalysis, BMD).

Statistical Methods: Please refer to the Statistics Review for details regarding the SAP. Briefly, it was estimated that 110 subjects would be randomized (2:1) to NPSP558 or placebo, and 84 subjects (56 active and 28 placebo) were estimated to complete the trial. With expected responder rates of 40% and 10% for the active and placebo groups, respectively, 80% power can be expected based on 2-tailed test and alpha of 0.05.

Protocol Amendments ("Changes in the Conduct of the Study")
There were multiple protocol amendments in this trial, some of which require further discussion. Specifically and most prominently, in the original protocol the third component of the primary endpoint read as *"patients should have a clinically stable serum calcium level that is established to the satisfaction of the Investigator at Baseline and is maintained or normalized by Week 24 of the study. At the end of the treatment phase it is aimed that patients should have a serum calcium level that is clinically stable in the opinion of the Investigator and just below or within the lower half of the normal range."* This is an appropriate component given that the serum calcium of patients with hypoparathyroidism should be maintained at the lower end of the normal range (approximately 8.0 to 8.5 mg/dL).[8]

In Amendment 7, approximately 16 months after the original Protocol, the third component of the primary endpoint was changed to: "*an albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value (≥7.5 mg/dL) and does not exceed the upper limit of the laboratory*

8 Shoback D "Hypoparathyroidism", New England Journal of Medicine 2008.

normal range." In the application, the Sponsor does not consider this to be a "substantive change".

The Original Protocol was issued on August 27, 2008. There were 7 Amendments submitted. Only those that included substantive changes are mentioned here:

- Amendment 2.0 (12/5/2008): exclusion criteria were expanded to include use of oral bisphosphonates
- Amendment 3.0 (12/23/08): women of childbearing potential (WOCBP) were allowed to enroll in the trial
- Amendment 4.0 (2/18/09): text that allowed WOCBP to enroll in the trial was removed
- Amendment 6.0 (9/15/09): changes that allowed WOCBP to be enrolled in the trial providing that these women have a negative pregnancy test at randomization and are willing to use two medically acceptable methods of contraception for the duration of the trial with pregnancy testing at every visit.

The albumin-corrected total serum calcium goal was defined in Protocol Amendment 7. Prior to this, this parameter was defined as a clinically stable serum calcium level established at baseline and normalized by Week 24. (There were nine subjects deemed responders prior to the specification of this criterion).

The changes made after unblinding include simplification of tables, identifying potential safety signals in regard to hypocalcemia, and to provide clarification of parameters included in exploratory analyses:

- Study-prescribed supplements (calcium and calcitriol) were removed from the concomitant medication tables.
- After database lock, the list of AEs generated by MedDRA PTs and SOCs was reviewed by clinical experts (was done blinded). The experts then identified a list of PTs that were classified into a group of medical synonyms that best defined symptoms of hypocalcemia. The list was further refined by the Applicant and was used as the bases for the secondary efficacy parameter analyzing the frequency of clinical symptoms of hypocalcemia during Weeks 16 to 24.
- The normal range for calcium-phosphate product was defined in the protocol as 35 to 55 mg^2/ dl^2 and therefore any value below 35 mg^2/ dl^2 were to be included as abnormal in the calculation of the exploratory endpoint "proportion of subjects who maintained a calcium-phosphate product in the normal range". Since only products >55 mg^2/ dl^2 are considered to be clinically significant, the normal range was re-defined as ≤55 mg^2/ dl^2 for this analysis.

- An additional exploratory endpoint was added in order to look at the number and percentage of subjects who met the 3 criteria of the primary endpoint at Study Week 16 and maintained this response through Week 24.

Long-term, open-label trial (Trial 008, or RACE)

This is an ongoing, long-term (52 weeks plus extension period), open-label trial in adults with hypoparathyroidism. There is no control group. To be eligible, subjects had to have previously completed Study 040 (REPLACE) and /or Study 007 (RELAY). The purpose of the trial was to assess the safety and tolerability of varying doses of NPSP558 during long-term treatment, while reducing requirements for supplemental calcitriol and oral calcium supplementation to as low as safely possible while maintaining total serum calcium levels and controlling hypercalciuria. The starting doses were 25 or 50 µg, depending on an algorithm (further discussed below). The Applicant states that this trial simulated a more real-world setting as up-titration was allowed at any time.

During the first 12 months, visits were to take place at Weeks 1, 4, 8, and then every 8 weeks up to Week 48 (Visit 8). The Week 52 visit was to be scheduled 4 weeks later.

At the end of Week 52, subjects were invited to enter a second year extension period. During this time, subjects were to return to the clinic every 2 months.

The dose of NPSP558 could be increased in increments of 25 µg to a maximum of 100 µg at any time during the trial, with the goal of achieving or maintaining total serum calcium levels in the range of 8-9 mg/dL. The dose could be down-titrated at any time for efficacy or safety reasons.

Adjustment of calcium and calcitriol was based on serum calcium levels, with the goal to be a reduction or removal of calcitriol treatment to the maximum clinically possible and to decrease calcium supplementation to ≤500 mg daily. Blood draw were performed 3-5 days after any dose adjustment of NSPP558 or after any significant change in supplements.

If any pre-dose calcium level was >11.9 mg/dL, study drug was to be stopped. Once serum calcium was in the normal range again, study drug was reintroduced: at the previous dose level if reductions in supplements took place or at the next lowest dose level if calcium had previously been reduced to ≤500 mg daily and calcitriol was eliminated.

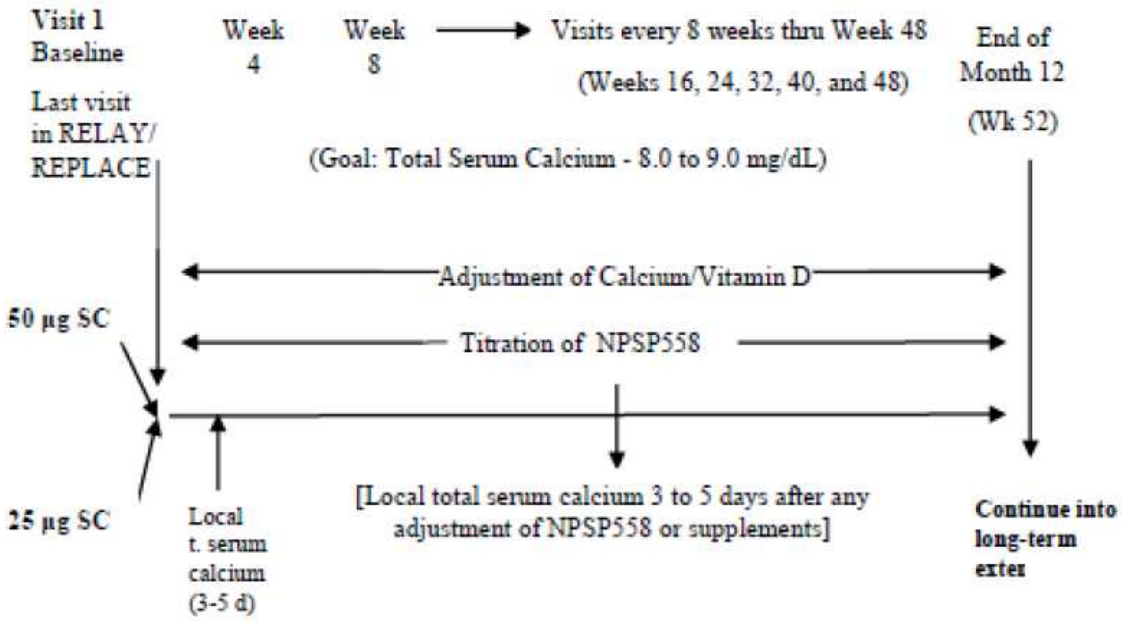
If the pre-dose serum calcium level remained above 10 mg/dL for two or more assessments, the NPSP558 dose was to be reduced at the next lowest dose

level. If it remained above the ULN for 2 or more assessments at the lowest dose level, study drug was to be stopped following withdrawal of all supplements.

At any time following Week 16 (Visit 4), subjects who were on a stable dose of NPSP558 and a 24-hour urine calcium >300 mg (males) or >250 mg (females) were allowed to be treated for hypercalciuria with calcium-sparing diuretics, if not already introduced. The dose of the diuretic could subsequently be adjusted. Monitoring of urine calcium was done at Weeks 16, 32, and 52 and every 4 months thereafter.

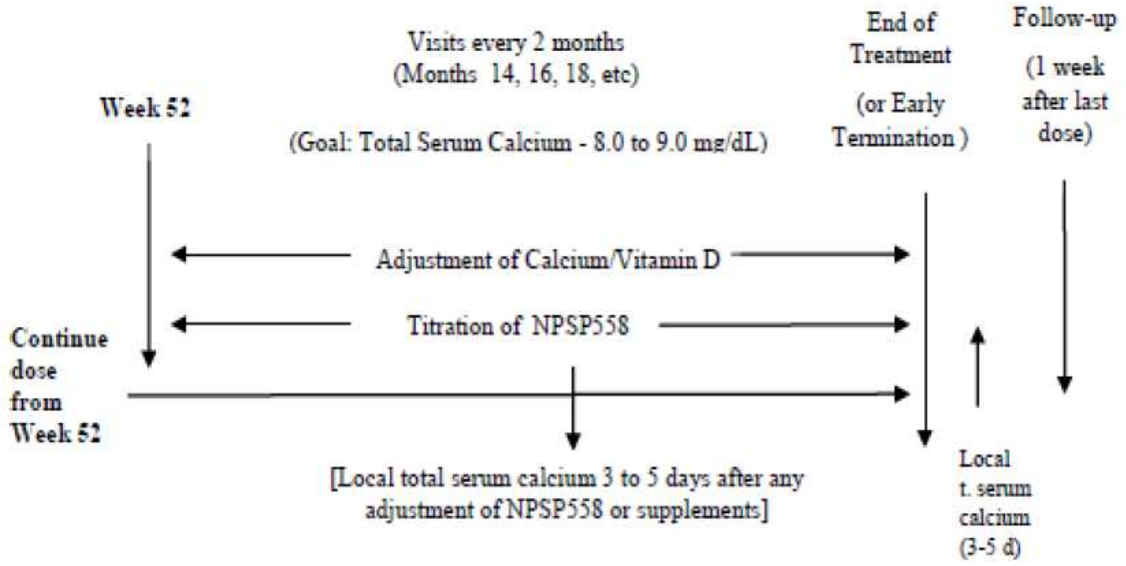
The figure below depicts the overall trial design:

Figure 2 Study design for the initial 12 months in Trial 008



From Applicant's CSR, Figure 9-1

Figure 3 Study design for the long-term extension in Trial 008



From Applicant's CSR, Figure 9-1

Oral calcitriol was provided by the Applicant for the first 52 weeks of the trial but not for the long-term extension. Oral calcium was provided during the entire trial.

Although the trial was initiated with the Ypsomed pen, this was switched to the Haselmeier pen. Therefore, this trial provides the best data to compare the safety of the 2 pen injectors.

The primary objective of the trial is to demonstrate long-term safety and tolerability of NPSP558 as hormone replacement therapy for the treatment of adults with hypoparathyroidism.

The secondary objectives differed somewhat than the previous trials. They are:

- To evaluate the impact of different preparations of calcium and calcitriol on the response to NPSP558 therapy
- To demonstrate that dosing with NPSP558 across a dose range of 25 to 100 µg SC can be implemented in a safe and effective manner and can be maintained throughout long-term treatment.
- To evaluate the impact of calcium-sparing diuretics on serum and urinary calcium

There were no exploratory objectives.

Given that this trial was open-label without a comparator, only the primary efficacy results will be discussed below, unless there are particularly notable findings.

As per the primary efficacy endpoint, a subject was considered a responder if they met the following 3 criteria at Week 52 (Visit 9) and at End of Treatment:

- A ≥50% reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of ≤500 mg
  AND
- A ≥50% reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of ≤0.25 µg
  AND
- An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value (≥7.5 mg/dL) and does not exceed the ULN of the central laboratory

There were multiple secondary efficacy endpoints including:

- Mean change from baseline in 24-hour urine calcium excretion
- Mean percentage change from baseline in albumin-corrected total serum calcium
- Change from baseline in bone turnover markers
- Change from Baseline in Bone Mineral Density
- Proportion of subjects that maintained a calcium-phosphate product in the normal range of 35 to 55 mg^2/dL^2

The baseline parameters for the efficacy variables for RACE were the end of study parameters from RELAY or REPLACE.

Key Inclusion Criteria were:

1) Previously completed RELAY and/or completed REPLACE
2) Women must be postmenopausal, surgically sterilized, or of childbearing potential with a negative pregnancy test at screening and willing to use two acceptable methods of contraception.
3) Serum creatinine <1.5 mg/dL at enrollment
4) Total serum calcium ≤ULN prior to enrollment
5) Serum 25(OH) vitamin D≤1.5 times the ULN within approximately 16 weeks prior to enrollment

Key exclusion criteria were:

1) Any disease or condition that had a high probability of precluding the subjects from completing the trial
2) Pregnant or lactating women

3) Prohibited concomitant medications: raloxifene, bisphosphonates (oral or IV), calcitonin, fluoride tablets

Study Dose and Design:
In this trial, the starting dose of NPSP558 was 25 µg or 50 µg daily. Subjects with total serum calcium of ≤9.5 mg/dL had a starting dose of 50 µg. Subjects with a total serum calcium of >9.5 mg/dL had a starting dose as follows:

- Subjects who were taking supplements (≥ 500 mg calcium and/or any calcitriol) had the supplements reduced or stopped and started at a dose of 50 µg SC QD.
- Subjects who were taking minimal or no supplemental calcium (< 500 mg) and no calcitriol had a starting dose of 25 µg SC QD.

Safety evaluations were similar to those in the pivotal trial.

Trial 007 (RELAY)
This was a randomized, dose-blinded trial to investigate the safety and efficacy of NPSP558 at fixed doses of 25 µg and 50 µg for the treatment of adults with hypoparathyroidism.

Because the lowest dose in the pivotal trial was 50 µg, the Applicant conducted this 8-week trial using fixed doses of either 25 or 50 µg to explore additional dosing options. The Applicant also sought to gather additional safety data.

This was a randomized, dose-blinded study of NPSP558 for the treatment of adult male and female subjects with hypoparathyroidism. The study included subjects from previous NPSP558 studies. All references to “baseline” in this study report refer to the baseline of this study (PAR-C10-007).

Study Design
Subjects were randomized to receive either NPSP558 25 µg SC once daily (QD) or 50 µg SC QD in a dose-blinded and fixed-dose fashion. Subjects recruited into this trial could have previously completed either the pivotal trial, or Study C09-002, which included 2 single doses of NPSP558 followed by a 4-week washout period. There was not maximum time from completion of either previous trial to entry into this trial. Also, the following categories of subjects were permitted to enroll in this trial:

- Subjects who were enrolled and in the optimization phase of the pivotal trial when randomization was closed
- Subjects new to the NPSP558 program and fulfilled the inclusion and exclusion criteria

Subject randomization was stratified by the subject’s current calcium source (carbonate or citrate).

Subjects who did not meet the calcium and 25 (OH) vitamin D criteria (normal ranges) could be reconsidered for study entry following attainment of appropriate levels, within the following 4 weeks.

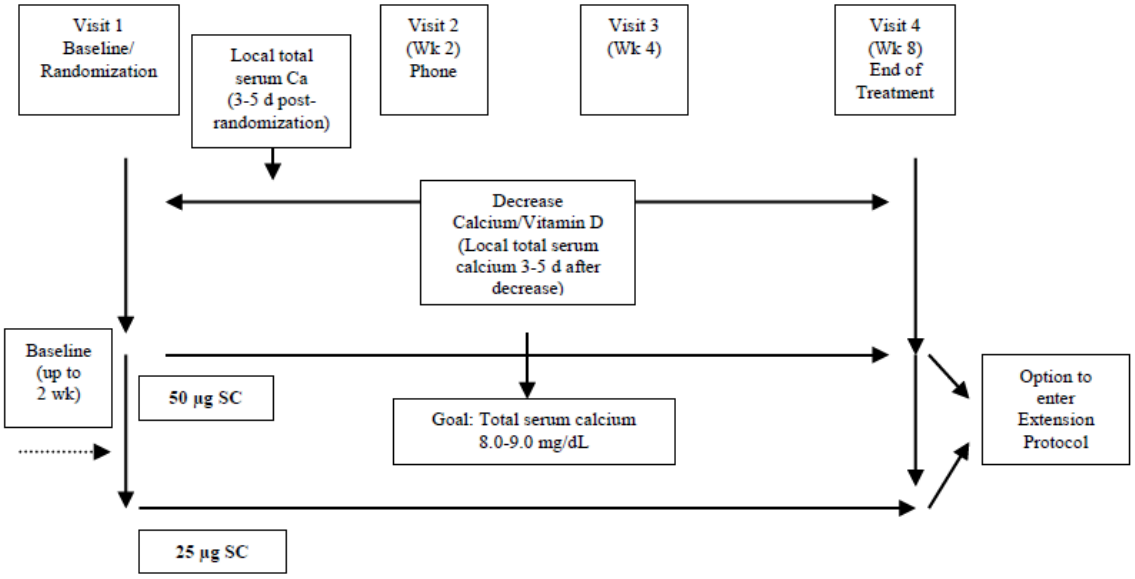
There were 4 scheduled study visits: baseline, Weeks 2, 4, and 8. Total serum calcium levels were determined by a local laboratory for all subjects 3 to 5 days following the baseline visit. The Week 2 visit consisted of a local laboratory assessment and a telephone contact, in order to assess safety parameters. Subjects also had interim blood draws for determination of total serum calcium levels following any titration of calcium and/or calcitriol.

The goal of supplement titration was to reduce the need for calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible, while maintaining total serum calcium ideally between 8.0 and 9.0 mg/dL. Down-titration of calcitriol and calcium was undertaken by the investigator based on total serum calcium concentrations using an algorithm described in the Titration Guideline in which it was recommended that calcitriol be reduced first by up to 50%, followed by a reduction of up to 50% in oral calcium supplementation. The order and magnitude of subsequent reductions in either calcitriol or oral calcium supplementation was left to the investigator's discretion, based on individual subject response. Titration was performed while assessing symptoms and following calcium levels, which were measured 3 to 5 days after each adjustment of supplements.

Study drug was to be stopped of the pre-dose calcium level remained above the ULN for 2 more consecutive safety assessments (no more than 5 days apart), following withdrawal of all supplements. If any calcium level was above 11.9 mg/dL, treatment with study drug was to be stopped immediately. When calcium levels returned to normal, the decision to restart NPSP558 was done in consultation with the medical monitor.

The study design is shown here:

Figure 4 Study Design for Trial 007



From Applicant's CSR, Figure 9-1

At the end of the 8-week treatment period, subjects had the option of enrolling in PAR-C10-008 RACE), a 12-month extension trial.

The primary objective of this trial was to evaluate the efficacy and tolerability of subcutaneous (SC) NPSP558 [rhPTH(1-84)] doses of 25 µg and 50 µg as replacement therapy for the treatment of adult patients with hypoparathyroidism.

The secondary objectives were:
• To evaluate the effect of NPSP558 at 25 µg and 50 µg SC on oral calcium and calcitriol supplementation and
• To compare response rates and tolerability of dosing with NPSP558 25 µg and 50 µg SC.

The primary efficacy endpoint was the proportion of subjects in the NPSP558 25 µg and
NPSP558 50 µg dosage groups that by Week 8 (Visit 4) achieved each of the following:
• A reduction in oral calcium supplementation to ≤ 500 mg/day and
• A reduction in calcitriol dose to ≤ 0.25 µg/day and
• An albumin-corrected total serum calcium level between 7.5 mg/dL and the upper limit of normal (ULN) for the central laboratory

The components of this endpoint were somewhat different than those in the pivotal trial, which focused on reductions of 50% for calcium and vitamin D supplements.

There was also a secondary efficacy endpoint, which was achieved if the following 3 criteria were met:
• A ≥ 50% reduction from baseline (prior to randomization) in dose of oral calcium supplementation and
• A ≥ 50% reduction from baseline (prior to randomization) in dose of oral calcitriol supplementation and
• An albumin-corrected total serum calcium concentration that was normalized or maintained compared to the baseline value (≥ 7.5 mg/dL) and did not exceed the ULN for the central laboratory

Investigator data were primarily used for both primary and secondary endpoints.

There were multiple exploratory endpoints, which are not discussed in this Review.

Safety endpoints included: adverse events, incidence of clinical episodes of hypocalcemia and hypercalcemia, laboratory test results (including 24-hour urinary calcium and PTH antibody), and EKG.

Inclusion and Exclusion Criteria:
For subjects previously enrolled in an NPSP558 trial, the following were key inclusion criteria:

- Total serum calcium ≤ ULN based on local laboratory results prior to randomization
- Serum 25(OH) vitamin D ≤ 1.5 times the ULN within approximately 16 weeks prior to Randomization

Subjects new to the NPSP558 program had to meet the following criteria:

- Males or females 18 to 85 years of age
- History of hypoparathyroidism for ≥ 18 months post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia and concomitant serum intact PTH concentrations below the lower limit of the laboratory normal range on 2 test dates at least 21 days apart within 12 months prior to randomization
- Requirement for calcitriol ≥ 0.25 µg per day prior to randomization
- Requirement for supplemental oral calcium treatment ≥ 1000 mg per day over and above normal dietary calcium intake prior to randomization
- Serum thyroid function tests WNL at baseline for all subjects not receiving thyroid hormone replacement therapy. For subjects receiving thyroid hormone replacement therapy, the dose must have been stable for at

least 3 months prior to baseline (i.e., changes < 25% of the total weekly dose) and the levothyroxine value could be outside the laboratory limits of normal.

Exclusion criteria were generally similar to those in the pivotal trial.

6 Review of Efficacy

Efficacy Summary

See Dr. Jennifer Clark's review for statistical details.

This clinical program included one pivotal trial, which was placebo-controlled and the only trial with a standard-of-care comparator. The other trials included a randomized, dose-blinded short-term trial that compared the 25 µg dose to the 50 µg dose (Trial 007), one long-term open-label trial (Trial 008), and an additional open-label trial of Hungarian subjects.

The primary endpoint in the pivotal trial was the percentage of responders at Week 24, based on investigator-prescribed data relating to a composite endpoint of 3 components. A subject was considered a responder if he/she achieved:

- At least a 50% reduction from the baseline oral calcium supplementation dose and
- At least a 50% reduction from the baseline active vitamin D metabolite/analog dose and
- An albumin-corrected total serum calcium concentration that as maintained or normalized compared to the baseline value (≥7.5 mg/dL) and did not exceed the upper limit of normal

The primary endpoints in the other trials were similar, but not equivalent, to this and are detailed below.

The secondary endpoints for the pivotal trial included:

- percent reductions in calcium supplementation dose at Week 24
- proportion of subjects who achieved independence from supplemental active vitamin D metabolite/analog usage and a calcium supplementation dose of ≤500 mg/day by Week 24
- the frequency of clinical symptoms of hypocalcemia (including paresthesia, muscle cramping, tetany, seizures) during Week 16 to Week 24

Exploratory endpoints in the pivotal trial were:

- change from baseline in 24-hour urine calcium excretion at Week 24

- proportion of patients that maintain a calcium –phosphate product in the normal range of 35-55 mg^2/dL^2 at Week 24 in the NPSP558 treatment group vs placebo
- change in bone mineral density (BMD) as measured by DXA at Week 24
- change in bone turnover markers at Week 24
- change in QoL score from baseline to Week 24

Exploratory endpoints for the other trial are not discussed.

In the long-term Trial 008, secondary endpoints included:

- Mean change from baseline in 24-hour urine calcium excretion
- Mean percentage change from baseline in albumin-corrected total serum calcium
- Change from baseline in bone turnover markers
- Change from Baseline in Bone Mineral Density
- Proportion of subjects that maintained a calcium-phosphate product in the normal range of 35 to 55 mg^2/dL^2

In the pivotal trial, the primary endpoint was met: 54.8% of subjects were considered responders.

Also, in the pivotal trial, the following secondary and exploratory endpoint observations were made at Week 24:

- There was a mean percentage decrease of approximately 52% in daily calcium dose.
- A total of 43% of NPSP-558-treated subjects achieved independence from supplemental active vitamin D analog and a calcium supplementation dose ≤500 mg/day.
- Mean and median decrease in 24-hour urine calcium was not greater in the NPSP558 group compared to placebo: there was a 79 mg/24 hour decrease, compared to a 91 mg/24 hr decrease.
- Increases in all bone turnover markers were observed
- There were no clinically important changes in BMD

In Trial 008, at the end of treatment, approximately 52% of subjects met the pre-specified primary endpoint. The following secondary endpoint observations were made, which must be viewed without a comparator:

- At baseline (n=52), the mean (±SD) 24-hour urinary calcium excretion was 354.33 (±196.96) mg/24 hr. At Week 52 (n=48), the mean 24-hour urinary calcium excretion was 317.31 (±174) mg/24 hr.
- Mean calcium levels changed little from baseline to Week 52. Mean levels at both time points were within the target range (8 to 9 mg/dL), which was

slightly below the normal range of total serum calcium levels (8.6 to 10.2 mg/dL).
- Increases in Bone turnover markers were observed.

In Trial 007, response was low in this fixed dose trial. However, response was very low (21%) in the 25 µg group, suggesting that few can achieve efficacy on this lowest dose.

6.1 Indication

The Applicant proposed indication is “a replacement for endogenous parathyroid hormone (1-84) indicated for the long-term treatment of hypoparathyroidism”.

6.1.1 Methods

The results of the pivotal trial were the primary data used in the efficacy analysis. These were the only randomized, double-blind, placebo-controlled data. Supportive data come primarily from the ongoing, long-term trial 008 (RACE) as well as 007 (RELAY), the only randomized trial that studied the lower 25 µg dose. This Section focuses on Trial 040 but also discusses supportive data from the ongoing long-term Trial 008 as well as Trial 007, which studied the lower dose. Certain endpoints were considered secondary in one trial but exploratory in another and because of this they are presented in the respective sections under Primary and Secondary Endpoints below. Trial 009, the small, Hungarian, open-label trial is reviewed in the Appendix, but is not included in this discussion.

6.1.2 Demographics

Trial 040 (REPLACE)
General demographics and baseline characteristics as well as hypoparathyroidism-related characteristics are presented in the tables below.

Overall, demographics were similar between the two groups. The mean age for all subjects was 47.3 years and most subjects were in the 45 to 64 years of age category. The majority of subjects were female (79%) and white (96%).

Subjects in the NPSP558 group had hypoparathyroidism for a mean of 14.6 years at the time of enrollment, compared to 11.6 years in the placebo group. The majority of subjects overall (47.6 %) had hypoparathyroidism for over 10 years. Also, the vast majority of subjects (66.4%) was taking high vitamin D metabolite/analog doses at baseline but took 2000 mg of calcium or less daily (69.4%).

Table 2 Demographics and General Baseline Characteristics—ITT Population, Excluding Site 1002

Variable	Placebo N=40 n (%)	NPSP558 N=84 n (%)	Total N=124 n (%)
Age (years)			
Mean (SD)	48.9 (13.7)	46.6 (12.2)	47.3 (12.7)
Median	52	47.0	48.5
Min, Max	21, 73	19, 74	19, 74
Age Category			
<45 years	13 (32.5)	35 (41.7)	48 (38.7)
45 to 64 years	23 (57.5)	45 (53.6)	68 (54.8)
≥65 years	4 (10)	4 (4.8)	8 (6.5)
Gender[a]			
Female	33 (82.5)	65 (77.4)	98 (79)
Male	7 (17.5)	19 (22.6)	26 (21)
Race			
White	39 (97.5)	80 (95.2)	119 (96)
Black	0	1 (1.2)	1 (0.8)
Asian	1 (2.5)	1 (1.2)	2 (1.6)
Native Hawaiian/Pacific Islander	0	1 (1.2)	1 (0.8)
Other	0	1 (1.2)	1 (0.8)
Ethnicity			
Hispanic or Latino	0	2 (2.4)	3 (2.2)
Not Hispanic or Latino	40 (100)	82 (97.6)	122 (98.4)
Body mass index (kg/m^2)			
Mean (SD)	28.9 (5.3)	29.2 (6.4)	29.2 (6.1)
Median	29.6	29.1	29.2
Min, Max	18.2, 38.9	18.9, 48.4	18.2, 48.4
Geographic Region of Enrollment			
North America	21 (52.5)	43 (51.2)	64 (51.6)
Western Europe	12 (30)	25 (29.8)	37 (29.8)
Central and Eastern Europe	7 (17.5)	16 (19)	23 (18.5)

[a] Subject 1007-003 had gender transformation before study enrollment.
From Applicant Submission dated May 27, 2014, Table B-14.1.2.1

Table 3 Baseline Characteristics Related to Hypoparathyroidism

Variable	Placebo N=40 n (%)	NPSP558 N=84 n (%)	Total N=124 n (%)
Duration of hypoparathyroidism (years)			
Mean (SD)	11.6 (8.1)	14.6 (11.2)	13.6 (10.3)
Median	8.5	10.5	9
Min, Max	2, 38	2, 50	2, 50
Duration of hypoparathyroidism			
≤ 5 years	10 (25)	15 (17.9)	25 (20.2)
> 5-10 years	13 (32.5)	27 (32.1)	40 (32.3)

> 10 years	17 (42.5)	42 (50)	59 (47.6)
Prescribed active vitamin D metabolite/analog at baseline[a]			
Low dose	3 (7.5)	6 (6.7)	10 (7.5)
Medium dose	12 (30)	23 (25.6)	35 (26.1)
High dose	25 (62.5)	61 (67.8)	89 (66.4)
Prescribed calcium at baseline			
0-2000 mg/day	29 (72.5)	57 (67.9)	86 (69.4)
>2000 mg/day	11 (27.5)	27 (32.1)	38 (30.6)

[a] For calcitriol: low dose 0-0.25 µg/day, medium dose >0.25-0.5 µg/day, high dose >0.5 µg/day; for alfacalcidol: low dose 0-0.50 µg/day, medium dose >0.50-1.0 µg/day, high dose >1.0 µg/day
From Applicant Submission dated May 27, 2014, Table B-14.1.2.1

The table categorizes subjects by etiology of hypoparathyroidism, including whether the disease was child or adult-onset. In both groups, adult-onset hypoparathyroidism was overwhelmingly more common than childhood-onset (95% and 83% of placebo and NPSP558 subjects, respectively). Among adults, post-surgical was the most-common general etiology, with thyroidectomy being the most common surgery to have resulted in the deficiency. Idiopathic accounted 25% in both the NPSP558 group (for childhood- and adult-onset).

Table 4 Summary of Etiology of Hypoparathyroidism—All Subjects Randomized CL1-11-040, Excluding Site 1002

	Placebo N=40			NPSP558 N=84		
Etiology	Childhood n (%)	Adult n (%)	All Age n (%)	Childhood n (%)	Adult n (%)	All Age n (%)
Post-Surgical	0	29 (72.5)	29 (72.5)	5 (6)	55 (65.5)	60 (71.4)
Thyroidectomy	0	28 (70)	28 (70)	4 (4.8)	51 (60.7)	55 (65.5)
Autoimmune Thyroiditis	0	1 (2.5)	1 (2.5)	0	0	0
Basedow's Disease	0	4 (10)	4 (10)	2 (2.4)	6 (7.1)	8 (9.5)
Goiter	0	4 (10)	4 (10)	0	7 (8.3)	7 (8.3)
Larynx Cancer	0	0	0	0	1 (1.2)	1 (1.2)
Thalassemia	0	0	0	0	1 (1.2)	1 (1.2)
Thyroid Cancer	0	7 (17.5)	7 (17.5)	1 (1.2)	18 (21.4)	19 (22.6)
Unknown	0	12 (30)	12 (30)	1 (1.2)	18 (21.4)	19 (22.6)
Parathyroidectomy	0	1 (2.5)	1 (2.5)	1 (1.2)	4 (4.8)	5 (6)
Autoimmune Hypoparathyroidism	0	1 (2.5)	1 (2.5)	1 (1.2)	0	1 (1.2)
Di George Syndrome	1 (2.5)	0	1 (2.5)	2 (2.4)	0	2 (2.4)
Idiopathic Hypoparathyroidism	1 (2.35)	8 (20)	9 (22.5)	6 (7.1)	15 (17.9)	21 (25)
Total	2 (5)	38 (95)	40 (100)	14 (16.7)	70 (83.3)	84 (100)

From Applicant's Response to FDA for Request for Information, January 24, 2014

As expected, there were differences between screening and baseline of certain laboratory parameters and oral supplement doses in randomized subjects. This reflects the optimization period, during which doses of supplements were adjusted to achieve a target serum calcium concentration. Some of these parameters are summarized below. It is notable that the mean 24-hour urine calcium increased from screening to baseline, perhaps in part reflecting the increase in calcium supplementation recorded.

Table 5 Summary of Supplements and Selected Laboratory Assessment at Screening and Baseline—All Subjects with Both Screening and Baseline Data, Excluding Site 1002

Variable	Screening N=124	Baseline N=124
Active Vitamin D metabolite/analog (µg)		
n	124	124
Mean (SD)	1 (0.8)	0.9 (0.4)
Median	0.8	0.8
Min, Max	0.3, 4.3	0.3, 2
Calcium Supplement (mg)		
n	124	124
Mean (SD)	2074 (1581)	2108 (1321)
Median	1500	2000
Min, Max	500, 12000	1000, 12000
Total Serum Calcium (mg/dL)		
n	123	123
Mean (SD)	8.47 (1)	8.91 (0.78)
Median	8.5	8.88
Min, Max	4.88, 12.3	5.76, 11.40
Serum 25-Hydroxyvitamin D (ng/mL)		
n	120	120
Mean (SD)	41.9 (25.9)	43.1 (16.3)
Median	34	38
Min, Max	8, 150	11, 109
Serum 1,25-Dihydroxyvitamin D (pg/mL)		
n	99	99
Mean (SD)	30.8 (19.4)	33.8 (19.8)
Median	26	30
Min, Max	9, 148	9, 148
24-Hour Urine Calcium (mg/day)		
n	100	100
Mean (SD)	267.8 (175.88)	343.76 (181.09)
Median	227.30	320.60
Min, Max	17.20, 803	26, 973

From Applicant's Submission dated May 28, 2014, Table B-14.4.5

Baseline Medical Conditions

The following table summarizes baseline medical conditions for both groups. This summary only includes conditions present in at least 9% in either group.

Table 6 Summary Baseline Medical History for Conditions Present in ≥9% in Either Group, Excluding Site 1002

Preferred Term	Placebo (N=40) n (%)	rhPTH (1-84) (N=84) n (%)	Total (N=124) n (%)
Hypoparathyroidism	38 (95)	82 (97.6)	120 (96.8)
Thyroidectomy	27 (67.5)	52 (61.9)	79 (63.7)
Hypothyroidism	22 (55)	42 (50)	64 (51.6)
Hypertension	10 (25.0)	29 (34.5)	39 (31.5)
Seasonal Allergy	6 (15)	18 (21.4)	24 (19.4)
Thyroid Cancer	6 (15)	19 (22.6)	25 (20.2)
Drug Hypersensitivity	7 (17.5)	13 (15.5)	20 (16.1)
Gastroesophageal Reflux Disease	7 (17.5)	9 (10.7)	16 (12.9)
Depression	7 (17.5)	7 (8.3)	14 (11.3)
Goiter	7 (17.5)	7 (8.3)	14 (11.3)
Hysterectomy	4 (10)	10 (11.9)	14 (11.3)
Appendectomy	8 (20)	6 (7.1)	14 (11.3)
Menopause	7 (17.5)	6 (7.1)	13 (10.5)
Migraine	5 (12.5)	8 (9.5)	13 (10.5)
Tonsillectomy	7 (17.5)	5 (6)	12 (9.7)
Basedow's Disease	4 (10)	8 (9.5)	12 (9.7)
Cholecystectomy	3 (7.5)	8 (9.5)	11 (8.9)
Nephrolithiasis	2 (5)	8 (9.5)	10 (8.1)
Cataract	2 (5)	8 (9.5)	10 (8.1)
Obesity	4 (10)	6 (7.1)	10 (8.1)
Hypercholesterolemia	5 (12.5)	3 (3.6)	8 (6.5)
Osteoarthritis	5 (12.5)	2 (2.4)	7 (5.6)
Fibromyalgia	4 (10)	2 (2.4)	6 (4.8)
Hypocalcemia	4 (10)	2 (2.4)	6 (4.8)
Insomnia	4 (10)	2 (2.4)	6 (4.8)

From Applicant's Submission Dated May 30, 2014, Table 3b

These were reviewed and in general, there were no clinically important differences between the two groups.

The Applicant was asked why not all subjects were coded as having hypoparathyroidism. Their response was that the diagnosis of hypoparathyroidism was evident due to the inclusion criteria.

A comprehensive comparison of concomitant drugs for the two groups is not provided here. This data was reviewed, and there were no clinically important differences between the two groups in this respect. Approximately 89% of total

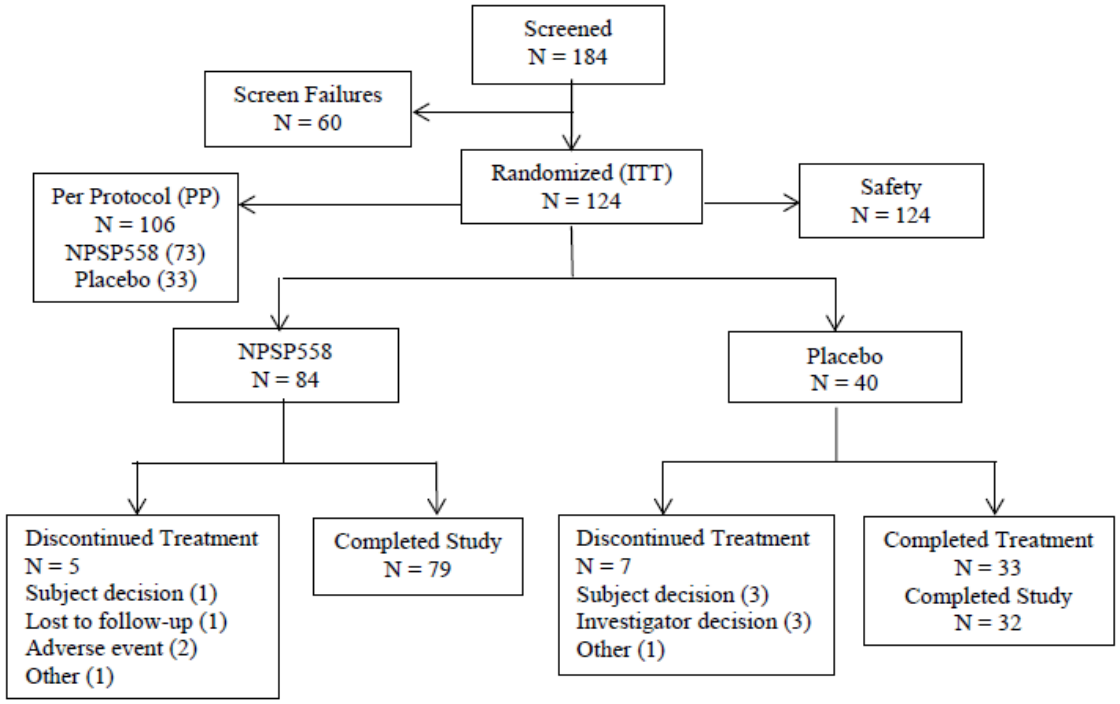
subjects took vitamins and 55% took mineral supplements (excluding calcium and vitamin D analogs) and 70% were on thyroid hormone therapy.

Demographic data for the other trials can be found in the individual study reviews in the Appendix.

6.1.3 Subject Disposition

Trial 040 (REPLACE)
A total of 33 sites in 8 countries (USA 20, Canada 3, Denmark 3, Hungary 3, Belgium 1, France 1, Italy 1, UK 1) screened 196 subjects in order to randomize 134 subjects. Sixty-two subjects failed screening. Twenty-nine sites randomized subjects. The diagram below depicts all subjects disposition.

Figure 5 Subject Disposition—All Subjects



From Applicant's Submission dated May 29, 2014, Figure 10-1

The following table and figure summarize subject disposition for the ITT population.

Table 7 Subject Disposition—ITT Population, Excluding Site 1002

Category	Placebo	NPSP558	Total

	N=40 n (%)	N=84 n (%)	N=124 n (%)
Completed treatment	33 (82.5)	79 (94)	112 (90.3)
Discontinued treatment early	7 (17.5)	5 (6)	12 (9.7)
Subject's decision	3 (17.5)	1 (1.2)	4 (3.2)
Lost to follow up	0	1 (1.2)	1 (0.8)
Adverse event	0	2 (2.4)	2 (1.6)
Investigator decision	3 (7.5)	0	3 (2.4)
Death	0	0	0
Other	1 (2.5)	1 (1.2)	2 (1.6)
Completed study/follow-up	32 (80)	79 (94)	111 (89.5)

From Applicant Submission dated May 27, 2014, Table B-14.1.1.5.1

In the NPSP558 group, 2 subjects discontinued due to AEs:

1) Subject 1010-0006, who had a history of hypertension and a previous 24-year history of smoking, discontinued on Day 122 after experiencing a cerebrovascular accident (also an SAE)
2) Subject 4002-0003 withdrew on Day 58 due to multiple non-serious adverse events, including anxiety, depression, injection site erythema, nausea as well as an event of hypercalcemia (11 mg/dL) which was described as resolved. A more complete narrative is included in Section 7.

The other discontinuations in the NPS group were unrelated to safety.

Protocol Deviations

The following table summarizes pre-specified significant protocol violations. Significant protocol violations included but were not limited to:

- Missing informed consent
- Compliance outside the 80% to 120% range
- Randomized but not treated
- Subjects received treatment previously, but was re-randomized
- No week 24 visit and efficacy determinations
- No baseline efficacy determinations
- Prior PTH usage without exemption by NPS
- Use of prohibited medications during treatment period
- Key inclusion/exclusion criteria violations
- Receipt of wrong treatment kit

Overall, approximately 14% of subjects had a significant protocol violation. They were included in the ITT population but excluded from the PP population.

Table 8 Summary of Significant Protocol Violations by Categories—All Randomized Subjects

Significant Protocol Violation	Placebo	NPSP558	Total

	N=44 n (%)	N=90 n (%)	N=134 n (%)
Have at least 1 significant protocol violation	7 (15.9)	12 (13.3)	19 (14.2)
Study drug compliance outside of 80-120% range	7 (15.9)	8 (8.9)	15 (11.2)
No Week 24 efficacy determinations	7 (15.9)	6 (6.7)	13 (9.7)
Use of prohibited medications during the treatment period	0	1 (1.1)	1 (0.7)
Received wrong treatment kit	0	1 (1.1)	1 (0.7)
Key inclusion/exclusion criteria violation	0	1 (1.1)	1 (0.7)
Other	0	2 (2.2)	2 (1.5)

Percentages are based on the number of randomized subjects in each treatment arm. Subjects may be counted in more than one category.
Compliance is defined as study drug doses outside of 80% to 120% of expected 24 weeks of administration.
Significant protocol violations were prospectively defined
From CSR CL1-11-040, Table 10-2

Table 9 Summary of Significant Protocol Violations by Categories—All Randomized Subjects, Excluding Site 1002

Significant Protocol Violation	Placebo N=40 n (%)	NPSP558 N=84 n (%)	Total N=124 n (%)
Have at least 1 significant protocol violation	7 (17.5)	11 (13.1)	18 (14.5)
Study drug compliance outside of 80-120% range	7 (17.5)	7 (8.3)	14 (11.3)
No Week 24 efficacy determinations	7 (17.5)	5 (6)	12 (9.7)
Use of prohibited medications during the treatment period	0	1 (1.2)	1 (0.8)
Received wrong treatment kit	0	1 (1.2)	1 (0.8)
Key inclusion/exclusion criteria violation	0	1 (1.2)	1 (0.8)
Other	0	2 (2.4)	2 (1.6)

From Applicant Submission dated May 27, 2014, Table B-14.1.1.4

Overall, there were 900 non-significant protocol deviations (NPSP558, 616; placebo 284), excluding Site 1002 (including the site there were a total of 974). The majority of these were out-of-window visits (33% of total deviations), procedure errors (missing labs, visits, etc. 206/974, 18%), and study drug-related issues (lost/damaged supplies, non-compliance, concomitant medication, etc. 196/974, 21%). There were no major differences in the deviations between the two treatment groups and none were found which impacted the ITT analyses.

Looking at Site 1002 alone, it is notable that there were 52 procedure-related protocol deviations. The majority of these (31/52) were missed labs and missed procedures (12/52).

Compliance was assessed from subject diaries and is summarized below for the trial. Percent treatment compliance was calculated as: [100 x doses administered/days on treatment], where 'days on treatment' was calculated as (date of last dose to date of first dose) + 1. Subjects were considered compliant if the calculated compliance was ≥80%. Overall, compliance was high in both groups. No subject exceeded 100% compliance.

Table 10 Summary of Treatment Compliance—Safety Population, Excluding Site 1002

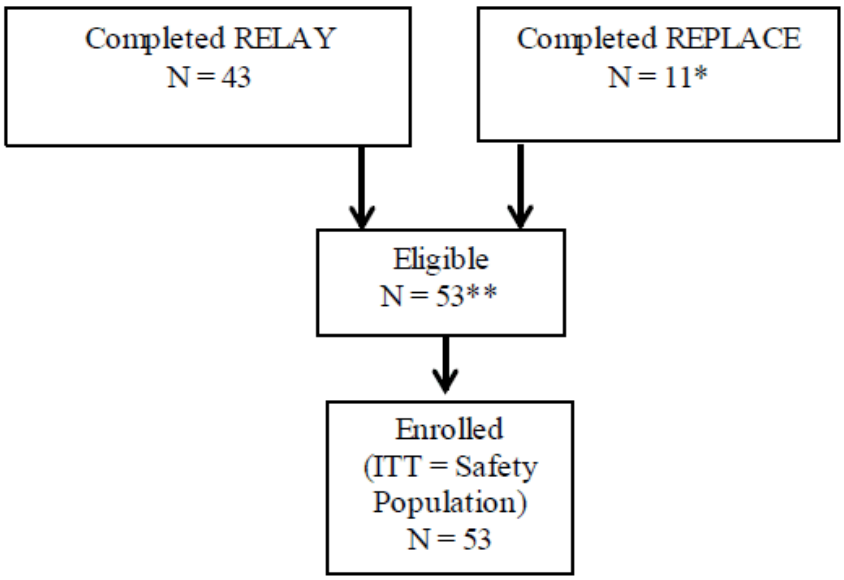
Treatment Compliance	Placebo (N=40) n (%)	NPSP558 (N=84) n (%)
n	4	84
Mean (SD)	96.5 (10.1)	97.1 (6.9)
Median	99.4	99.4
Min, Max	42, 100	51, 100
≥80%	38 (95)	82 (97.6)
<80%	2 (5)	2 (2.4)

From Applicant's Submission dated May 28, 2014, Table B-14.3.8.1

Trial 008

The figure and table below summarize subject disposition in the long-term trial. The majority of subjects had previously completed RELAY. Also, as of the data cut-off for the report, 92.5% of subjects were on-going with treatment. Two subjects discontinued during the first 12 months, both due to 'subject's decision'. One subject discontinued during the extension due to becoming tired of the daily injections. There was an additional subjects not captured in the table below who did not 'formally' discontinue at the time of data cut-off who did not participate in the trial because of metastatic lung cancer.

Figure 6 Subject Disposition for Trial 008—All Subjects



ITT = Intent-to-Treat; RELAY = PAR-C10-007; REPLACE = CL1-11-040
*One subject dropped-out during optimization in REPLACE but met inclusion and exclusion criteria.
** Two subjects were noted as eligibility failures.
From Applicant's CSR, Figure 10-1

Table 11 Subject Disposition—All Subjects, Excluding Site 1002

Disposition, n (%)	All Subjects N=49 (100)
First 12 months of trial	
Completed	47 (95.9)
Discontinued	2 (4.1)
Extension period	
Entering extension period	46 (93.9)
Discontinued in extension	2 (4.1)
Subject's decision	1 (2)
Adverse event	1 (2)
On-going with treatment	44 (89.8)

Applicant's Submission dated June 2, 2014, Table B-14.1.1.4.1

Trial 007

Subject Disposition is shown below. While 50% of subjects came from the pivotal trial, approximately 33% were new to the development program. There was one early discontinuation, in the 25 µg group: this subject was discontinued on Day 38 because of arthralgia, which was considered unrelated to study drug.

Table 12 Subject Disposition—All Randomized Subjects, Excluding Site 1002

Category	NPSP558 25 µg n (%)	NPSP558 50 µg n (%)	Total N=47 n (%)
Randomized	19	23	42
Completed 24 wks of therapy and 4 wks of follow- up in CI-11-040	12 (63.2)	9 (39.1)	21 (50)
Enrolled in CL-11-040 but not randomized	0	4 (17.4)	4 (9.5)
New to NPSP558 program	6 (31.6)	8 (34.8)	14 (33.3)
Enrolled in C09-002	1 (5.3)	2 (8.7)	3 (7.1)
ITT Population	19 (100)	23 (100)	42 (100)
Per-protocol Population	16 (84.2)	23 (100)	39 (92.9)
Safety Population	19 (100)	23 (100)	42 (100)
Completed Study	18 (94.7)	23 (100)	41 (97.6)
Discontinued study early	1 (5.3)	0	1 (2.4)
Adverse event	1 (5.3)		1 (2.4)

From Applicant's Information Request, Table B-14.1.1.3 dated June 5, 2014

6.1.4 Analysis of Primary Endpoint(s)

In the pivotal trial, a subject was considered a responder at EOT if they met the composite endpoint.

Based on investigator-prescribed data in the analysis below, approximately 55% of subjects in the NPSP558 group were responders, compared to 2.5% in the placebo group. Conversely, approximately 45% of subjects in the NPSP558 group were non-responders compared to 97.5% of the placebo group. The results were statistically significant.

Table 13 Analysis of Responder Rate at End of Treatment Based on Investigator-prescribed Data—ITT Population, Excluding Subjects from Site 1002

Status	Placebo N=40		NPSP558 N=84		Treatment Difference (95% CI)[a]	p-value[b]
	n (%)	(95% CI)	n (%)	(95% CI)		
Responder	1 (2.5)	(0.1, 13.2)	46 (54.8)	(43.5, 65.7)	52.3 (40.6, 64)	<0.001
Non-Responder	39 (97.5)		38 (45.2)			

CI=confidence interval; ITT=intent-to-treat

[a] treatment difference is calculated as responder rate of NPSP558 minus the responder rate of placebo, the 2-sided asymptotic 95% CI is based on normal approximation
[b] based on Fisher's Exact test
Applicant's Submission May 28, 2014, Table B-14.2.1.1.1

Section 5.3 included a discussion of the change in definition of the 'normal calcium' component of the primary endpoint. The Statistical Reviewer re-analyzed the data using an alternate definition (from the Original Protocol) for normal calcium. Therefore, in addition to the other 2 components, serum calcium had to be in the 8-9 mg/dL range. Using this alternate definition, the number of responders dropped. Although the efficacy results remain significant, these results may be less clinically significant, particularly if a clinician's goal is to keep a patient's serum calcium in a tighter, lower range (and not allowed to ascend to the ULN).

Table 14 Alternate Analysis of Responder Rate at End of Treatment Using Serum Calcium Range of 8-9 mg/dL as Normal

Status	Placebo N=40		NPSP558 N=84		Treatment Difference (95% CI)	p-value[b]
	n (%)	(95% CI)	n (%)	(95% CI)		
Responder	1 (2.5)	(0.1, 13.2)	27 (32.1)	(22.36,43.22)	29.64 (18.55, 40.74)	<0.0001
Non-Responder	39 (97.5)		57 (67.9)			

Analysis done by Dr. Jennifer Clark, FDA Statistician
CI=confidence interval

Changes in levels of vitamin D are discussed in Section 7.4.2.

Trial 008

Efficacy analysis was conducted at two evaluation points: Week 52 and EOT. A subject must have met all 3 criteria to have been considered a responder. The table summarizes the pre-defined responder rates at the two time points. Although this analysis represents data from an open-label without a comparator, the results do suggest sustainability of treatment beyond the 24 weeks seen in the pivotal trial.

The reason for the difference between the Week 52 and EOT analysis is unclear.

Table 15 Analysis of Responder Rate Based on Investigator-prescribed Data, Excluding Site 1002

	NPSP558 (N=49)

	n/m (%)	(95% CI)
Week 52		
Responder	34/45 (75.6)	(60.5, 87.1)
Non-responder	11/45 (24.4)	
End of Treatment		
Responder	25/48 (52.1)	(37.2, 66.7)
Non-responder	23/48 (47.9)	

Percentages are based on 'm', the number of ITT subjects with valid responder values available at the visit.
From Applicant's Submission dated June 2, 2014, Table B-14.2.1.1.1

Although not a primary endpoint, the following table summarizes the final dose of NPSP558 as of data cut-off. Similar to the pivotal trial, the majority of subjects required the highest dose.

Table 16 NPSP558 Dose Level as of data cut-off for Trial 008—ITT Population, Excluding Site 1002

NPSP558 Dose Level	**NPSP558 N=49 n (%)**
25 µg	0
50 µg	10 (20.4)
75 µg	6 (12.2)
100 µg	33 (67.3)

From Applicant's Submission dated June 2, 2014, Table B-14.2.8.1

Trial 007

The primary analysis of the primary endpoint was based on the investigator-prescribed data, and therefore those results are shown below. Four subjects in the 25 µg group and six subjects in the 50 µg group met the primary endpoint. There was no statistically significant treatment difference between the two groups.

However, if patient diary data is used, only 1 subject in each group met the primary endpoint.

Table 17 Primary Response Rate at Week 8 Based on Investigator-prescribed Data –ITT Population, Excluding Site 1002

	rhPTH (1-84) 25 µg N=19		**rhPTH (1-84) 50 µg N=23**			
Status	n (%)	(95% CI)	n (%)	(95% CI)	Treatment Difference (95% CI)	p-value
Responder	4 (21.1)	(6.1, 45.6)	6 (26.1)	(10.2, 48.4)	5.0 (-20.6, 30.7)	>0.999
Non-responder	15 (78.9)		17 (73.9)			

From Applicant's Submission dated June 5, 2014, Table B-14.2.1.1.1

Percentages are based on the number of ITT subjects in each treatment arm. Responder is defined as subjects whose daily calcium supplementation at Week 8 was ≤500 mg/day and the daily calcitriol dose was ≤0.25 µg/day and the albumin-corrected calcium level at Week 8 was between 7.5 mg/dL and the upper limit of normal. Subjects who terminated early or had missing lab data at Week 8 were considered non-responders.

6.1.5 Analysis of Secondary Endpoints(s)

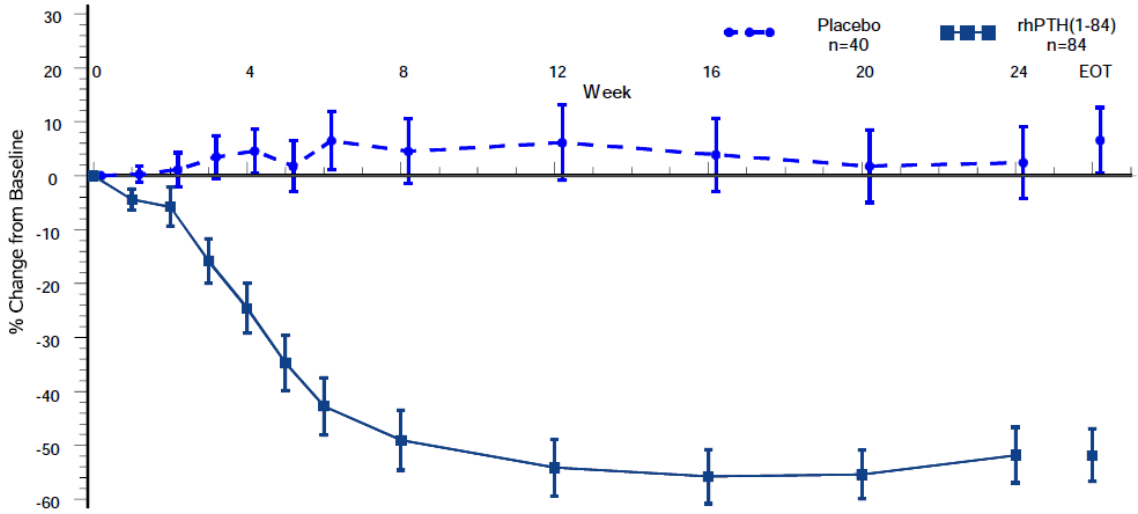
Trial 040

The first of the two secondary endpoints must be viewed in context of the mean serum calcium levels during the trial, which are presented in Section 7.

Percentage Change from Baseline in Daily Calcium Dose at Week 24

The figure below depicts the results of this secondary endpoint. At Week 24, there was a mean percentage decrease of 51.8% (±45.7%) in the NPSP558 group, compared to an increase of 2.4% (±38.5%) in the placebo group.

Figure 7 Mean (±SE) of Percent Change from Baseline in Calcium Supplementation Dose Based on Investigator-prescribed Data-ITT Population, Excluding Site 1002



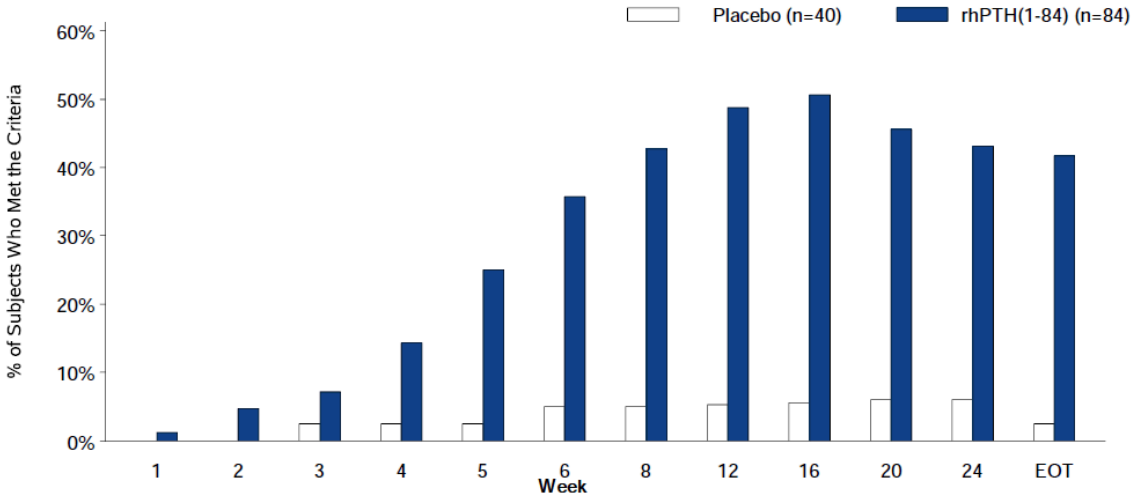
Applicant Submission dated May 28, 2014, Figure B-14.2.2.1.1

Proportion of Subjects Who Achieved Independence from Supplemental Active Vitamin D Metabolite/Analog Usage and a Calcium Supplementation Dose of ≤500 mg/day

This secondary endpoint was intended to reflect the maximum feasible independence from oral supplements for hypoparathyroidism. This is reflected in the figure below, based on Investigator-prescribed data. By Week 24, a total of

34/84 (43%) of NPSP558-treated subjects achieved this goal, compared to 2/40 (6.1%) of the placebo group. This analysis using patient diary data showed some differences at Week 12 to Week 16, with lower percentages of subjects achieving this endpoint using patient data. This may reflect differences in what the Investigator prescribed and what supplement doses the patient actually took at home or how well subjects kept their diaries. This appears to be the only analysis which yielded disparate results from the two sources of data.

Figure 8 Proportion of Subjects Who Achieved Independence from Supplemental Active Vitamin D Metabolite/Analog Usage and a Calcium Supplementation Dose ≤500 mg/day Based on Investigator-Prescribed Data—ITT Population, Excluding Site 1002



Applicant Submission dated May 28, 2014, Figure B-14.2.1.2.1

The Applicant also measured "Frequency of Clinical Symptoms of Hypocalcemia During Week 16 to Week 24" as a secondary endpoint. This time point corresponded with the second half of the maintenance period. 'Frequency' was measured using a list of terms generated intended to reflect symptoms that defined hypocalcemia. The list was not comprehensive, however, and because it was generated post hoc, is not included in this Review.

Hypocalcemia, along with hypercalcemia, is discussed more thoroughly in Section 7.

Trial 008

Only the secondary endpoints considered most clinically relevant are discussed here.

Mean Change from Baseline in 24-hour Urinary Calcium Excretion

At baseline (n=52), the mean (±SD) 24-hour urinary calcium excretion was 354.33 (±196.96) mg/24 hr. At Week 52 (n=48), the mean 24-hour urinary calcium excretion was 317.31 (±174) mg/24 hr.

There were 5 subjects who used calcium-sparing diuretics at baseline, and the mean 24-hour urinary calcium of these subjects was 412.80 (±268.79) mg/24 hr at baseline. At Week 52, the 24-hour urinary calcium in these subjects was still higher compared with subjects not using them (423.60 (±180.65) vs. 304.95 (171.1), respectively).

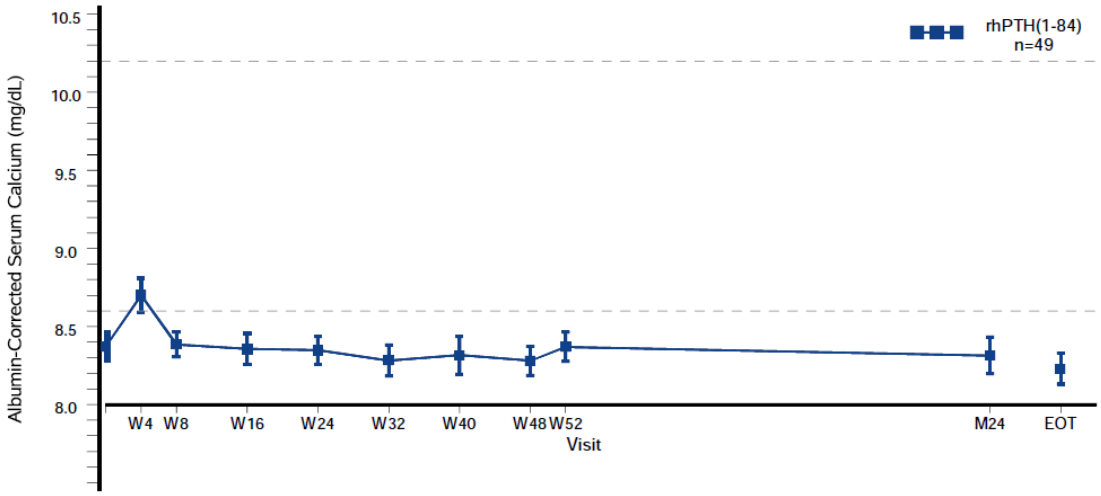
There were no subjects who had calcium-sparing diuretics added during the trial.

Change from Baseline in Albumin-corrected Total Serum Calcium and Serum Phosphate

Although this secondary endpoint was presented by the Applicant as percentage change, here the mean changes in the actual calcium levels are presented.

Mean calcium levels changed little from baseline to Week 52. Mean levels at both time points were within the target range (8 to 9 mg/dL), which was slightly below the normal range of total serum calcium levels (8.6 to 10.2 mg/dL).

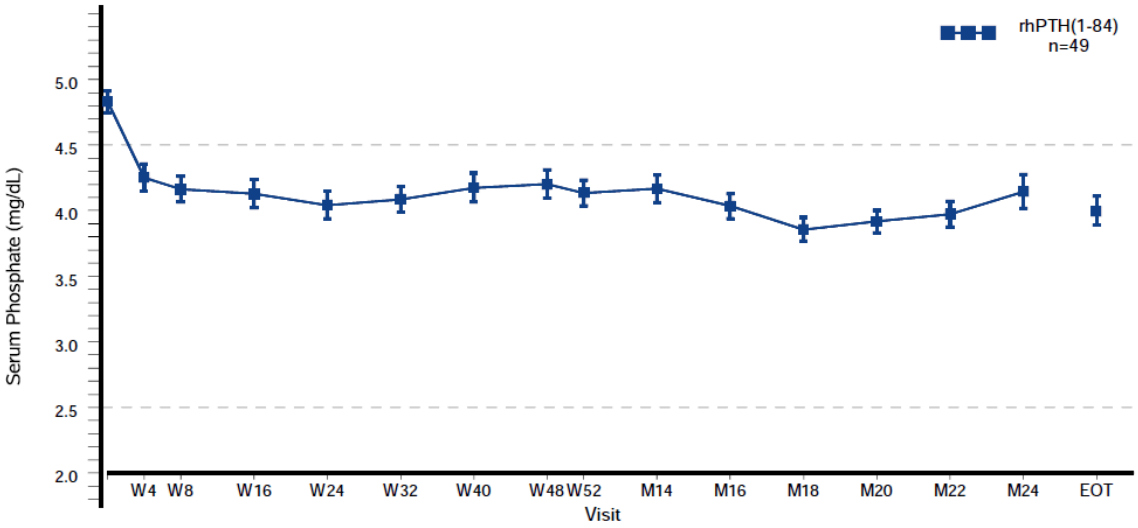
Figure 9 Mean (±SE) of Observed Values in Albumin-Corrected Serum Total Calcium by Visit—ITT Population



Applicant's Submission Dated June 2, 2014, Figure B-14.2.4.2

Although not a secondary endpoint, it is important to note that mean serum phosphate decreased into the range of normal during the trial.

Figure 10 Mean (±SE) of Observed Values in Serum Phosphate—ITT Population

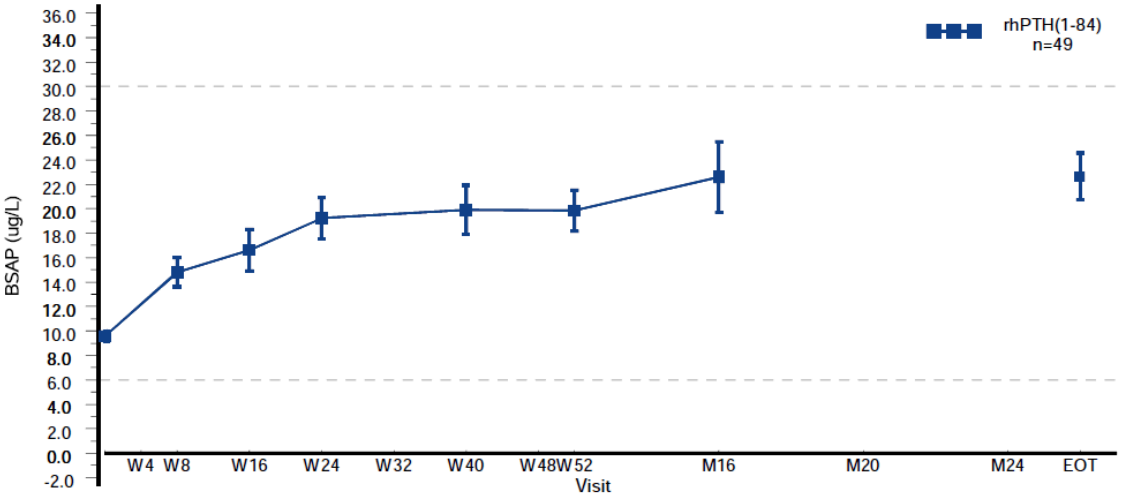


Applicant's Submission dated June 2, 2014, Figure B-14.2.6.2

Change from Baseline in Bone Turnover Markers

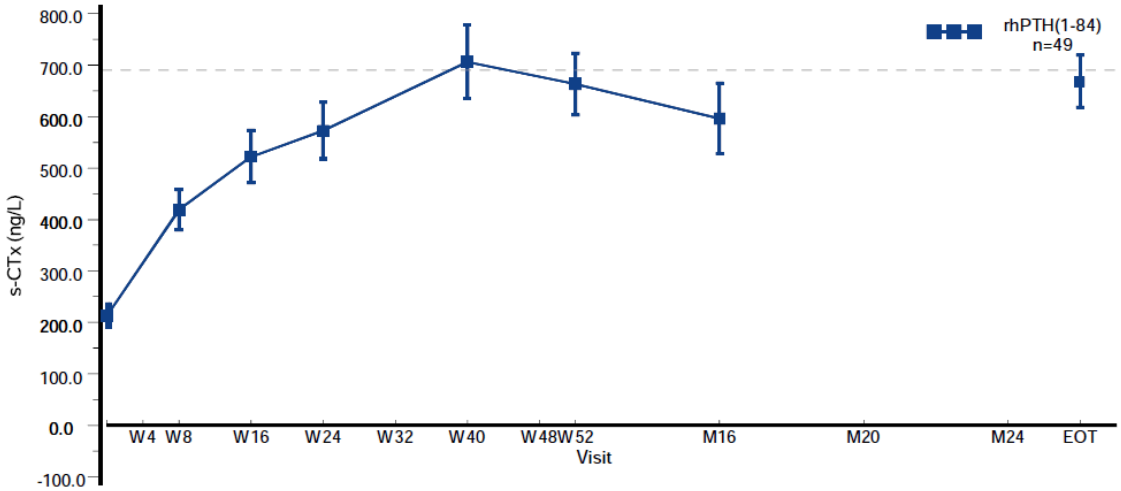
The figures below depict the changes in bone turnover markers during the 52 weeks. It should be noted that the baseline values in this trial reflected the final values from either RELAY or REPLACE, in which increases in subjects' bone markers were observed. With the exception of osteocalcin, levels of other markers appeared to plateau or decrease.

Figure 11 Mean (± SE) of Observed Values in Bone-Specific Alkaline Phosphatase (BSAP) – ITT Population



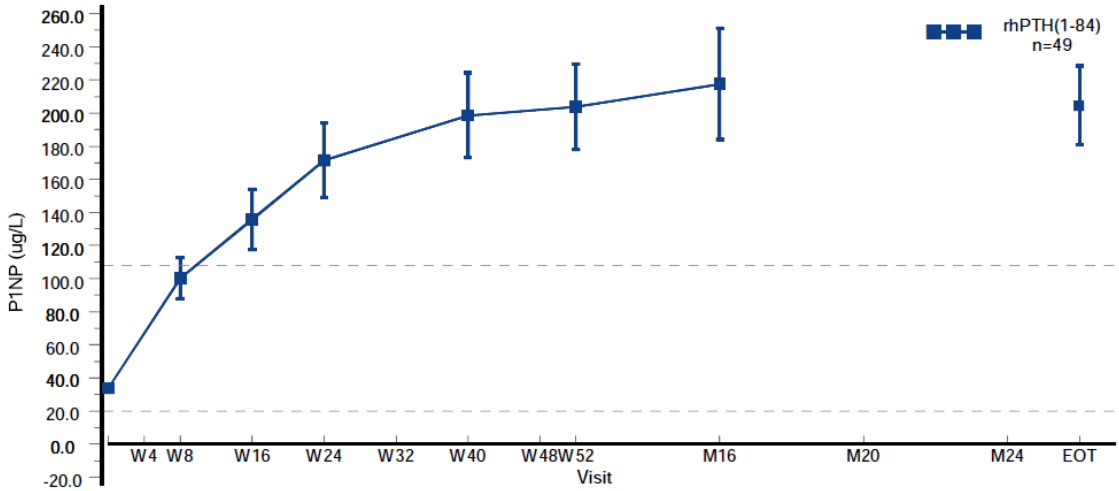
From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.1.2

Figure 12 Mean (± SE) of Observed Values in Serum Carboxy-Terminal Telopeptide of Type I Collagen (s-CTx) – ITT Population



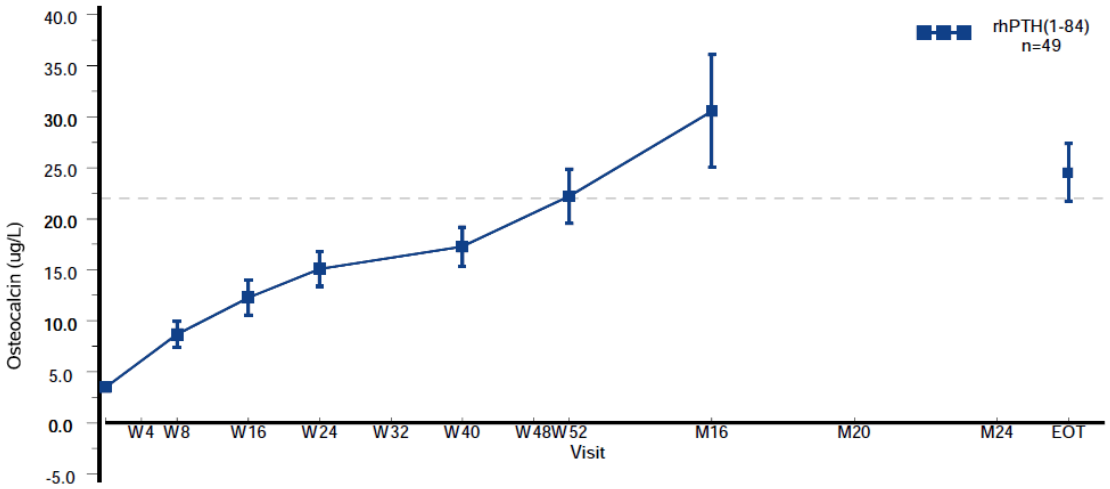
From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.2.2

Figure 13 Mean (± SE) of Observed Values in Serum Procollagen Type 1 Amino-terminal Propeptide (P1NP)—ITT Population



From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.3.2

Figure 14 Mean (± SE) of Observed Values in Osteocalcin—ITT Population



From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.4.2

Change from Baseline in Bone Mineral Density
DXA was done at baseline and at Week 52. Six subjects were excluded from the analysis because different machines were used at the two time points. The data are not presented here as there were minimal mean changes for all measurements.

Proportion of subjects that maintained a calcium-phosphate product in the normal range of 35 to 55 mg^2/dL^2
All subjects had a normal calcium-phosphate product at Week 52.

Trial 007
Secondary endpoint was the response rate at Week 8 based on the proportion of subjects with ≥50% reductions from baseline in oral calcium and calcitriol supplementation and albumin-corrected total serum calcium concentration that was normalized or maintained compared to the baseline value (≥7.5 mg/dL) and did not excess the ULN. The table below summarizes the secondary endpoint results.

Table 18 Secondary Response Rate at Week 8 Based on Investigator-prescribed Data—ITT Population, Excluding Site 1002

	rhPTH (1-84) 25 µg N=19		rhPTH (1-84) 50 µg N=23			
Status	n (%)	(95% CI)	n (%)	(95% CI)	Treatment Difference (95% CI)	p-value
Responder Non-responder	2 (10.5) 17 (98.5)	(1.3, 33.1)	6 (26.1) 17 (73.9)	(10.2, 48.4)	15.6 (-7.1, 38.2)	0.258

From Applicant's submission dated June 5, 2014, Table B-14.2.2.1.1

6.1.6 Other Endpoints

Trial 040

The exploratory endpoints that are discussed in this review are:

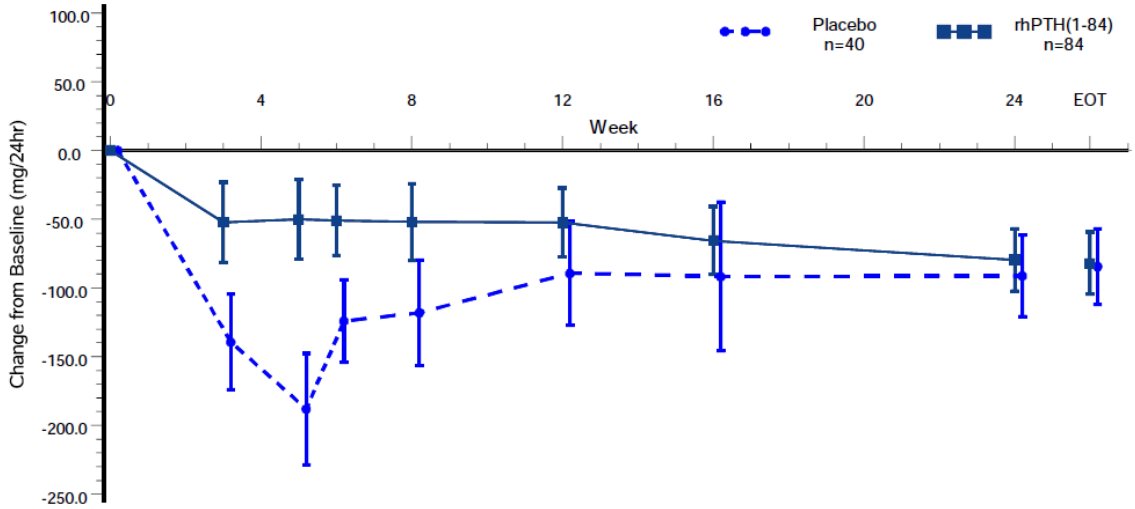
- change from baseline in 24-hour urine calcium excretion at Week 24
- change in bone turnover markers at Week 24
- proportion of patients that maintain a calcium –phosphate product in the normal range of 35-55 mg^2/dL^2 at Week 24 in the NPSP558 treatment group vs placebo
- change in bone mineral density (BMD) as measured by DXA at Week 24
- change in QoL score from baseline to Week 24

Given that the primary endpoint does not reflect a benefit in treating any symptoms of the disease itself, some of these endpoints are important in assessing drug efficacy. In particular, when replacing parathyroid hormone, one would expect an improvement and/or reversal of the hypercalciuria that is observed in patients with the disease. Also, given that hypoparathyroidism is a low bone turnover state, one would predict positive changes in bone markers.

Change from baseline in 24-hour urine calcium excretion at Week 24

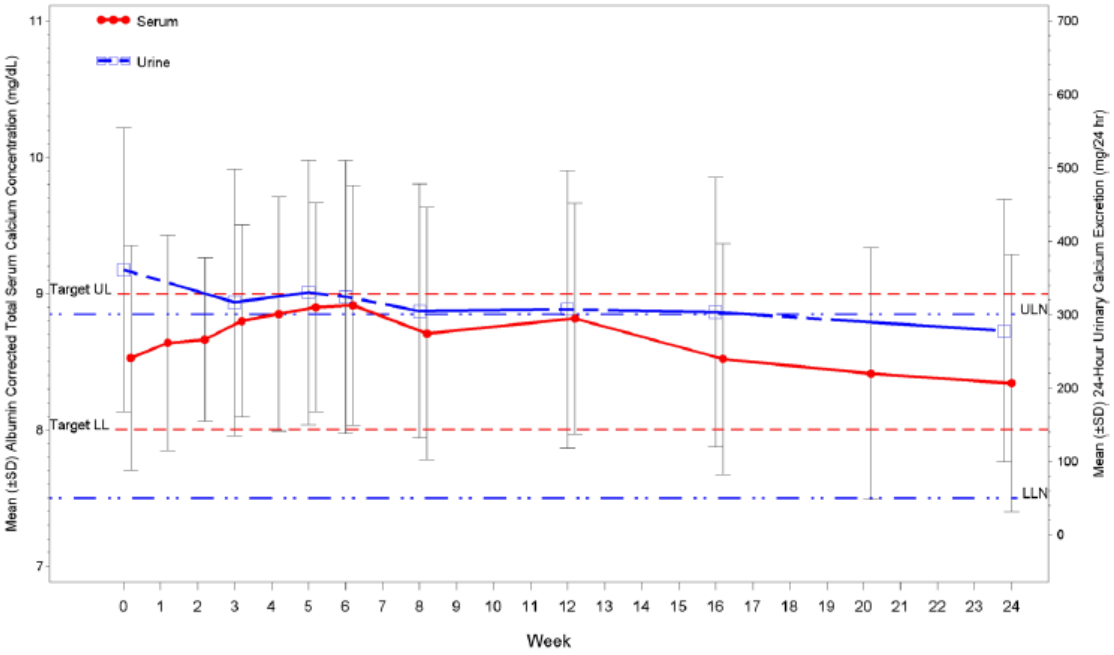
For a drug that is intended to treat hypoparathyroidism, observing a treatment-related decrease in 24-hour urine calcium is a clinically meaningful endpoint. This is because the hypercalciuria seen in hypoparathyroid patients causes much morbidity, particularly kidney stones and nephrocalcinosis. Figure 15 below depicts the mean change from baseline in 24-hour urinary calcium. Since urinary calcium changes with serum calcium, the graph needs to be viewed in context of the serum values, which are presented along with the urinary values in Figure 16 and Figure 17. Although Figure 15 shows that there were decreases in urinary calcium for both groups, the placebo group had a steeper decrease in the first 8-12 weeks, reflecting the hypocalcemia that occurred in the titration phase of the trial. By Week 24, there was little difference between the 2 groups.

Figure 15 Mean (±SE) of Change from Baseline in 24-Hour Urinary Calcium Excretion –ITT Population



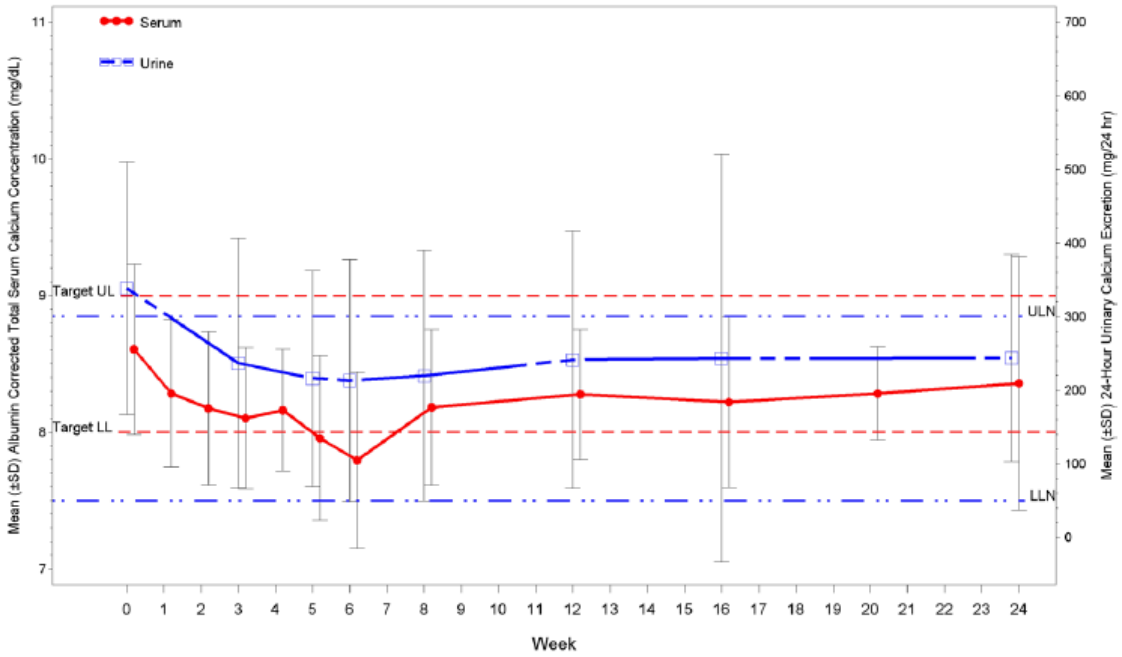
From Applicant's Submission dated May 28, 2014, Figure C-14.2.4.2

Figure 16 Mean (±SD) Albumin-corrected Total Serum Calcium and Mean (±SD) 24-Hour Urinary Calcium Excretion—Natpara Group, Excluding Site 1002



Applicant's Submission dated June 11, 2014, Figure 4.1

Figure 17 Mean (±SD) Albumin-corrected Total Serum Calcium and Mean (±SD) 24-Hour Urinary Calcium Excretion—Placebo Group



Applicant's Submission dated June 11, 2014, Figure 4.2

The table below summarizes the 24 hour urine calcium data. The mean and median values showed a greater decrease in the placebo group at Week 24.

Table 19 Analysis of Change from Baseline in 24-Hour Urine Calcium Excretion at Week 24—ITT Population, Excluding Site 1002

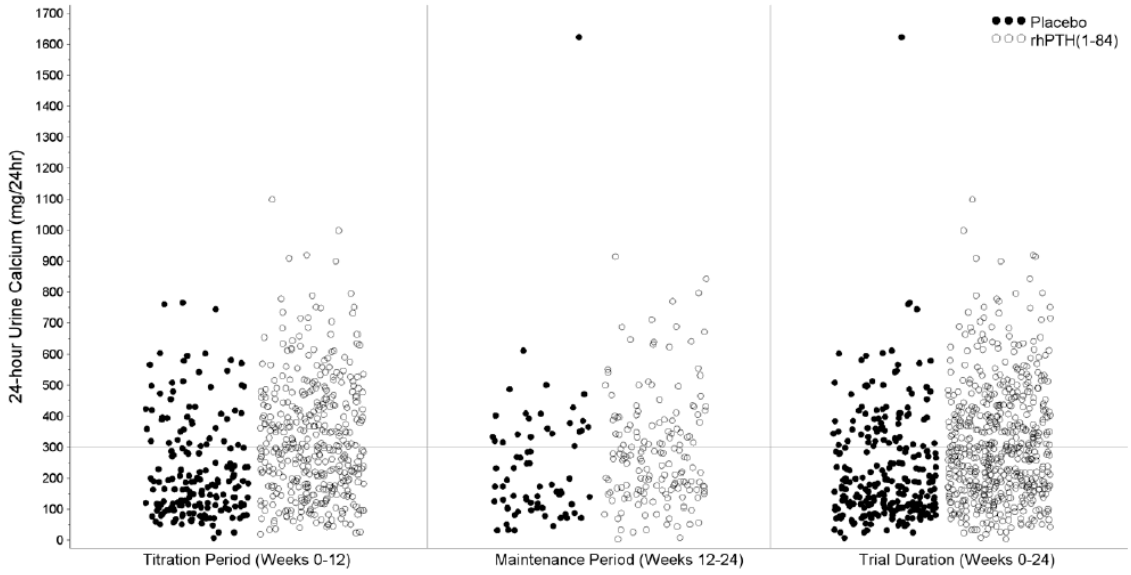
	Placebo N=40		NPSP558 N=84	
Visit	Actual Value (mg/24 hr)	Change from Baseline (mg/24 hr)	Actual Value (mg/24 hr)	Change from Baseline (mg/24 hr)
Baseline				
n	40		84	
Mean (SD)	339 (172)		361 (193)	
Median	306		339	
Min, Max	49, 770		26, 973	
Week 24				
n	33	33	74	74
Mean (SD)	244 (141)	-91 (171)	276 (178)	-79 (194)
Median	232	-94	231	-78.5
Min, Max	32, 612	-431, 247	26, 915	-677, 432
LS Mean (SE)[a]		-100 (26)		-75 (17)
95% CI[a]		(-151, -48)		-110, -40
EOT				
n	39	39	84	84

Mean (SD)	252 (160)	-85 (171)	279 (175)	-82 (207)
Median	232	-59	244	-79
Min, Max	32, 761	-431, 247	26, 915	-677, 432
LS Mean (SE)[a]		-95 (25)		-77 (17)
95% CI[a]		-144, -45		-111, -43

EOT=End of Treatment
[a]= Based on ANCOVA model with actual change as the dependent variable and the treatment as the factor and baseline 24-hour urine calcium excretion as the covariate.
From Applicant's Submission dated May 28, 2014, Table B-14.2.3.2

The following analyses were requested of the Applicant. The first graph below is a scatterplot showing the distribution of 24-hour urine calcium measurements, by trial period. Not all study subjects had 24-hour urine collections. The total number of data points is described below the graph. The second graph is a scatterplot of all 24-hour urine calcium levels with serum calcium recorded on the same day. Overall, hypercalciuria was problematic in both groups, although the rhPTH(1-84) group appeared to be associated with higher 24-hour urine calcium levels. The higher 24-hour urine calcium levels did not necessarily correlate with higher serum calcium levels.

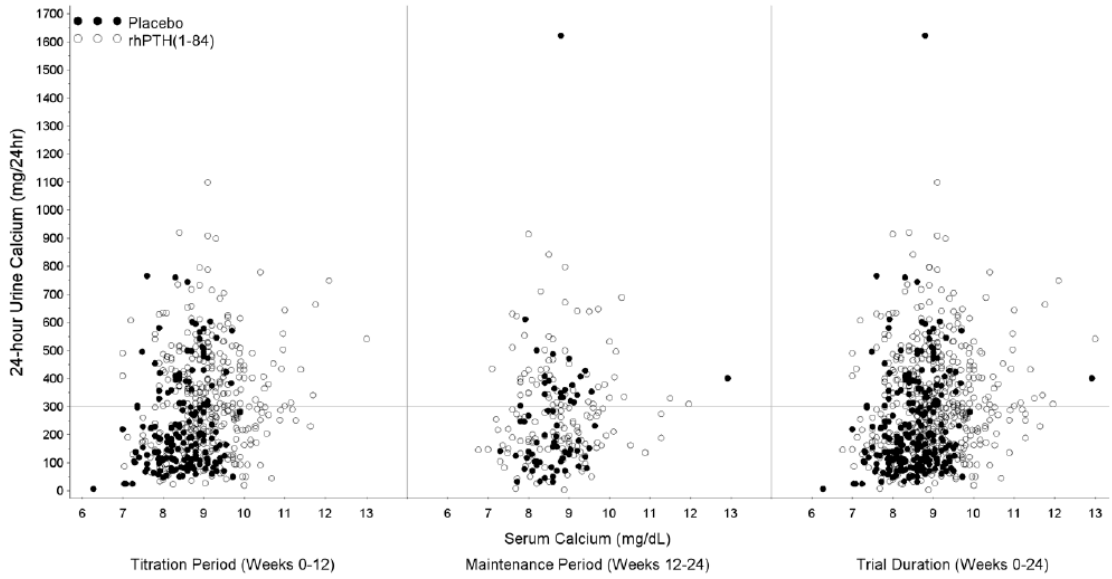
Figure 18 24-hour urine calcium (mg/24 hours) by Study Period—ITT Population, Excluding Site 1002



Note:During the Titration Period, there are 181 data points in the Placebo group, representing 39 subjects. There are 399 data points in the rhPTH (1-84) group, representing 84 subjects. During the Maintenance Period, there are 69 data points in the Placebo group, representing 34 subjects. There are 161 data points in the rhPTH (1-84) group, representing 79 subjects. Within the Trial Duration, there are 250 data points in the Placebo group, representing 39 subjects. There are 560 data points in the rhPTH (1-84) group, representing 84 subjects.. Baseline values are excluded from the analysis. Week 12 is included in the Titration Period.
24-hour Urine Calcium Upper Limit of Normal = 300 mg/24hr

From Applicant's Submission dated May 31, 2014, Figure 3b

Figure 19 24-hour Urine Calcium (mg/24hr) and Serum Calcium (mg/dL) by Study Period—ITT Population, Excluding Site 1002



Note:During the Titration Period, there are 173 data points in the Placebo group, representing 39 subjects. There are 383 data points in the rhPTH (1-84) group, representing 84 subjects. During the Maintenance Period, there are 67 data points in the Placebo group, representing 34 subjects. There are 152 data points in the rhPTH (1-84) group, representing 79 subjects. Within the Trial Duration, there are 240 data points in the Placebo group, representing 39 subjects. There are 535 data points in the rhPTH (1-84) group, representing 84 subjects. Baseline values are excluded from the analysis. Week 12 is included in the Titration Period.
24-hour Urine Calcium Upper Limit of Normal = 300 mg/24hr

From Applicant's Submission dated May 31, 2014, Figure 4b

Finally, the table below summarizes the percentage of subjects in each group with normal or abnormal 24-hour urine calcium values by visit. Week 16 was the beginning of the maintenance period.

With the exception of Week 24, a higher percentage of rhPTH(1-84)-treated subjects had abnormal levels during the trial. In both groups there was an increase in the percentage of subjects with normal values.

Table 20 Number (%) of Subjects with Normal or Abnormal Urine Calcium Values (mg/24 hr) by Visit—Safety Population, Excluding Site 1002

	Placebo N=40			**rhPTH(1-84) N=84**		
Visit	M	Normal (≤300) n (%)	Abnormal (>300) n (%)	m	Normal (≤300) n (%)	Abnormal (>300) n (%)
Baseline	40	19 (47.5)	21 (52.5)	84	36 (42.9)	48 (57.1)
Week 3 (Titration)	21	17 (81)	4 (19)	61	36 (59)	25 (41)
Week 5	21	18 (85.7)	3 (14.3)	58	25 (43.1)	33 (56.9)
Week 6	27	20 (74.1)	7 (25.9)	63	37 (58.7)	26 (41.3)
Week 8	38	27 (70.1)	11 (28.9)	80	41 (51.3)	39 (48.8)

Week 12	32	22 (68.8)	10 (31.3)	77	41 (53.2)	36 (46.8)
Week 16 (maintenance)	33	23 (69.7)	10 (30.3)	72	38 (52.8)	34 (47.2)
Week 24	33	20 (60.6)	13 (39.4)	74	49 (66.2)	25 (33.8)

m=number of subjects with 24-hour urine calcium excretion tested at each visit
From Applicant's Submission dated June 2, 2014 (no table number)

Change in bone turnover markers at Week 24

At baseline, bone turnover markers (bone specific alkaline phosphatase (BSAP), serum carboxy-terminal collagen crosslinks (s-CTx), serum type 1 procollagen (P1NP), and osteocalcin) were low in both groups, reflecting low bone metabolism in hypoparathyroid subjects. Not unexpectedly, all markers increased in the NPSP558 group but did not change in the placebo group at Week 24. Results are shown below. However, it is not understood well how the observed changes translate into a meaningful clinical benefit.

The plots below show actual mean values over time. At Week 24, all bone turnover markers were above normal levels in NPSP558-treated subjects.

The lab reference ranges for these markers are also summarized here. It is important to note, however, that the ranges were developed to allow physicians to detect osteoporosis on the basis of increased bone resorption and bone formation markers. Therefore, the upper limits of the reference range have been determined to allow for the distinction between normal bone and osteoporotic bone. The interpretation for the values at the lower end of the reference range is that this reflects low bone metabolic activity.[9]

Table 21 Lab Ranges for Serum Bone Turnover Markers

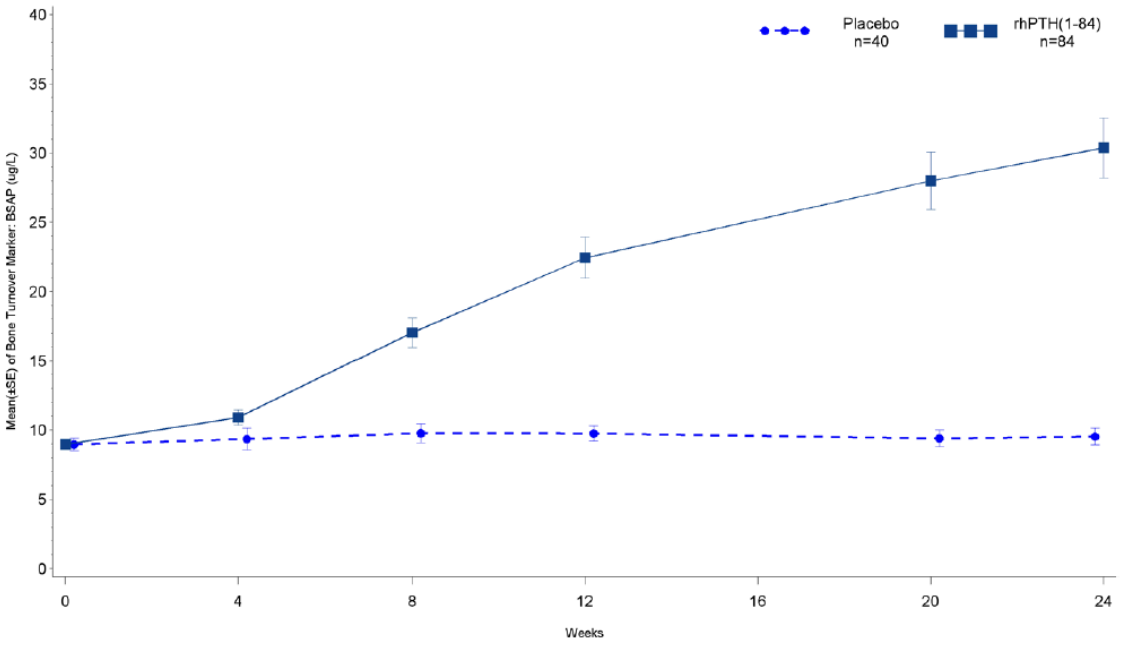
Parameter	Age	Gender	Cycle	Reference Range Low	Reference Range High
BSAP	≥25y	M		6	30
	25-44y	F	Pre-menopause	3	19
	≥45y	F	Post-menopause	6	26
s-CTx	19-30y	M		NA	<1040
	31-50y	M		NA	<580
	51-70y	M		NA	<700
	>70y	M		NA	<850
	≥18y	F	Pre-menopause	NA	<570
	≥18y	F	Post-menopause	NA	<1010
P1NP	≥18y	M		NA	≤75
	≥18y	F		NA	≤75
osteocalcin	≥18y	M		NA	≤22
	≥18y	F		NA	≤22

From Applicant's Response to Information Request, April 29, 2014

9 From Applicant's Response to FDA Request for Information (IR 23) dated May 16, 2014

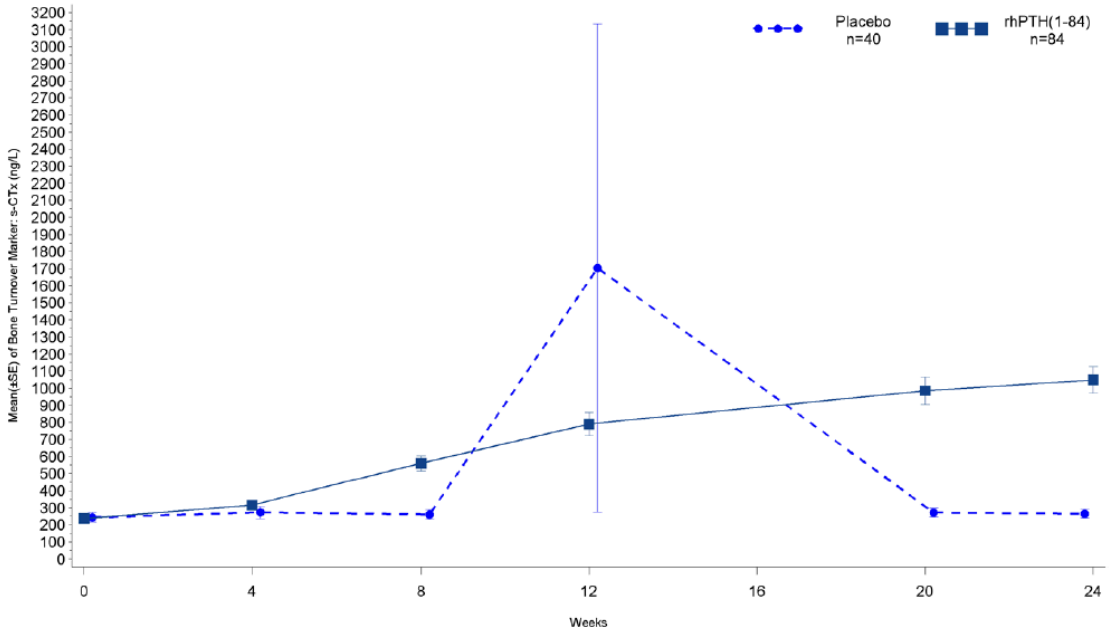
Y=years of age, NA=not applicable

Figure 20 Mean (±SE) of BSAP (ug/L) by Trial Week—ITT Population, Excluding Site 1002



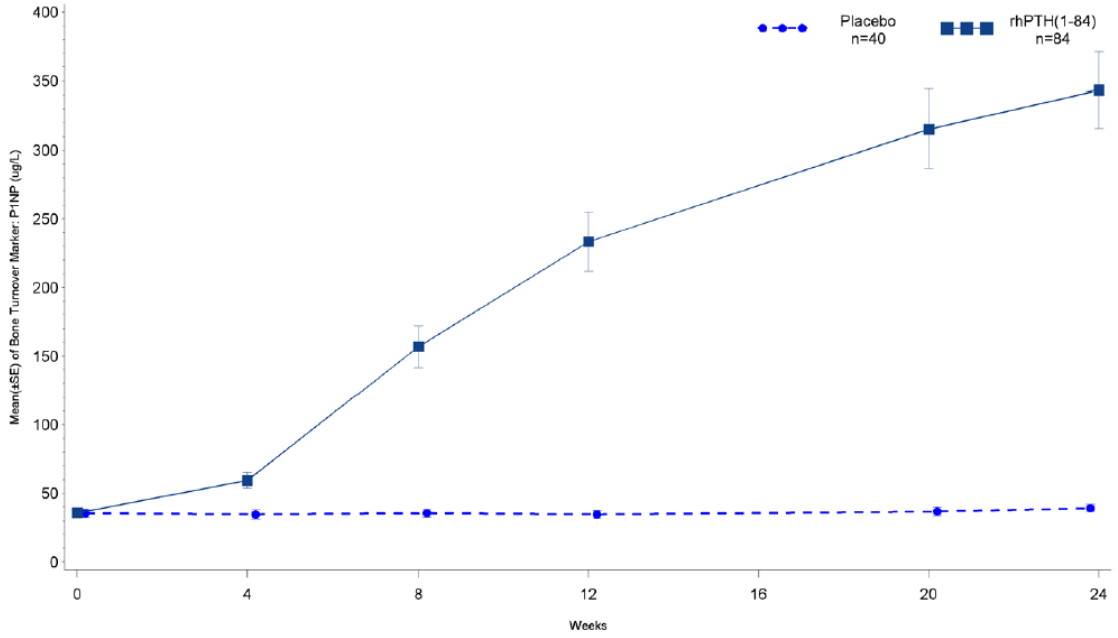
From Applicant's Submission dated June 2, 2014, Figure 1b

Figure 21 Mean (±SE) of s-CTx (ng/L) by Trial Week—ITT Population, Excluding Site 1002



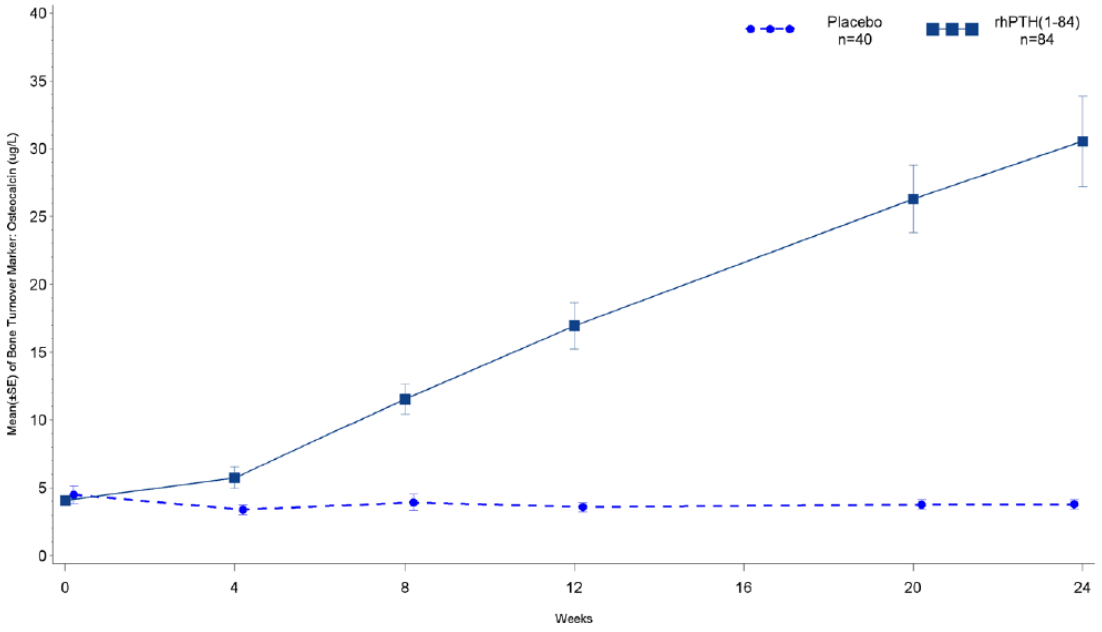
From Applicant's Submission dated June 2, 2014, Figure 2.1b
One subject had a value of 46,000 at Week 12 due to a lab error.

Figure 22 Mean (±SE) of P1NP (ug/L) by Trial Week—ITT Population, Excluding Site 1002



From Applicant's Submission dated June 2, 2014, Figure 3b

Figure 23 Mean (±SE) of osteocalcin (ug/L) by Trial Week—ITT Population, Excluding Site 1002



From Applicant's Submission dated June 2, 2014, Figure 4b

Subjects Who had a Calcium-Phosphate Product Greater Than 55 mg^2/dL^2 at Week 24

The following analyses were done by the Applicant in response to the Division's request. Figure 24 is a scatterplot for calcium-phosphate product for the pivotal trial. Included only are individual pairs of calcium and phosphate measurements that were measured on the same day, and the data are presented for titration and maintenance periods.

At baseline, no subject in the placebo group and one subject in the NPSP558 group had a calcium-phosphate group had a calcium-phosphate product greater than 55 mg^2/dL^2. The following table summarizes subjects with a high calcium-phosphate product during titration, reflected in the data points below.

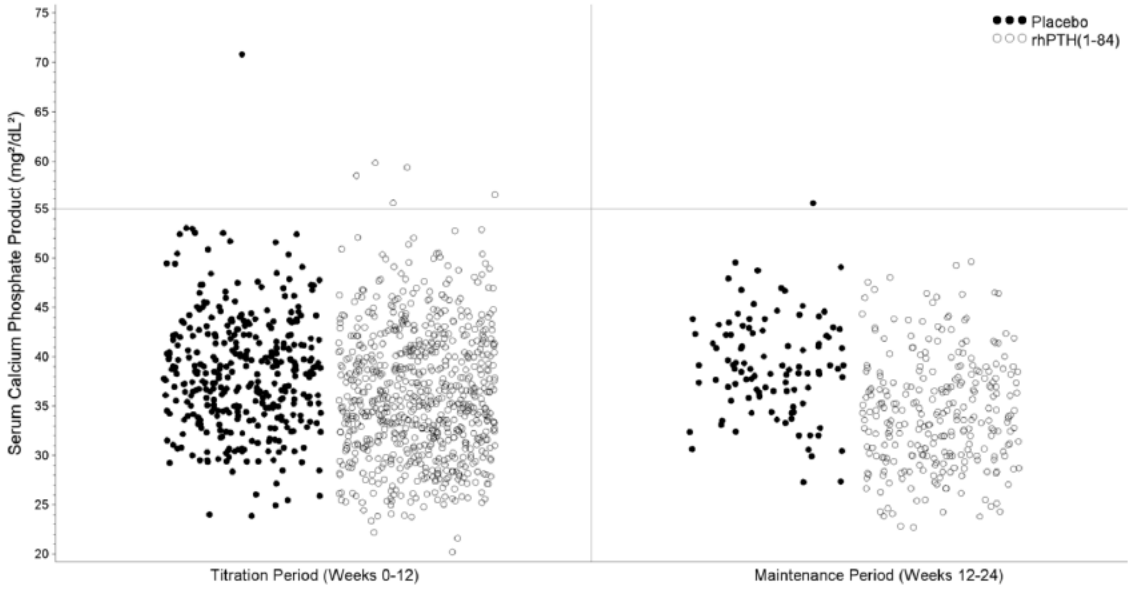
Table 22 Subjects with a calcium-phosphate product greater than55 mg^2/dL^2 during the pivotal trial

Subject ID	Treatment	Visit (week of treatment)	Calcium-phosphate product
0002-0003	Natpara	2	59.85
2001-0007	Natpara	4	56.45
2001-0009	Natpara	8 (unscheduled)	68.56
8001-0001	Natpara	3	55.61
8002-0001	Natpara	4	59.39

1014-0003	Placebo	8 (unscheduled)	70.81

From Applicant's Submission dated June 6, 2014

Figure 24 Serum Calcium-Phosphate Product (mg^2/dL^2) by Study Period—ITT Population, Excluding Site 1002



Note:During the Titration Period, there are 358 data points in the Placebo group, representing 40 subjects. There are 736 data points in the rhPTH (1-84) group, representing 84 subjects. During the Maintenance Period, there are 104 data points in the Placebo group, representing 35 subjects. There are 278 data points in the rhPTH (1-84) group, representing 79 subjects Baseline values are excluded from the analysis. Week 12 is included in the Titration Period.
Upper Limit of Normal = 55 mg^2/dL^2

From Applicant's Submission Dated May 31, 2014

Change in bone mineral density (BMD) as measured by DXA at Week 24
It is known that the state of chronic hypoparathyroidism is associated with increased BMD, particularly at the lumbar spine.[10] Therefore, one would predict that replacement of PTH would result in decreased bone density.

DXA was measured at baseline and Week 24. Seven locations were scanned. Clinically significant changes in bone density may not be seen with only 24 weeks of therapy.

In general, the baseline Z-scores of subjects was high, consistent with low-turnover bone disease. At Week 24, the mean changes from baseline in scores for total hip and hip femoral neck were significantly better (lower) ($p<0.001$) in the rhPTH(1-84) group compared to placebo (-0.160 [± 0.213] vs 0.015 [± 0.110] and -0.196 [± 0.299] vs 0.013 [±0.208], respectively). The other locations did not

10 F Chan et al. Increased Bone Mineral Density in Patients with Chronic Hypoparathyroidism. The Journal of Clinical Endocrinology and Metabolism July 2003.

show improvement or the changes were not statistically significant. Overall, the changes observed by DXA do not indicate a robust response during this 24-week treatment period.

As reference, the complete DXA results are in the Appendix.

Change in Quality of life (QoL) score from baseline to Week 24
QoL was measured using the Short Form-36 (SF-36) Questionnaire. This instrument is comprised of 36 individual questions in 8 domains: physical functioning, role/physical, bodily pain, general health, vitality, social functions, role/emotional, and mental health). The 8 domains were transformed to a scale from 0 to 100, which was used in the analysis. Although scores in the NPSP558 group trended toward better values, there were no statistically significant between-group differences between NPSP558 and placebo. Because of this and because this was an exploratory endpoint, detailed scores are not shown in this Review.

6.1.7 Subpopulations

The Applicant pre-specified subgroup analyses done for the primary efficacy endpoint. These included baseline demographic factors as well as disease-related factors.

The subgroup analysis below was done by the Statistical Reviewer, Dr. Clark. The CMH test was done for a general association between treatment arm and response for at least one stratum in each subgroup. Fisher's exact test was run within each strata to test for differences. Testing for subgroups based on race was neither pre-specified nor done by the Applicant, but was done by Dr. Clark.

Dr. Clark concludes that the subgroup analysis results remained consistent with the overall efficacy results. However, the results should be interpreted with caution because of the *post hoc* nature of this analysis and the lack of control for Type I error. The issue of power, as seen in some of the very small subgroups below, may have contributed to some of the borderline associations with treatment.

Table 23 Subgroup Analysis Excluding Site 1002

			Placebo (N=40)	RhPTH(1-84) (N=84)	
			n (%)	n (%)	Exact P
Age	<65 Years	Non-Responder	35 (97.2%)	38 (47.5%)	
		Responder	1 (2.8%)	42 (52.5%)	<.001
	≥65 Year	Non-Responder	4 (100%)	0 (0%)	
		Responder	0 (0%)	4 (100%)	0.029
Gender	Male	Non-Responder	7 (100%)	9 (47.4%)	
		Responder	0 (0%)	10 (52.6%)	0.023
	Female	Non-Responder	32 (97%)	29 (44.6%)	
		Responder	1 (3%)	36 (55.38%)	<.001
Baseline Active Vitamin D	Low Dose	Non-Responder	2 (66.7%)	1 (16.7%)	
		Responder	1 (33.3%)	5 (83.3%)	0.226
	Medium Dose	Non-Responder	12 (100%)	11 (50%)	
		Responder	0 (0%)	11 (50%)	0.003
	High Dose	Non-Responder	25 (100%)	26 (46.4%)	
		Responder	0 (0%)	30 (53.6%)	<.001
Calcium Supplementation at Baseline	Baseline CA ≤ 2000 mg	Non-Responder	28 (96.6%)	22 (38.6%)	
		Responder	1 (3.5%)	35 (61.4%)	<.001
	Baseline CA > 2000 mg	Non-Responder	11 (100%)	16 (59.3%)	
		Responder	0 (0%)	11 (40.7%)	0.016
Duration of Hypoparathyroidism	≤ 5 Years Hypoparathyroidism	Non-Responder	9 (90%)	3 (20%)	
		Responder	1 (10%)	12 (80%)	<.001
	5-10 Years Hypoparathyroidism	Non-Responder	13 (100%)	10 (37%)	
		Responder	0 (0%)	17 (63%)	<.001
	>10 Years Hypoparathyroidism	Non-Responder	17 (100%)	25 (59.5%)	
		Responder	0 (0%)	17 (40.5%)	0.001
Geographic Region	North America	Non-Responder	20 (95.2%)	17 (39.5%)	
		Responder	1 (4.8%)	26 (60.5%)	<.001
	Europe	Non-Responder	19 (100%)	21 (51.2%)	<.001

		Responder	0 (0%)	20 (48.8%)	
Race	**White**	**Non-Responder**	38 (97.4%)	35 (43.8%)	
		Responder	1 (2.6%)	45 (56.3%)	<.001
	Other	**Non-Responder**	1 (100%)	3 (75%)	
		Responder	0 (0%)	1 (25%)	1

From the Statistical Review and Evaluation for BLA 125,511, Dr. Jennifer Clark

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Results from all trials suggest that the highest dose, 100 µg daily, is required to achieve the specified primary endpoint in the majority of subjects. There are a few subjects, in Trial 007, who achieved the primary efficacy endpoint at the 25 µg dose.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Trial 008 is of the longest duration and therefore appropriate for a discussion of persistence of efficacy. Although the definition of responder was somewhat different than that of the pivotal trial, after 52 weeks approximately 75% of subjects met the primary efficacy endpoint. Because of the open-label nature, conclusions are limited. However, the results do suggest some sustainability of treatment beyond a 24-week period.

6.1.10 Additional Efficacy Issues/Analyses

None

7 Review of Safety

Safety Summary

There were no deaths in any of the trials.

In the pivotal trial, SAEs were observed at a similar frequency in both NPSP558-treated and placebo subjects. However, calcium-related SAEs were seen more often in the NPSP558 group: 2 subjects with hypocalcemia SAEs and 2 subjects with hypercalcemia SAEs compared to one hypocalcemia SAE in the placebo group.

The goal in the pivotal trial was to maintain serum calcium in the 8-9 mg/dL range. At Week 24, both groups were in this range. However, the NPSP558 group tended to have higher serum calcium levels throughout the trial. The lower calcium levels in the placebo

group, particularly in the first half of the trial, were to be expected with the decrease in vitamin D analogs and calcium.

Although the analysis of mean serum calcium levels was important, additional analyses using scatterplots was necessary. The scatterplot of serum calcium for the pivotal trial showed that from baseline to Week 24 there was little change in the general pattern of serum calcium levels for both groups. Also, at Week 24, NPSP-558 treated subjects had a wider range of calcium levels, with more hypo- and hypercalcemia. Placebo subjects tended to have a tighter range of calcium levels. The same pattern was observed for serum phosphate levels.

In another analysis of calcium-related events, hypercalcemia was observed much more frequently in the NPSP558 group, however most events were limited to the titration period. On the other hand, and not unexpectedly, hypocalcemia was observed more frequently in the placebo group in the titration period. Both groups had frequent laboratory-confirmed hypocalcemia during the maintenance period.

In Trial 007, mean serum calcium levels remained lower in the 25 µg group compared with the 50 µg group, in which an increase in serum calcium was observed over the 8-week trial.

Analyses of changes in 24-hour urine calcium for the pivotal trial are discussed under Efficacy.

There were no clinically important observations for changes in other laboratory parameters, vital signs, and EKGs.

The immunogenicity program was complicated. Overall, the incidence of anti-drug antibodies was 16.1%. There were no adverse events that correlated with the presence of antibodies nor was their evidence for loss of efficacy associated with antibodies.

Data from Trial 008 was used for the analysis of pen complaints, since there was a change in pen to the to-be-marketed pen (Haselmeier) midway through this trial. Leaking medication was the most frequent complaints for the Haselmeier pen. At the time this review was finalized, the analysis related to these complaints was ongoing by the Division and CDRH.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

As in the discussion of Efficacy, the focus in this Section is on Trial 040 with supportive data from Trial 008 and Trial 007. Data from Trial 009 is used in the discussion of immunogenicity.

7.1.2 Categorization of Adverse Events

Adverse events were coded using MedDRA Version 12.0. Adverse event listings provided the verbatim term as well as the SOC and PT for each recorded event.

For analyses of calcium-related events (hypocalcemia, hypercalcemia, and hypercalciuria), the Applicant used several types of analyses. These included using laboratory measurements alone, using AEs (defined *post hoc*), and using a combination of both laboratory and clinical AEs. Because the list of AEs was generated *post hoc* and was not necessarily comprehensive, this Review focuses on the objective laboratory measurements. The clinical AEs associated with the terms are used when analyzing SAEs, AEs leading to discontinuation, and AEs of special interest. In any case, multiple analyses were done for any one parameter in order to best understand the safety profile of Natpara.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Data from trials in this program were not pooled.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Error! Reference source not found. summarizes exposure to study drug in the pivotal trial. Approximately 82% of subjects were exposed to study drug for a minimum of 24 weeks.

Table 24 Summary of Exposure—Safety Population, Excluding Site 1002

Extent of Exposure	Placebo N=40 n (%)	NPSP558 N=84 n (%)
Any exposure	40 (100)	84 (100)
< 1 week	0	0

1 to < 4 weeks	0	0
4 to < 8 weeks	1 (2.5)	2 (2.4)
8 to < 12 weeks	2 (5)	0
12 to < 16 weeks	3 (7.5)	2 (2.4)
16 to < 20 weeks	1 (2.5)	1 (1.2)
20 to < 24 weeks	2 (5)	10 (11.9)
≥ 24 weeks	31 (77.5)	69 (82.1)
Exposure duration (days)		
Mean (SD)	157.3 (34.5)	168 (25.9)
Median	169	170
Min, Max	48, 185	40, 213

From Applicant's Submission Dated May 28, 2014, Table B-14.3.8.2

Trial 008

The mean duration of exposure was 576.8 days (±129) days. The minimum time on study drug was 41 days and the maximum was 719 days. Three subjects had an exposure of at least 24 months.

Trial 007

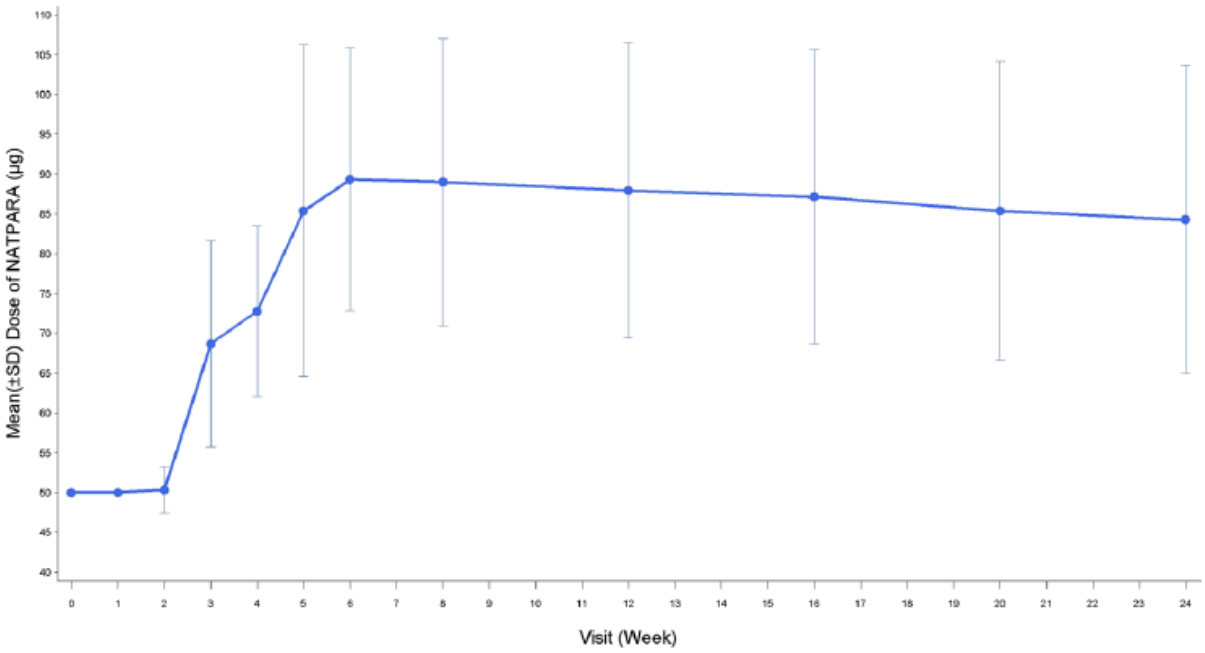
The mean exposure was 56.2 and 58 days, respectively, in the 25 µg and 50 µg groups. The majority of subjects were exposed for at least 8 weeks (84% and 91%, respectively).

7.2.2 Explorations for Dose Response

Dose response is discussed in the Clinical Pharmacology review, which is not complete at the time this document was finalized.

The figure below depicts the mean Natpara dose over time. The peak mean dose coincided with Week 6, and then saw a small decline to Week 24.

Figure 25 Mean (±SD) Daily Dose of Natpara by Visit—ITT Population, Excluding Site 1002



From Applicant's Submission dated May 30, 2014, Figure 4b
Dose level at each visit is determined as the actual dose the subject received in or immediately prior to the day albumin-corrected serum calcium was tested for that visit.

Table 25 summarizes the final NPSP558 doses in the ITT population. The majority (56%) of subjects were titrated to the highest dose. Again, in this trial, down-titration to 25 µg was not an option.

Table 25 Summary of Final NPSP558 Dose—ITT Population, Excluding Site 1002

Final NPSP558 Dose	NPSP558 N=84 n (%)
50 µg	15 (17.9)
75 µg	22 (26.2)
100 µg	47 (56)

From Applicant's Submission dated May 28, 2014, Table B-14.2.3.11

7.2.3 Special Animal and/or In Vitro Testing

None

7.2.4 Routine Clinical Testing

Measures of safety are discussed in Section 5.3.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to Dr. Manoj Khurana's review.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Because hypercalcemia was a safety issue in NDA 21,847 (Preos), it was considered an AE of special interest in this trial. However, since the two study populations are different (PTH-sufficient vs PTH-deficient), it was unclear to what extent hypercalcemia would be a safety concern in this program.

7.3 Major Safety Results

Adverse Events
Monitoring for AEs was done at every visit, as detailed in the Schedule of Study Evaluations and Procedures, found in the Appendix. AEs were to be recorded by the Investigator from the signing of informed consent through the last visit and follow-up period.

There were no deaths during the trial. An overall summary of treatment-emergent adverse events (defined as from the first dose through follow-up, referred to hereafter as AEs) is below. Most subjects experienced at least one AE, but there were few reported discontinuations due to an AE. Approximately 10% in each group experienced an SAE. The SAEs for the NPSP558 group are described in Section 7.3.2. The AEs leading to discontinuation are mainly discussed in Section 6.1.3.

Table 26 Summary of Adverse Events—Safety Population, Excluding Site 1002

	Placebo		**NPSP558**	
Category	**Subjects N=40 n (%)**	**Events**	**Subjects N=84 n (%)**	**Events**
Any AE No Yes	 0 40 (100)	 321	 6 (7.1) 78 (92.9)	 807
AE leading to discontinuation	0	0	3 (3.6)*	14
Any SAE	4 (10)	5	9 (10.7)	11
Deaths	0	0	0	0

From Applicant's Submission dated May 28, 2014, Table B-14.3.1.1.1

* This table lists 3 AEs leading to discontinuation, whereas the table under Subject Disposition above lists 2 AEs leading to discontinuation. This discrepancy is due to inconsistent reporting of the status of Subject 1008-0002 on two different case report forms: subject disposition and adverse events. The Adverse Event CRF for this subject reported "Study Drug Discontinued" for the action taken for a drug-related rash, which triggered inclusion of this subject in the category of discontinuation due to AEs in the AE tables and listings (Table B-14.3.1.1.1). However, this subject was reported as completed since the subject completed 24 weeks of treatment, all post-treatment visits, and missed only the last dose of study drug.

For Trial 008, the focus of the safety discussion is on calcium-related events. Other safety issues are discussed in the individual study review in the Appendix.

7.3.1 Deaths

There were no deaths during any of the trials.

7.3.2 Nonfatal Serious Adverse Events

Serious Adverse Events (SAEs) were defined as an AE that results in any of the following outcomes:

- death
- was life-threatening
- persistent of significant incapacity of substantial disruption of ability to conduct normal life functions
- hospitalization or prolongation of existing hospitalization
- congenital anomaly/birth defect
- Important medical events that did not result in death, but were life-threatening, or required hospitalization were considered as an SAE when, based upon appropriate medical judgment, they jeopardized the subject or required medical or surgical intervention to prevent one of the other outcomes listed in this definition.

Table 27 below summarizes SAEs during the trial, including during the follow-up period. Narratives for events in the NPSP-558 group that occurred while receiving study drug are further below. Overall, 10.7% of subjects in the NPSP558 group had an SAE, compared to 10% in the placebo group. Only one SAE of hypercalcemia appeared to be related to study drug. All 3 SAEs of hypocalcemia occurred after study drug was stopped and was related to the re-starting of supplements. When Site 1002 was excluded, there was one less SAE in the NSPP558 group: hypocalcemia which occurred in the post-treatment period.

Table 27 Summary of Treatment-Emergent Serious Adverse Events by SOC and PT—Safety Population, Excluding Site 1002

	Placebo		NPSP558	
	Subjects		Subjects	

MedDRA SOC PT	N=40 n (%)	Events	N=84 n (%)	Events
Any SAE				
No	36 (90)		75 (89.3)	
Yes	4 (10)	5	9 (10.7)	11
Metabolism and Nutrition Disorders	2 (5)	2	4 (4.8)	4
Hypocalcemia	1 (2.5)	1	2 (2.4)	2
Hypercalcemia	0	0	2 (2.4)	2
Dehydration	1 (2.5)	1	0	0
Gastrointestinal Disorder	0	0	2 (2.4)	3
Diarrhea	0	0	1 (1.2)	1
Pancreatitis	0	0	1 (1.2)	1
Vomiting	0	0	1 (1.2)	1
Infections and Infestations	0	0	2 (2.4)	2
Diverticulitis	0	0	1 (1.2)	1
Erysipelas	0	0	1 (1.2)	1
Musculoskeletal and Connective Tissue Disorder	0	0	1 (1.2)	1
Back pain	0	0	1 (1.2)	1
Nervous System Disorders	0	0	1 (1.2)	1
Cerebrovascular accident	0	0	1 (1.2)	1
Reproductive system and breast disorders	1 (2.5)	1	0	0
Epididymal tenderness	1 (2.5)	1	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.5)	1	0	0
Asthma	1 (2.5)	1	0	0
COPD	1 (2.5)	1	0	0

Applicant's Submission dated May 28, 2014, Table B-14.3.2.3.1

The Division also asked the Applicant to provide a list of subjects/events in the pivotal trial that required an Emergency Room visit due to hypocalcemia but were not coded as an SAE. The following is a list. All of these subjects have narratives below (except events that occurred during screening).

Table 28 Subjects in Natpara group in Trial 040 who required hypocalcemia-related ER visits

Subject	Timing of ER Visit
0002-0004	7 days after last dose—Day 174
0003-0001	Day 71 4 days after last dose—Day 178
1015-0003	Screening phase—Day 34
1020-0005	5 days after last dose—Day 176
2001-0001	Day 146
2001-0007	Day 133
6001-0009	Day 82
8002-0001	Day 125
8002-0008	8 days after last dose –Day 176

From Applicant's Submission dated June 6, 2014

Narratives

The following are narratives for the subjects in the Natpara group who had SAEs and AEs of special interest during treatment. Brief narratives for subjects who were discontinued due to AEs are in Section 6.1.3, but the narrative for Subject 4002-0003 is included here in order to include important details. ACSCa refers to albumin-corrected serum calcium.

Adverse events of special interest in this trial were limited to hypocalcemia (with PTs 'hypocalcemia and 'blood calcium increased'), hypercalcemia (PTs 'hypercalcemia and blood calcium increased'), and hypercalciuria (PTs' hypercalciuria' and 'urine calcium increased'). Investigators classified an AE as one of these three based on clinical symptoms and/or based on laboratory findings being deemed clinically significant. For example, an investigator could report an event of hypocalcemia based on symptoms alone or based on a lower than reference range albumin corrected serum calcium value that was deemed clinically significant (<8.4 mg/dL; normal range: 8.4 mg/dL to 10.6 mg/dL). The same is true for hypercalcemia and hypercalciuria, except the albumin corrected serum calcium value had to be >10.6 mg/dL and 24 hour urine calcium >300mg/dL.[11]

SAEs

Subject 0002-0002: This was a 52 year old woman with idiopathic hypoparathyroidism. She was initiated on Natpara 50 µg and 8 days later, her ACSCa was 10.7 mg/dL and the calcium supplement was decreased to 1000 mg from 2000 mg daily. One week later, Natpara was up-titrated to 75 µg and then again up-titrated to 100 µg approximately 2 weeks later. Several days later her ACSCa was 10.6 mg/dL and she requested that she be discontinued from the trial due to 'inability to attend all visits'. Her last dose of Natpara was given 6 days later. She came for an early termination visit 2 days later and her ACSCa level was 11.3 mg/dL. At that time she began taking calcitriol TDD 0.5 µg and calcium carbonate TDD 1500 mg. One day later she developed vomiting and epigastric pain. Several days later (7 days after the last dose of study drug), she numbness of her hand s and face was hospitalized with **hypercalcemia** and hypokalemia with an ACSCa level of 13.5 mg/dL and a potassium level of 2.3 mEql/L (normal range 3.5-5.1). She was treated medically and discharged with normal chemistry levels. At a follow-up visit several weeks later her calcium level was normal. It is more likely that the hypercalcemia was related to restarting her supplements rather than Natpara itself.

Subject 1007-0002: This was a 38 year old woman who was titrated up to Natpara 100 µg who developed **diverticulitis** approximately 16 weeks after starting study drug. The event resolved and was considered unrelated to Natpara.

[11] Explained in Applicant's Response to IR15, April 15, 2014

Subject 1007-0003: This was a 29 year old transgender female to male subject with idiopathic hypoparathyroidism. One week after being titrated up to 75 µg (32 days after drug was initiated), his calcium level was 12.5 mg/dL. Two days later study drug and calcium supplements were temporarily stopped. One day later the calcium level still increased to 14.2 mg/dL (8.-10.2). One day later it decreased to 12.2 mg/dL. He was admitted to the hospital with **hypercalcemia**, received normal saline intravenously, and was discharged. Several days later he was taking calcium TDD 750 mg with no calcitriol with a calcium level of 9.3 mg/dL. The event was considered resolved. His calcium supplement was increased to a TDD of 1500 mg and calcitriol was resumed at a TDD of 0.25 µg. The event was considered related to study drug. One day later, he experienced hypocalcemia with a calcium level of 8.2 mg/dL. Calcium as increased to a TDD of 2000 mg and calcitriol was increased to a TDD of 0.50 µg. Study drug was resumed the next day at the lower 50 µg dose; calcium was decreased to TDD 750 mg and calcitriol was stopped. Calcium supplements and calcitriol were further titrated during the remainder of the treatment period, and calcium was stopped altogether while maintaining normal calcium levels.

Subject 1008-0002: This was a 28 year old woman who had been up-titrated to Natpara 100 µg, which was maintained up until the last dose. Following the end of study visit she was to start calcitriol 0.25 µg and calcium carbonate TDD 3375 mg. The day after this visit, following taking calcitriol and calcium citrate 1000 mg, she developed tetany and tingling and was found to have **hypocalcemia** with a level of 7.8 mg/dL (8.9-10.1). She was hospitalized after not improving with an intravenous dose of calcium. Treatment was continued and she was discharged two days later without symptoms. This event was related to re-starting her supplements rather than study drug itself.

Subject 1009-0002: This was a 40 year old woman who was up-titrated to 75 µg, on which she remained for the remainder of the trial. Approximately 3 weeks after the last dose of study drug, she developed **gallstone pancreatitis**. She underwent surgery and recovered. The event was unrelated to study drug.

Subject 1010-0006: This was a 69 year old man with hypertension and a long history of tobacco use. Because of uncontrolled blood pressure, his anti-hypertensive drugs were modified during the optimization period. After approximately 12 weeks of receiving study drug, the study staff learned that this subject had a **cerebrovascular accident** and was unable to function independently. It does not appear that this event was related to study drug. This subject discontinued the trial.

Subject 1014-0005: This was a 26 year old woman who was up-titrated to Natpara 100 µg. She completed the treatment phase of the trial and was instructed to restart calcium citrate TDD 3000 mg and calcitriol TDD 1.0 µg. After multiple laboratory measurements indicating **hypocalcemia** as well as intermittent symptoms suggestive of it, she was admitted and given intravenous calcium. Upon discharge her daily doses were calcium 3600 mg and calcitriol 2.0 µg. This event was unrelated to study drug.

Subject 3001-0009: This was a 49 year old woman who was up-titrated to Natpara 100 µg. After receiving study drug for 121 days, she was admitted to the hospital with fever and abdominal pain. She was found to have **erysipelas** on her lower limb. She was treated and discharged. The event was considered unrelated to study drug.

Subject 8003-0004: This was a 60 year old woman who was up-titrated to Natpara 100 µg. She had a history significant for spine ventrofixation. Approximately 3 months after study drug was initiated, she was hospitalized with **back pain** which was treated medically. This was considered unrelated to study drug. Two days after completing study drug treatment, she was hospitalized for **diarrhea** and **vomiting**. The narrative states that she also had a non-serious event of hypocalcemia at this time which was treated with intravenous calcium.

Subject 1020-0005: This was a 31 year old woman who was up-titrated to Natpara 100 µg. After multiple reductions in supplements while taking study drug, 105 days after initiation of Natpara, subject reported that she had symptoms of **hypocalcemia**, Her calcium level at that time was 6.7 mg/dL and she was treated with intravenous calcium. Although she was discharged with a higher dose of an increased dose of calcium citrate, she reportedly returned to the ER with hypocalcemia (no calcium value) and was discharged on another increased dose of calcium citrate (3000 mg/day). She remained symptom-free for the remainder of the trial. The event was unrelated to the study drug. She had additional event of **hypocalcemia** upon completion of study drug and re-starting her supplements. This is also considered an AE of special interest.

AEs of Special Interest

Subject 0002-0004: This was a 35 year old woman with post-surgical hypoparathyroidism following thyroid surgery who was titrated up to 100 µg and completed the treatment phase of the trial. After the final dose, she was advised to take calcium citrate TDD 6000 mg and calcitriol TDD 1.0 µg. Approximately one week later, she developed tingling, numbness, and tetany. She was found to have **hypocalcemia** and her ACSCa level in the ER was 7.64 mg/dL. She was treated with intravenous calcium and calcitriol was increased to 0.75 µg in the morning and 0.50 µg in the evening. A follow-up calcium level was normal. This event was related to under-dosing calcitriol post-trial.

Subject 0003-0001: This was a 35 year old woman with primary hypoparathyroidism and was up-titrated to Natpara 100 µg. Approximately 8 weeks after study drug was initiated, calcium supplementation was discontinued. Approximately two weeks later she developed tingling and was found to have **hypocalcemia** (ACSCa=7.6 mg/dL) and hypomagnesemia. She was treated medically. She was restarted on calcium supplementation at 500 mg daily, which was then decreased to 250 mg. She was discharged and finished the treatment phase, and was restarted on calcitriol TDD 0.5 µg and calcium TDD 1000 mg. One day later she reported feeling unwell and she was

advised to increase calcium to 1500 mg. At that time her calcium level was 6.88 mg/dL. Because calcium did not normalize, her calcium was increased to 2000 mg and calcitriol as increased on 0.75 µg. Symptoms did not improve, and tin the ER her calcium level was 6.56 mg/dL. She was treated intravenously and although symptoms improved her calcium remained low. Her final follow-up calcium level was 7.6 mg/dL. This event was unrelated to study drug, but was related to re-starting her supplements.

Subject 1015-0003: This was a 34 year old woman who experienced tetany and **hypocalcemia** prior to randomization, as her calcium supplements were being decreased during optimization. This event was unrelated to study drug.

Subject 2001-0007: This was a 50 year old who was up-titrated to 75 µg and maintained at this dose. The subject experienced tetany and had **hypocalcemia** 133 days after starting study drug (approximately Week 19 of treatment). Her calcium level was 6.92 mg/dL. She received intravenous calcium and the event resolved.

Subject 6001-0009: This was a 53 year old woman who was up-titrated to Natpara 100 µg. She experienced tingling 81 days after initiating study drug which continued, leading her to be treated in the ER where she was found to have **hypocalcemia** with a calcium level of 6.6 mg/dL. She was treated with intravenous calcium. Several days later after discharge she remained hypocalcemic with a level of 7 mg/dL. It is unclear what actions were taken, but this subject completed the trial.

Subject 8002-0001: This was a 61 year old man who was up-titrated to Natpara 100 µg. At baseline, he required calcium TDD 3000 mg and alfacalcidol 2.0 µg/day. He was found to have **hypercalcemia** with a calcium value of 11 mg/dL (8.4-10.6) 56 days after initiating study drug. Calcium supplementation was interrupted and a repeat value several days later was 12.92 mg/dL. The subject received intravenous sodium chloride and the calcium normalized. The dose of study drug was down-titrated to 75 µg. Several days later the calcium level was 10.92 and the subject was instructed to not inject study drug. One day later Natpara was again down-titrated to 50 µg. Several days later the calcium value was 11.08 mg/dL. Over the next week the hypercalcemia resolved and the calcium was re-started to 1000 mg TDD two weeks later. This event was considered related to study drug. Several weeks later, 125 days after initiating study drug, he experienced numbness and was found to have **hypocalcemia** with a value of 5.76 mg/dL. He was given intravenous calcium and his calcium supplements were increased to 1500 mg. Six days later, he remained hypocalcemia was a value of 6.8 mg/dL and alfacalcidol 1.0 µg was initiated. Two weeks later the hypocalcemia was resolved. The subject completed the trial on Natpara 50 µg.

Subject 8002-0002: This was a 56 year old woman who was up-titrated to Natpara 100 µg. Approximately 12 weeks after study drug was initiated, her calcium level was 12.72 mg/dL and supplements were discontinued because of **hypercalcemia**. She received

intravenous sodium chloride and potassium. Study drug was stopped for 2 days and then down-titrated to 75 µg.

Subject 8002-0008: This was a 45 year old woman who was up-titrated to Natpara 100 µg. She completed the trial but then in the post-treatment phase experienced **hypocalcemia** requiring intravenous calcium.

Subject 2001-0001: This was a 25 year old woman who was up-titrated to Natpara 100 µg. At screening, this subject's TDD of calcium as 10,500 mg/day. Prior to the optimization phase of the trial, she had **hypocalcemia** 4 different times which required intravenous calcium (not included in narratives under SAEs because was pre-treatment). At approximately Week 20, her calcium level was 7.1 mg/dL (8.4-10.6) and her TDD of calcium was increased from 2250 mg to 2500 mg and her calcitriol dose was increased from 1.0 µg to 1.5 µg. One day alter, she had tetany and cramps and was admitted to the hospital with **hypocalcemia**, where she received intravenous calcium. Several days later, after discharge, her calcium value was 8.16 mg/dL. It is unclear why this subject became hypocalcemic towards the end of the trial, but clearly given her high baseline dose of calcium supplements, she required a higher dose during the trial. This patient had a strong tendency to develop hypocalcemia.

Discontinuations due to AEs
Subject 4002-0003: This was a 44 year old woman who was up-titrated to Natpara 75 µg. Approximately one month after study drug was initiated she experienced multiple non-serious AEs, including: headache, eye twitch, arthralgia, pain in extremities, depression, asthenia, reduced appetite, nausea, drowsiness and anxiety. Study drug was discontinued. She then was found to have hypercalcemia one day following Natpara discontinuation, with a calcium level of 11 mg/dL. All events were considered resolved approximately 2 weeks later. It is unclear which events, if any, were related to study drug.

7.3.3 Dropouts and/or Discontinuations

Discontinuations are discussed in Section 6.1.3 and 7.3.2 above.

7.3.4 Significant Adverse Events

In this program, AEs related to calcium were considered significant. These are discussed in 7.3.5.

7.3.5 Submission Specific Primary Safety Concerns

Hypocalcemia and hypercalcemia are major safety concerns for this drug and are discussed here. In the hypoparathyroid population, management of hypocalcemia while attempting to avoid hypercalciuria is a serious and daunting therapeutic challenge. Replacement of the deficient hormone, on the other hand, should not cause hypercalcemia, as hypercalcemia itself carries significant risks. Hypercalcemia also leads to worsening hypercalciuria, which ideally should improve or resolve with replacement of parathyroid hormone.

Because of these complicated issues, a number of analyses related to the effects of Natpara on calcium are discussed in this section

Trial 040

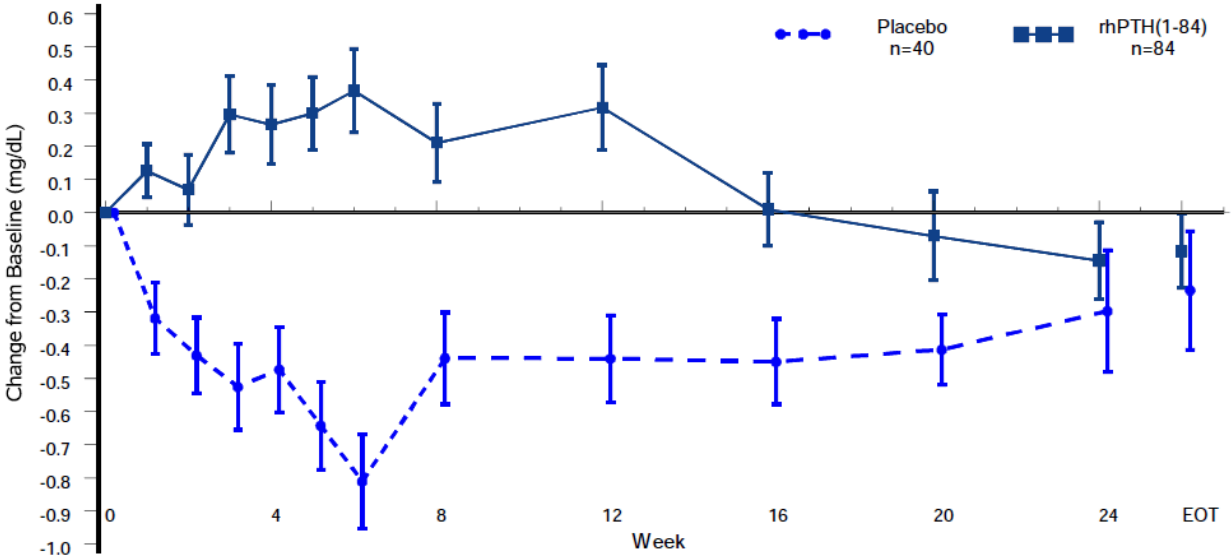
Albumin-Corrected Total Serum Calcium Concentration

This subsection analyzes changes in serum calcium levels by several different methods: mean changes, scatterplots of available data points, and incidence of both hypercalcemia and hypocalcemia according to specific levels. Most of these analyses were done by the Applicant in response to the Division's requests.

The Protocol guidelines included the goal of maintaining total serum calcium in the range of 8.0 to 9.0 mg/dL. Figure 26 depicts the mean changes in serum calcium over 24 weeks. As one would predict, with the immediate 50% reduction in active vitamin D metabolite/analog and introduction of study drug, the placebo group had a decrease in serum calcium. On the other hand, there was a trend toward increasing serum calcium values in the NPSP558 group.

Following Week 12, once the titration period was completed, mean calcium levels in the NPSP558 group trended back to baseline values. A trend toward baseline values was also observed in the placebo group.

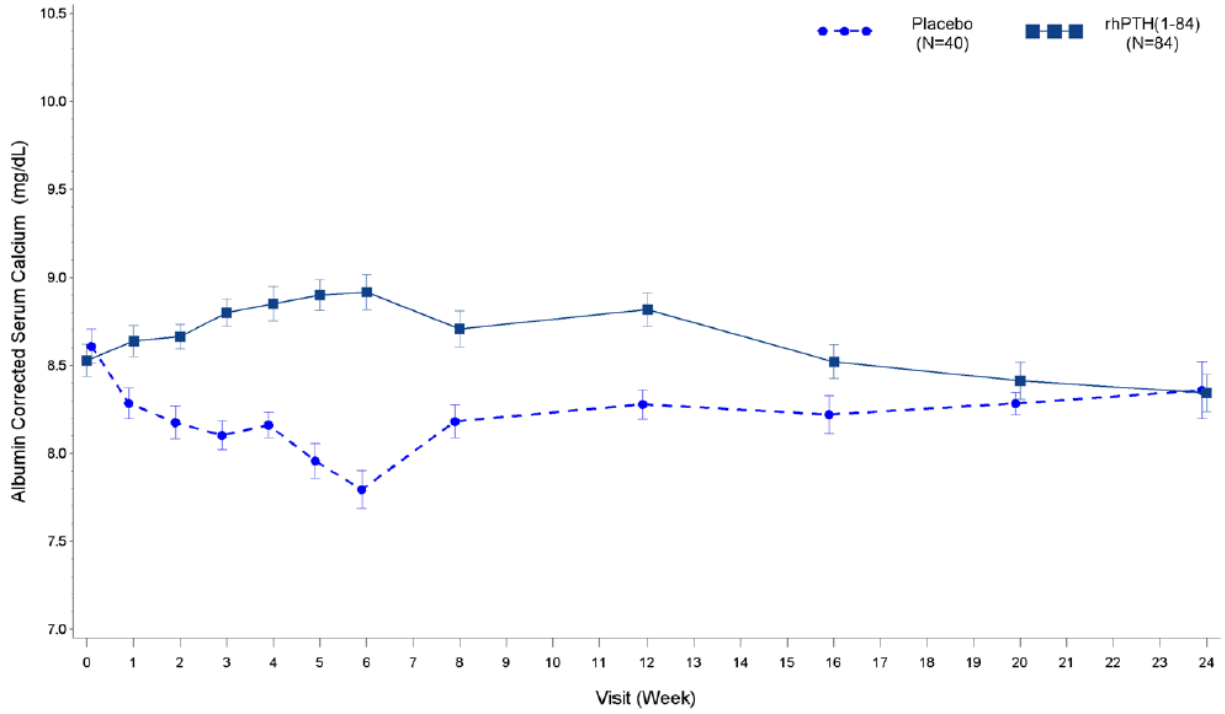
Figure 26 Mean (±SE) Change from Baseline in Albumin-corrected Total Serum Calcium—ITT Population



Applicant's Submission dated May 28, 2014, Figure B-14.2.4.1

Figure 27 depicts the actual mean values over time. In general, mean serum calcium values remained within the goal of 8.0 to 9.0 mg/dL.

Figure 27 Mean (±SE) of Albumin-corrected Total Serum Calcium –ITT Population, Excluding Site 1002



Applicant's Submission dated May 30, 2014, Figure 1-b

The table below summarizes the specific serum calcium data at baseline, Week, 24, and EOT.

Table 29 Analysis of Albumin-corrected Total Serum calcium Concentration—ITT Population, Excluding Site 1002

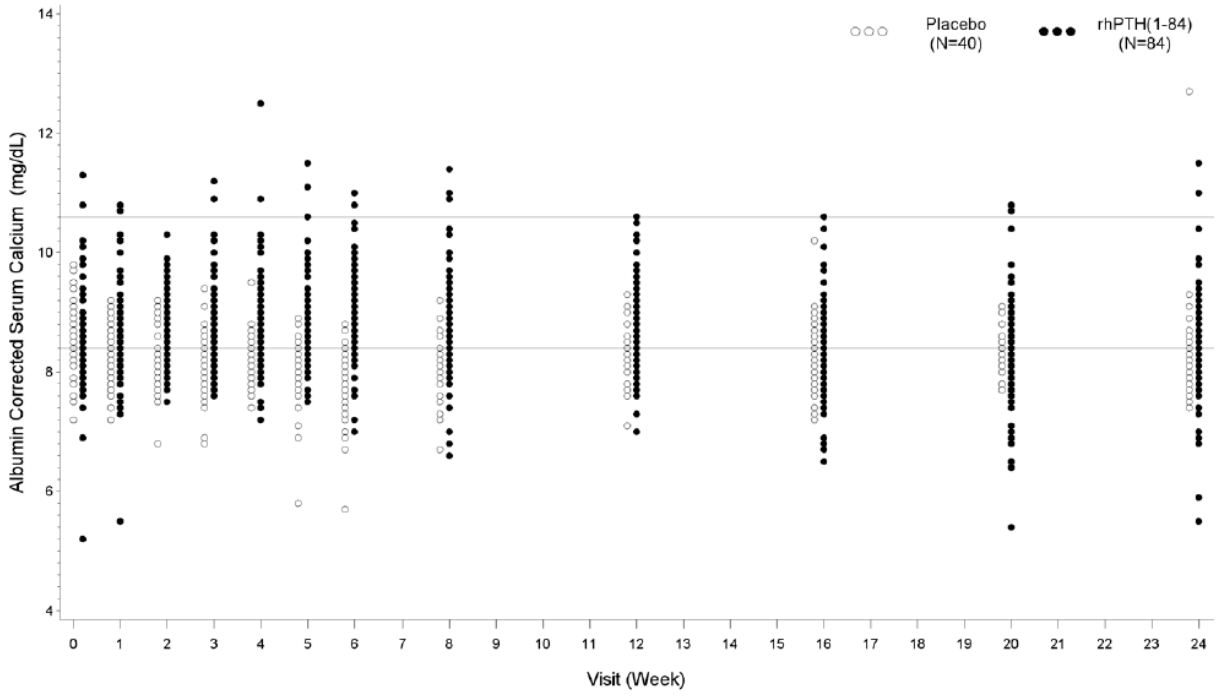
	Placebo N=40		NPSP558 N=84	
Visit	Actual Value (mg/24 hr)	Change from Baseline (mg/24 hr)	Actual Value (mg/24 hr)	Change from Baseline (mg/24 hr)
Baseline				
n	40		84	
Mean (SD)	8.6 (0.6)		8.5 (0.8)	
Median	8.6		8.5	
Min, Max	7.2, 9.8		5.2, 11.3	
Week 24				
n	33	33	78	78
Mean (SD)	8.4 (0.9)	-0.3 (1.2)	8.3 (0.9)	-0.1 (1.0)
Median	8.3	-0.4	8.3	-0.1
Min, Max	7.4, 12.7	-2.2, 4.1	5.5, 11.5	-2.6, 3.5
LS Mean (SE)[a]		-0.2 (0.1)		-0.2 (0.1)
95% CI[a]		-0.5, 0.1		-0.4, 0.0

EOT				
n	40	40	84	84
Mean (SD)	8.4 (0.9)	-0.2 (1.1)	8.4 (0.9)	-0.1 (1.0)
Median	8.3	-0.4	8.3	-0.1
Min, Max	7.1, 12.7	-2.4, 4.1	6.8, 11.5	-2.6, 3.5
LS Mean (SE)[a]		-0.2 (0.1)		-0.1 (0.1)
95% CI[a]		-0.5, 0.1		-0.3, 0.1

From Applicant's Submission dated May 28, 2014, Table B-14.2.3.8
[a]= Based on ANCOVA model with actual change as the dependent variable and the treatment as the factor and baseline 24-hour urine calcium excretion as the covariate.

Although the mean serum calcium levels are necessary in understanding results, it is equally important to understand the range of serum calcium levels observed in treated subjects. The figure below is a scatterplot of all serum calcium data points for the noted study visits for both groups. The two shaded horizontal lines represent the upper and lower limits of normal for serum calcium. In the placebo group, hypercalcemia was rarely observed. In the Natpara group, hypercalcemia and hypocalcemia was observed. Interestingly, the ranges are similar for Week 0 and Week 24 for the Natpara group.

Figure 28 Scatterplot of Albumin-corrected Serum Calcium (mg/dL) by Study Visit—ITT Population, Excluding Site 1002



From Applicant's Submission dated May 30, 2014, Figure 5b
ULN=10.6 mg/dL and lower limit of normal=8.4 mg/dL

The 5 lowest points in the figure above, all subjects in the Natpara group, are summarized in the following table:

Table 30 Subject characteristics with lowest recorded calcium values in Trial 040 (all subjects from Natpara group)

Subject ID	Visit (week)	Albumin corrected serum calcium (mg/dL)
6001-0002	0	5.2
6001-0002	1	5.5
6001-0002	24	5.5
6001-0005	24	5.9
6001-0009	20	5.4

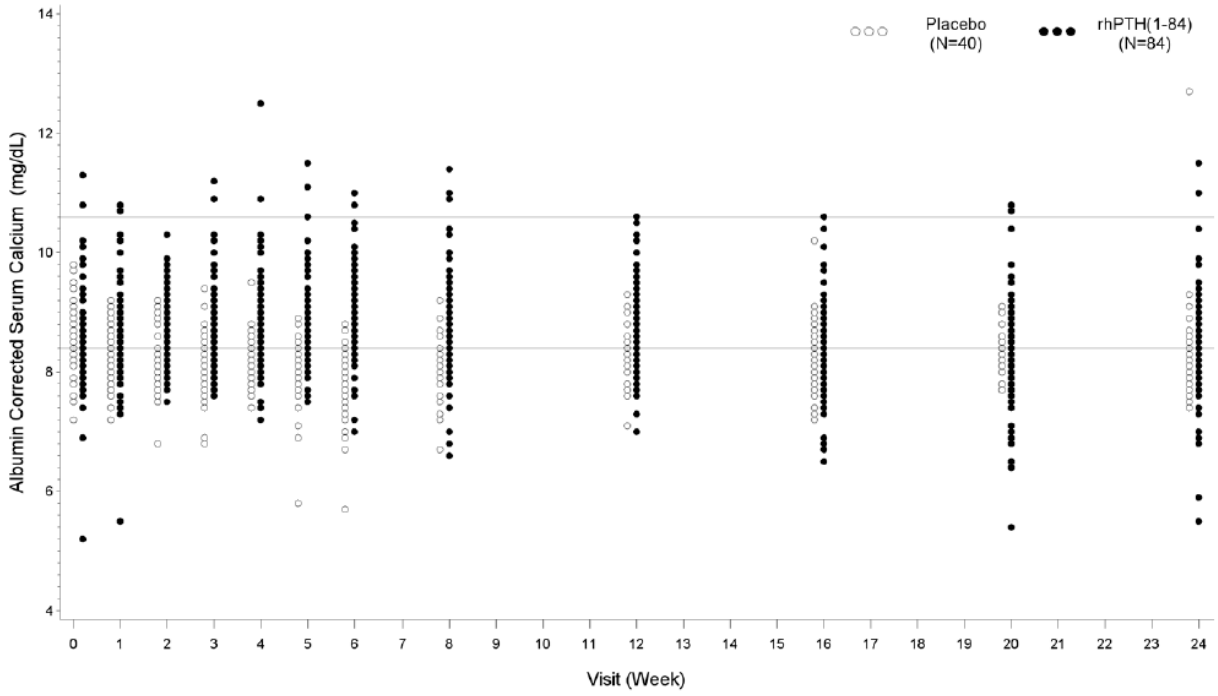
From Applicant's submission dated June 6, 2014

Here are brief narratives for the 3 Natpara subjects above:

- Subject 6001-0002: According to the Applicant, was not truly optimized before randomization. After up-titration of rhPTH(1-84) to 75 µg/d, the attempts to decrease calcium and active vitamin D resulted in hypocalcemia that resolved when supplements were increased again. This subject had three episodes of hypocalcemia (two during titration and one at the final visit).
- Subject 6001-0005: There was no clear explanation of hypocalcemia, since treatment and supplements doses were unchanged. AE of paresthesia was concomitant. This subject had been up-titrated to 100 µg.
- Subject 6001-0009: There was no clear explanation but was corrected with increased supplements. This subject had been up-titrated to 100 µg.

Similarly, the plot below represents all data points for phosphorus by trial visit. As expected, hyperphosphatemia was prevalent in both groups, particularly at baseline. This did not appear to change much by Week 24 in the Natpara group.

Figure 29 Scatterplot of Serum Phosphate (mg/dL) by Study Visit—ITT Population, Excluding Site 1002



From Applicant's Submission dated May 30, 2014, Figure 6b
ULN=4.8, LLN=2.4

Finally, the incidences of both hypercalcemia and hypocalcemia (from all available measured laboratory values) are summarized below by level of calcium (categories of hypercalcemia) and by study period. One would expect more abnormalities of both hyper- and hypocalcemia during the titration period and less during the maintenance period, when doses of Natpara were stable.

For hypercalcemia (Table 31), this was rarely observed in the placebo group. In the Natpara group, most measured hypercalcemia occurred during the titration period and there were no recorded values above 12 mg/dL in the maintenance period.

Table 31 Events (Number and Percentage) of Hypercalcemia—ITT Population, Excluding Site 1002

	Titration Period Weeks 0-12		Maintenance Period Week 12-24		Trial Duration Weeks 0-24	
Albumin-Corrected Serum Calcium	Placebo N=415 n (%)	rhPTH(1-84) N=871 n (%)	Placebo N=108 n (%)	rhPTH(1-84) N=291 n (%)	Placebo N=523 n (%)	rhPTH(1-84) N=1162 n (%)
>10.6 mg/dL	0	40 (4.6)	1 (0.9)	8 (2.7)	1 (0.2)	48 (4.1)
>10.6 and ≤11 mg/dL	0	24 (2.8)	0	6 (2.1)	0	30 (2.6)

>11 and ≤12 mg/dL	0	14 (1.6)	0	2 (0.7)	0	16 (1.4)
>12 and ≤13 mg/dL	0	2 (0.2)	1 (0.9)	0	1 (0.2)	2 (0.2)
>13 and ≤14 mg/dL	0	0	0	0	0	0
>14 mg/dL	0	0	0	0	0	0

From Applicant's Submission dated June 2, 2014, Table 1.1b
N is the total number of serum calcium tests performed during the respective study period in each treatment arm; n is the total number of serum calcium tests with a value that falls in one of the specified value categories during the respective study period in each treatment arm
Percentage is calculated as n/N. Baseline values were excluded from the analysis.

Hypocalcemia is a constant challenge in the hypoparathyroid population. In this analysis, it was not unexpected to observe more hypocalcemia values in the placebo group, particularly in the titration period. However, hypocalcemia was a problem in the Natpara group as well. During the maintenance period, there were a total of 16 measurements of calcium 7 mg/dL and below.

Table 32 Events (Number and Percentage) of Hypocalcemia-ITT Population

	Titration Period Weeks 0-12		**Maintenance Period Week 12-24**		**Trial Duration Weeks 0-24**	
Albumin-Corrected Serum Calcium	Placebo N=415 n (%)	rhPTH(1-84) N=871 n (%)	Placebo N=108 n (%)	rhPTH(1-84) N=291 n (%)	Placebo N=523 n (%)	rhPTH(1-84) N=1162 n (%)
<8.4 mg/dL	258 (62.2)	232 (26.6)	63 (58.3)	132 (45.4)	321 (61.4)	364 (31.3)
>8 and <8.4 mg/dL	90 (21.7)	96 (11)	26 (24.1)	44 (15.1)	116 (22.2)	140 (12)
>7 and ≤8 mg/dL	155 (37.3)	127 (14.6)	36 (33.3)	72 (24.7)	191 (36.5)	299 (17.1)
>6 and ≤7 mg/dL	11 (2.7)	8 (0.9)	1 (0.9)	13 (4.5)	12 (2.3)	21 (1.8)
>5 and ≤6 mg/dL	2 (0.5)	1 (0.1)	0	3 (1)	2 (0.4)	4 (0.3)
<5 mg/dL	0	0	0	0	0	0

From Applicant's Submission dated June 2, 2014, Table 1.2b
N is the total number of serum calcium tests performed during the respective study period in each treatment arm; n is the total number of serum calcium tests with a value that falls in one of the specified value categories during the respective study period in each treatment arm
Percentage is calculated as n/N. Baseline values were excluded from the analysis.

The analyses below use the number of subjects (rather than total available laboratory tests) as the denominator.

Table 33 Hypercalcemia Incidence—ITT Population, Excluding Site 1002

	Titration Period Weeks 0-12		**Maintenance Period Week 12-24**		**Trial Duration Weeks 0-24**	
Albumin-Corrected Serum Calcium	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)

>10.6 mg/dL	0	26 (31)	1 (2.5)	8 (9.5)	1 (2.5)	31 (36.9)
>10.6 and ≤11 mg/dL	0	19 (22.6)	0	6 (7.1)	0	23 (27.4)
>11 and ≤12 mg/dL	0	11 (13.1)	0	2 (2.4)	0	12 (14.3)
>12 and ≤13 mg/dL	0	2 (2.4)	1 (2.5)	0	1 (2.5)	2 (2.4)
>13 and ≤14 mg/dL	0	0	0	0	0	0
>14 mg/dL	0	0	0	0	0	0

From Applicant's Submission dated May 31, 2014, Table 5.1b
There are multiple scheduled lab tests for albumin-corrected serum calcium within each period. In each period, a subjects is counted only once at a given category, but could be counted at different categories. Percentages are based on the total number of subjects in each treatment group. Baseline values are excluded from analysis.

Table 34 Hypocalcemia Incidence—ITT Population, Excluding Site 1002

	Titration Period Weeks 0-12		**Maintenance Period Week 12-24**		**Trial Duration Weeks 0-24**	
Albumin-Corrected Serum Calcium	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)	Placebo N=40 n (%)	rhPTH(1-84) N=84 n (%)
<8.4 mg/dL	39 (97.5)	67 (79.8)	30 (75)	60 (71.4)	40 (100)	75 (89.3)
>8 and <8.4 mg/dL	35 (87.5)	55 (65.5)	22 (55)	34 (40.5)	37 (92.5)	64 (76.2)
>7 and ≤8 mg/dL	36 (90)	50 (59.5)	18 (45)	49 (58.3)	36 (90)	69 (82.1)
>6 and ≤7 mg/dL	8 (20)	7 (8.3)	1 (2.5)	10 (11.9)	9 (22.5)	14 (16.)
>5 and ≤6 mg/dL	1 (2.5)	1 (1.2)	0	3 (3.6)	1 (2.5)	3 (3.6)
<5 mg/dL	0	0	0	0	0	0

From Applicant's Submission dated May 31, 2014, Table 5.2b
There are multiple scheduled lab tests for albumin-corrected serum calcium within each period. In each period, a subjects is counted only once at a given category, but could be counted at different categories. Percentages are based on the total number of subjects in each treatment group. Baseline values are excluded from analysis.

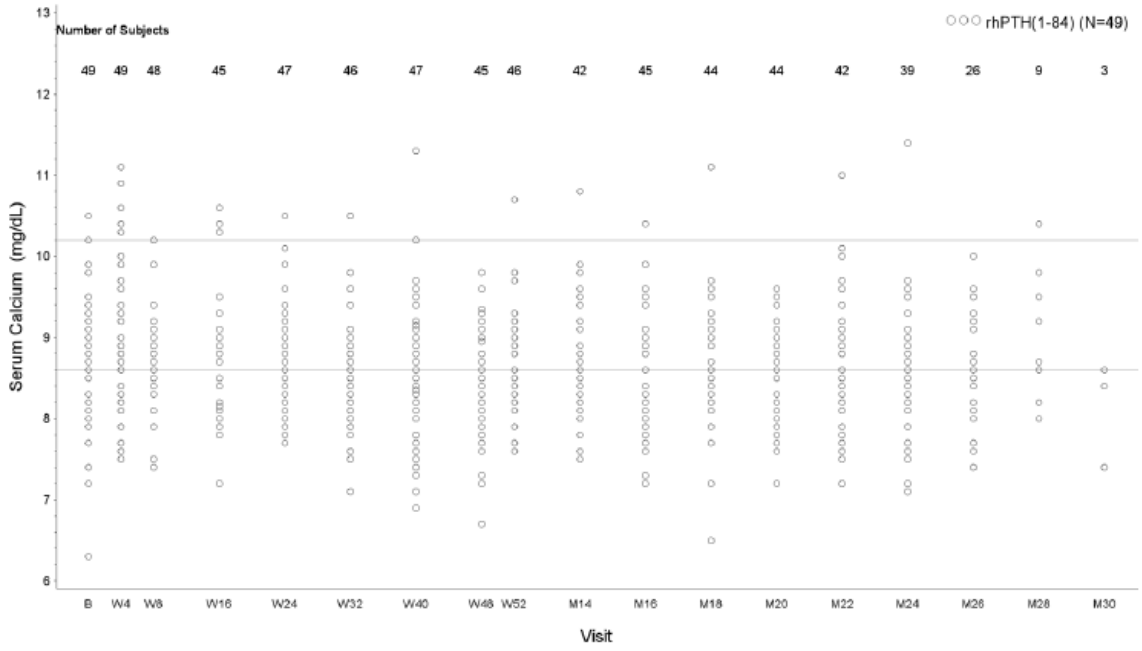
Trial 008

Given the nature of the trial design, the focus in this Review is on calcium-related events. Overall:

- Hypocalcemia was observed in 15 (30.6%) subjects (total of 26 events).
- Hypercalcemia was observed in 5 (10.2%) subjects (total of 7 events).
- Hypercalciuria was observed in 4 (8.2%) subjects (total of 7 events).

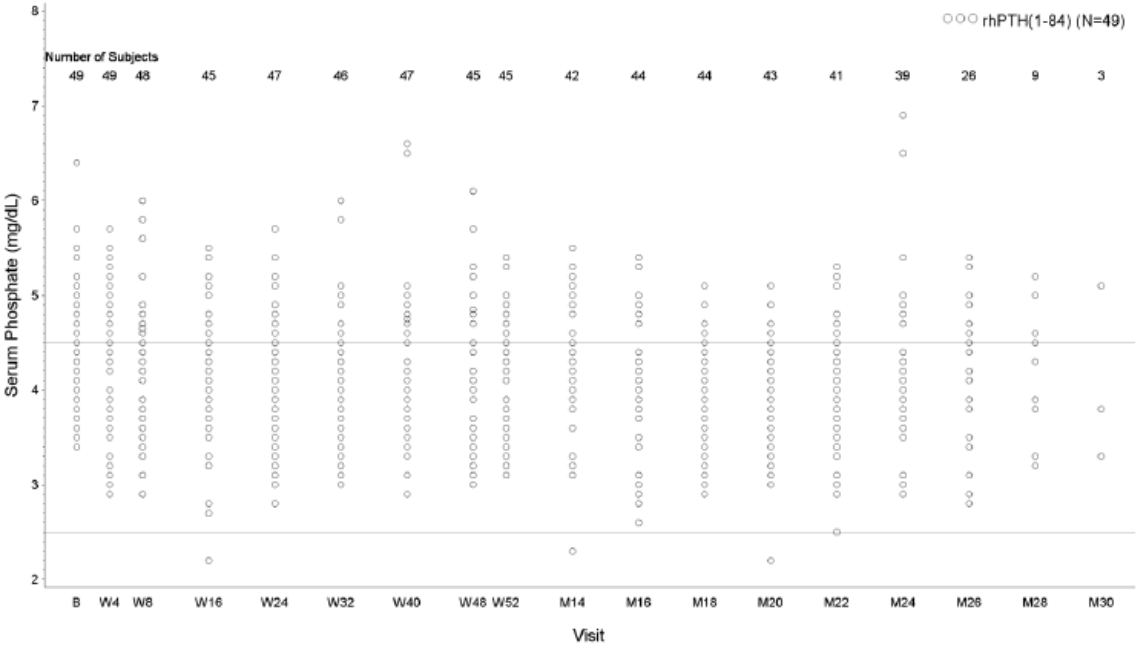
The following are scatterplots of serum calcium, serum phosphorus, and urinary calcium, requested by the Division and submitted by the Applicant. By the end of the extension period, there are few subjects with these measurements.

Figure 30 Scatterplot of Serum Calcium (mg/dL) by Visit—ITT Population, Excluding Site 1002



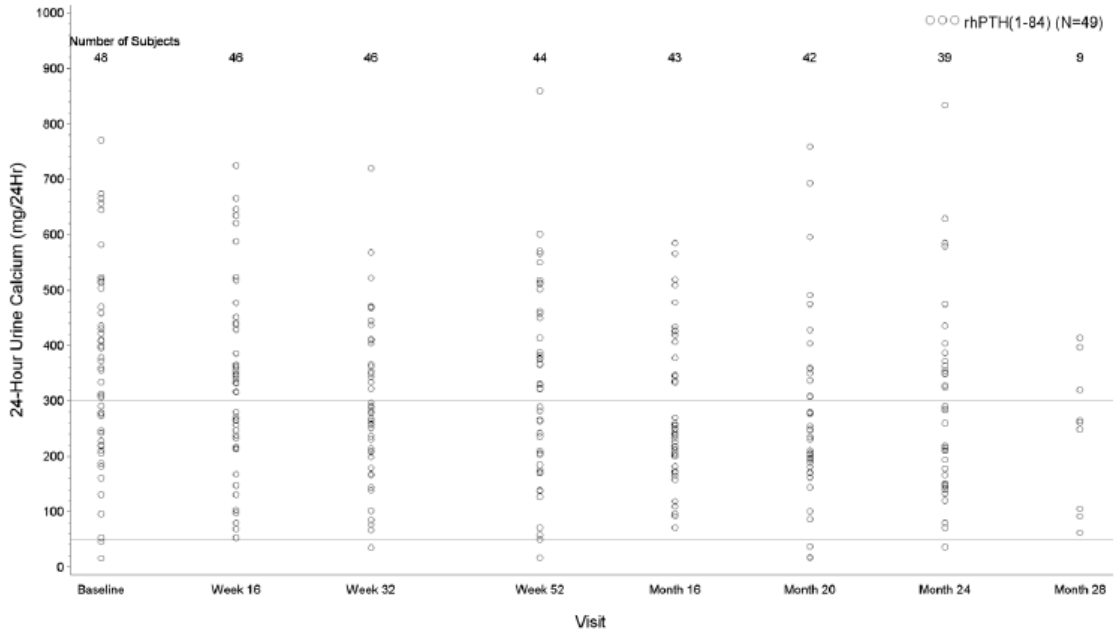
Upper Limit of Normal = 10.2 mg/dL, Lower Limit of Normal = 8.6 mg/dL

Figure 31 Scatterplot of Serum Phosphate (mg/dL) by Visit—ITT Population, Excluding Site 1002



Upper Limit of Normal = 4.5 mg/dL, Lower Limit of Normal = 2.5 mg/dL

Figure 32 Scatterplot of 24-hour Urinary Calcium, (mg/24h) by Visit—ITT Population, Excluding Site 1002



Upper Limit of Normal = 300 mg/24Hr, Lower Limit of Normal = 50 mg/24Hr

The following table summarizes subjects with normal or abnormal urine calcium by time. By Week 52, there was a slight increase in the percentage of subjects with normal urinary calcium. By Month 28, the number of subjects with measurements decreased sharply.

Table 35 Number (%) of Subjects with Normal of Abnormal Urine Calcium Values (mg/24 hr) by Visit—Safety Population, Excluding Site 1002

	rhPTH (1-84) N=49		
Visit	m	Normal (≤300) n (%)	Abnormal (>300) n (%)
Baseline	48	19 (39.6)	29 (60.4)
Week 16	46	19 (41.3)	27 (58.7)
Week 32	46	28 (60.9)	18 (39.1)
Week 52	44	20 (45.5)	24 (54.5)
Month 16	43	27 (62.8)	17 (37.2)
Month 20	42	28 (66.7)	14 (33.3)
Month 24	39	24 (61.5)	15 (38.5)
Month 28	9	6 (66.7)	3 (33.3)

m is the number of subjects with 24-hour urine calcium excretion tested at each visit

Trial 007

For this trial, the Applicant combined terms hypocalcemia, hypercalcemia, and hypercalciuria with blood calcium increased, blood calcium decreased, and urine

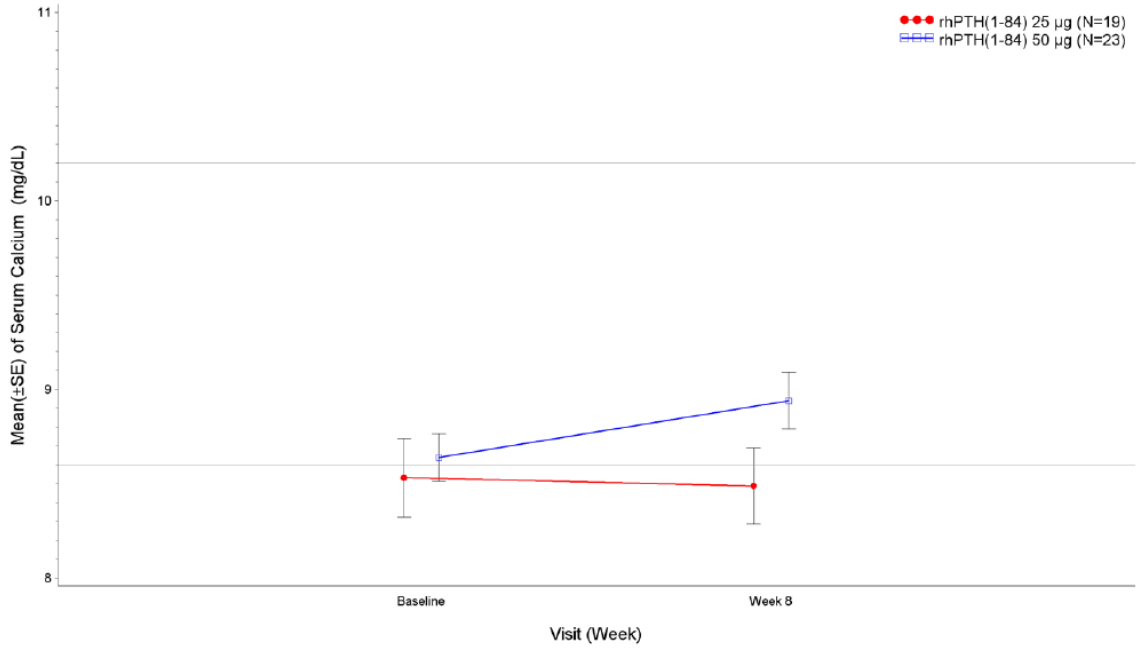
calcium decreased. Based on this, 3 subjects in the 25 µg group and 3 subjects in the 50 µg group experienced such an event during the treatment period.

In the 25 µg group, there was one subject with hypocalcemia and two subjects with hypercalcemia, one noted as severe (Subject 1007-0006). This one subject was a 60 year old woman who had a baseline calcium level of 9.3 mg/dL who had severe hypercalcemia at Week 4 (maximum value of 12.3 mg/dL). She experienced no symptoms. Calcium supplementation was discontinued and study drug was interrupted on Days 30 through 32. Serum calcium returned to normal and study drug was resumed with a calcium level of 10.8 mg/dL at Week 8.

In the 50 µg group, there was one subject with hypercalcemia, one with hypocalcemia, and one with hypercalciuria.

The figure below depicts the mean change in calcium levels for both groups. The 50 µg group remained close to the lower limit of normal, while the 25 µg group was just below or at the lower limit.

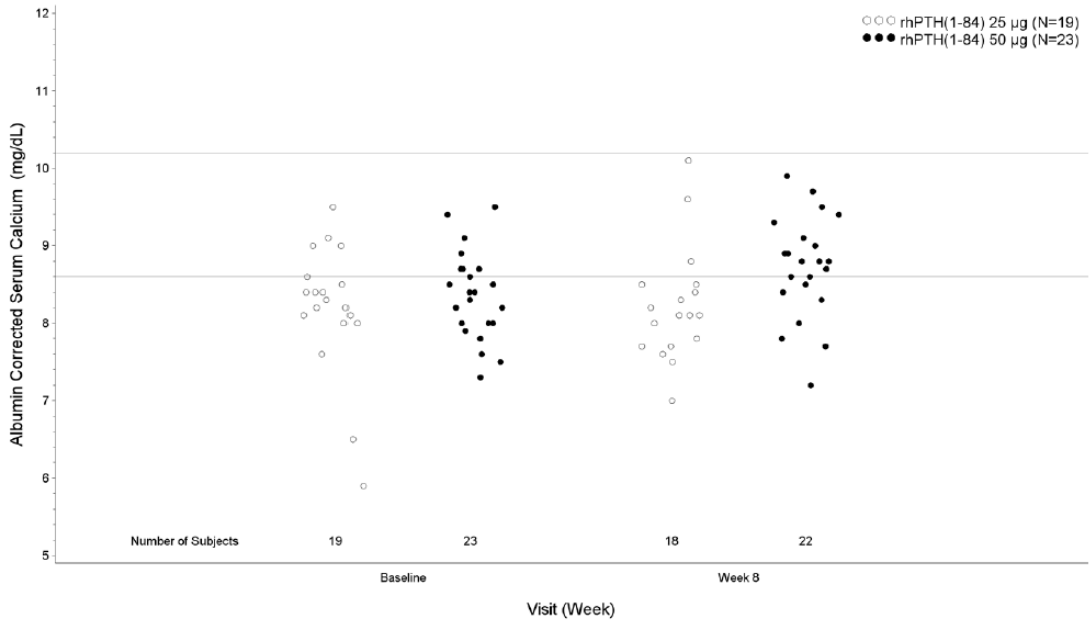
Figure 33 Mean (±SE) of Serum Calcium (mg/dL) by Visit for Trial 007, Excluding Site 1002



From Applicant's Submission dated June 2, 2014, Figure 1b

The figure below is a scatterplot of serum calcium at baseline and at Week 8 for both dose groups. Consistent with the figure above, there is a tendency for more hypocalcemia in the lower dose group at Week 8.

Figure 34 Scatterplot of Albumin-corrected Serum Calcium (mg/dL) at baseline and at Week 8-ITT Population, Excluding Site 1002



From Applicant's Submission dated June 2, 2014, Figure 2b

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

The table below summarizes treatment-emergent AEs by PT that occurred in greater than 4% of the study drug group and were more frequent compared to placebo, during the titration and maintenance phases (does not include post-treatment, where AEs related to the discontinuation of drug were observed). Laboratory-related AEs included below, such as hypocalcemia, were only those reported as AEs. Therefore the table below is only one piece in understanding the occurrence of calcium-related events.

Adverse events were frequent in both groups, but overall were more frequent in the placebo group. Hypercalcemia was observed in 16.7% of the NPSP558 group and in 2.5% of the placebo group.

Table 36 Summary of Adverse Events in >4% and greater in NPSP558 group compared to placebo, in decreasing order of frequency—Safety Population, Excluding Site 1002

	Placebo		NPSP558	
Preferred Term	Subjects N=40 n (%)	Events	Subjects N=84 n (%)	Events
Any TEAE>4%				
No	6 (15)		20 (23.8)	
Yes	34 (85)	142	64 (76.2)	438
Paresthesia	10 (25)	14	26 (31)	54
Headache	9 (22.5)	17	21 (25)	53
Hypocalcemia	8 (20)	8	21 (25)	34
Nausea	7 (17.5)	8	15 (17.9)	33
Hypercalcemia	1 (2.5)	1	14 (16.7)	17
Hypoesthesia	4 (10)	5	12 (14.3)	18
Diarrhea	1 (2.5)	1	10 (11.9)	13
Vomiting	0	0	10 (11.9)	12
Arthralgia	4 (10)	4	9 (10.7)	16
Pain in Extremity	3 (7.5)	3	8 (9.5)	11
URI	2 (5)	2	7 (8.3)	7
Sinusitis	2 (5)	2	6 (7.1)	6
Hypercalciuria	1 (2.5)	1	6 (7.1)	7
Neck Pain	1 (2.5)	1	5 (6)	5
Hypertension	2 (5)	2	5 (6)	5
Blood 25-Hydroxycholecalciferol decreased	1 (2.5)	1	5 (6)	5
Facial Hypoesthesia	1 (2.5)	1	5 (6)	5
Peripheral Edema	1 (2.5)	1	4 (4.8)	4
Thirst	0	0	4 (4.8)	5
Anxiety	0	0	4 (4.8)	4

From Applicant's Response to Information Request dated June 23, 2014
GERD=gastroesophageal reflux disease
URI=urinary tract infection

The following tables summarize the AE data using the same cutoff criteria, but organized by titration and maintenance phases.

Hypocalcemia was not more frequent in the NPSP558 group during the titration phase. This is an expected finding given that the placebo group was subjects to protocol-driven decreases in supplements.

Table 37 Summary of Adverse Events in >4% and greater in NPSP558 group compared to placebo, in decreasing order of frequency for titration phase only—Safety Population, Excluding Site 1002

	Placebo		NPSP558	
	Subjects N=40		Subjects N=84	

Preferred Term	n (%)	Events	n (%)	Events
Any TEAE>4%				
No	8 (20)		28 (33.3)	
Yes	32 (80)	105	56 (66.7)	274
Headache	9 (22.5)	16	19 (22.6)	44
Paresthesia	8 (20)	11	18 (21.4)	33
Hypoesthesia	4 (10)	5	10 (11.9)	13
Hypercalcemia	1 (2.5)	1	10 (11.9)	11
Tetany	3 (7.5)	12	8 (9.5)	13
Arthralgia	2 (5)	2	6 (7.1)	13
URI	2 (5)	2	6 (7.1)	6
Pain in Extremity	2 (5)	2	5 (6)	7
Sinusitis	0	0	5 (6)	5
Hypercalciuria	1 (2.5)	1	5 (6)	5
Upper Abdominal Pain	1 (2.5)	1	4 (4.8)	6
Diarrhea	1 (2.5)	1	4 (4.8)	4
Neck Pain	1 (2.5)	1	4 (4.8)	4

From Applicant's Submission dated June 9, 2014, Table 7.1b

However, hypocalcemia was recorded in the NPSP558 group during the maintenance phase, presumably once placebo subjects were receiving their baseline supplements.

Table 38 Summary of Adverse Events in >4% and greater in NPSP558 group compared to placebo, in decreasing order of frequency for maintenance phase only—Safety Population, Excluding Site 1002

	Placebo		NPSP558	
Preferred Term	Subjects N=40 n (%)	Events	Subjects N=84 n (%)	Events
Any TEAE>4%				
No	28 (75.7)		40 (49.4)	
Yes	9 (24.3)	12	41 (50.6)	87
Hypocalcemia	2 (5.4)	2	17 (21)	22
Paresthesia	3 (8.1)	3	13 (16)	21
Muscle Spasms	4 (10.8)	5	9 (11.1)	11
Diarrhea	0	0	8 (9.9)	9
Hypercalcemia	0	0	6 (7.4)	6
Headache	1 (2.7)	1	6 (7.4)	9
Vomiting	0	0	4 (4.9)	5

From Applicant's Submission dated June 9, 2014, Table 7.1b

Trial 007

Since this trial compared two doses, below is a summary of AEs in at least 10% of subjects in either treatment group. There were few events and did not appear to be more frequent in the higher dose group.

Table 39 Treatment-emergent Adverse Events Occurring in ≥ 10% of Subjects in Either Treatment Group, Excluding Site 1002

	NPSP558 25 µg N=23		NPSP558 50 µg N=24	
	n (%)	events	n (%)	events
Paresthesia	4 (21.1)	8	5 (21.7)	6
Headache	1 (5.3)	1	3 (13)	3
Nausea	2 (10.5)	2	3 (13)	4
Fatigue	3 (13)	5	2 (8.3)	2
Arthralgia	2 (10.5)	3	1 (4.3)	1
Muscle spasms	3 (15.8)	5	3 (13)	4
Hypercalcemia	2 (10.5)	2	1 (4.3)	1
Pollakiuria	2 (10.5)	2	1 (4.3)	1

Applicant's Submission to FDA dated June 5, 2014, Table B-14.3.1.1.3

7.4.2 Laboratory Findings

This section does not include any discussion of calcium. Table 42 summarizes laboratory evaluations for safety in the pivotal trial.

Table 40 Safety Laboratory Evaluations for the Pivotal Trial

Hematology	Biochemistry	Urine Measurements
Hemoglobin, hematocrit, platelets, WBC	Sodium potassium, chloride, magnesium, glucose, phosphate, calcium, 25-hydroxyvitamin D, serum 1,25-hydroxyvitamin D, acid phosphatase, ALT, AST, alkaline phosphatase, amylase, LDH, lipase, total bilirubin, BUN, CO2, cholesterol, CPK, creatinine, lactic acid, total protein, triglycerides, uric acid, TSH, t4, bone turnover markers, PTH antibodies, pregnancy test, serum PTH (1-84)	Pregnancy test, urinalysis, 24-hour creatinine clearance, 24-hour calcium, 24-hour phosphate, 24-hour sodium

Because it plays a vital role in the disease as well as the treatment of hypoparathyroidism, data regarding changes in vitamin D are shown first.

Serum 1,25-Dihydroxyvitamin D and Serum 25-Hydroxyvitamin D

Serum 1,25 vitamin D levels changed minimally in both groups by Week 24, even in the face of decreasing vitamin D analogs in the NPSP558 group. The mean 25(OH) vitamin D level also decreased in both groups; however, the decrease was markedly steeper in

the NPSP558 group. At Week 24, the change from baseline in mean serum 25(OH) vitamin D levels was -11.23 (±19.02) ng/mL in the NPSP558 group compared to -1.38 (±13.15) ng/mL in the placebo group. The Applicant explains this decrease by the PTH-induced conversion of 25(OH) vitamin D into 1,25-dihydroxyvitamin D.

Table 41 Summary of Serum 1,25-Dihydroxyvitamin D and Serum 25-Hydroxyvitamin D by Visit—Safety Population

	Placebo N=40		NPSP558 N=84	
Parameter (Unit) Visit	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Serum 1,25-dihydroxyvitamin D (pg/mL)				
Baseline				
n	40		82	
mean (SD)	32.7 (11.5)		33.7 (21.2)	
median	30		30	
min, max	14, 61		8, 148	
Week 24				
n	28	28	71	70
mean (SD)	33.6 (18.8)	-0.3 (17.3)	33 (12.9)	1 (20)
median	28	-1.0	33	1
min, max	8, 95	-27, 46	9, 60	-75, 46
EOT				
n	35	35	80	78
mean (SD)	31.9 (17.5)	-1.8 (16.4)	32.4 (12.8)	-1 (22.7)
median	28	-4	32.5	0.5
min, max	8, 95	-27, 46	9, 60	-97, 46
Serum 25-hydroxyvitamin D (ng/mL)				
Baseline				
n	40		84	
mean (SD)	44.5 (19)		42.3 (14.8)	
median	38		38.5	
min, max	25, 104		11, 109	
Week 24				
n	31	31	78	78
mean (SD)	42.6 (14.2)	-1.3 (13.5)	32.6 (11.4)	-10 (15.7)
median	40	3	29	-10
min, max	17, 78	-41, 18	18, 82	-82, 46
EOT				
n	40	40	84	84
mean (SD)	41.8 (13)	-2.7 (14.6)	32.4 (11.1)	-9.8 (15.3)
median	39	2	29	-9.5
min, max	17, 78	-51, 18	18, 82	-82, 46

Applicant's Submission dated May 28, 2014 Table B-14.3.6

Markedly Abnormal Values

Table 42 and Table 43 summarize markedly abnormal parameters for clinical chemistry and hematology, respectively. Criteria for markedly abnormal values are in the Appendix. Abnormal phosphorus (high) values were more frequent in the NPSP558 group.

In the NPSP558 group, 10 of the 15 subjects with markedly abnormal chemistry values had abnormally high phosphorus. Three subjects had high triglyceride levels ranging from 642 to 1115 mg/dL (ULN: 203 mg/dL).

Table 42 Summary of Markedly Abnormal Post-baseline Laboratory values—Clinical Chemistry—Safety Population

Laboratory Parameter	Placebo N=40 n/m (%)	NPSP558 N=84 n/m (%)
Subjects with at least one abnormal value	8/40 (20)	14/84 (16.7)
Alkaline phosphatase	0/44	1/87 (1.2)
AST	1/40 (2.5)	0/87
BUN	3/40 (7.5)	3/82 (3.7)
Phosphorus	3/40 (7.5)	9/84 (10.7)
Triglycerides	1/40 (2.5)	3/82 (3.7)
Uric Acid	0/44	3/82 (3.7)

Applicant's Submission dated May 28, 2014 Table B-14.3.3.1.2

All 3 subjects with elevated TG levels had values above normal at baseline which worsened during the trial. The following are brief summaries of these subjects:

- The first subject, who had a history of diabetes and hyperlipidemia, had a TG value of 1115 mg/dL (ULN: 203 mg/dL) after 98 days of Natpara exposure. His liver enzymes were elevated on the same day (ALT 161 U/L, AST 188 U/L, and LDH 340 U/L). TG levels and liver tests returned to baseline levels by the end of the trial. He was considered a responder in the trial.
- The second subject was overweight and had a TG value of 642 mg/dL at Week 24. In the middle of the trial he was also diagnosed with gout, which the Applicant asserts is related to the hypertriglyceridemia. Follow-up TH data on this patient is not provided. He was a non-responder in the trial.
- The third subjects had a TG value of 659 mg/L at Week 24 without follow-up levels. He was considered a non-responder in the trial.

Three subjects in the NPSP558 group had a markedly abnormal WBC count: 2 subjects with low WBC counts of 2.5 and 2.8 x 19^9/L and one subjects with an abnormally high value (20 x 10^9/L).

Table 43 Summary of Markedly Abnormal Post-baseline Laboratory values—Hematology—Safety Population

	Placebo	NPSP558

Laboratory Parameter	N=40 n/m (%)	N=84 n/m (%)
Subjects with at least one abnormal value	2/38 (5.3)	3/79 (3.8)
Hematocrit	2/38 (5.3)	0/84
Neutrophils	0/41	1/78 (1.3)
WBC count	0/42	3/79 (3.8)

Applicant's Submission dated May 28, 2014 Table B-14.3.3.1.1
N=number of subjects with at least one abnormal value and m=number of subjects who have valid measurements at any post-baseline visit

The following are narratives for the 3 subjects with abnormal WBC values:

- The first subject, with a screening WBC level of 12 x 10^9/L had a high WBC count of 20 x 10^9/L at Week 24. At this same, she had developed diarrhea and vomiting, and the elevated value was thought to be related. She was a responder in the trial and had a normal WBC level when she later participated in Study 009.
- The second subject had a normal WBC count at screening but a count of 2.8 x 10^9/L at Week 24. The Investigator believes this was related to treatment with meloxicam, an NSAID for a sprained ligament, which can rarely cause a decrease in WBCs. Additional data showed a return to normal WBC levels with continuing Natpara treatment.
- The third subject had a normal WBC count at screening and law WBC count of 2.5 x 10^9/L at Week 24. She continued onto Study 007 where her WBC levels were normal. The cause of the transient, low level is unclear. She was a non-responder in the trial.

Change in Mean Values

Table 44 and Table 45 below summarize mean changes from baseline for hematology and chemistry parameters. There were no clinically meaningful changes in hematology parameters.

Table 44 Change from Baseline to Week 24 According to Hematology Parameter and Treatment Group Excluding Site 1002

Parameter	Placebo N=40	NPSP558 N=84
Hematocrit (%)	0±0.02 0 (-0.04, 0.03)	0±0.03 0 (-0.07, 0.12)
Hemoglobin (g/L)	-2.1±6 -2 (-12,11)	-2.6±9.72 -2.5 (-27, 40)
WBC count (10^9/L)	-0.08±2.2 -0.1(-6.8, 4)	-0.41±2.4 -0.5 (-8, 8.1)
Platelet count (10^9/L)	2.3±70.4 4.5 (-245, 229)	-2.7±36.1 -4 (-85, 86)

Plus-minus values are mean±SD; values with parentheses are median (min, max)
Applicant's Submission dated May 28, 2014 Table B-14.3.3.2.1

Table 45 Change from Baseline to Week 24 According to Biochemistry Parameter and Treatment Group, Excluding Site 1002

Parameter	Placebo N=40	NPSP558 N=84
ALT (U/L)	-2.1±11.9 -2 (-38, 30)	-1.3±16.5 -1 (-118, 47)
AST (U/L)	-1.5±7.9 0 (-29, 19)	0.3±6.8 0 (-28, 29)
Total bilirubin (mg/dL)	0.09±0.25 0.08 (-0.4, 1.1)	-0.01±0.14 0 (-0.5, 0.4)
CPK (U/L)	-75.8±452 15 (-2576, 128)	-7.1±62.6 -10 (-258, 197)
Magnesium	-0.04±0.20 -0.07 (-0.44, 0.36)	-0.26±0.22 -0.24 (-1.09, 0.22)
phosphorus	-0.04±0.66 0 (-1.5, 1.2)	-0.48±0.80 -0.50 (-2.6, 2.2)
potassium	0.01±0.3 (-1.1, 0.6)	0.05±0.32 0.10 (-0.9, 1.1)
sodium	0.5±1.5 1 (-2, 3)	-0.27±1.6 -0.12 (-6, 5)
TSH	0.97±2.3 0.6 (-3.36, 7.41)	-0.60±4.12 -0.16 (-33.89, 6.28)

Plus-minus values are mean±SD; values with parentheses are median (min, max)
Applicant's Submission dated May 28, 2014 Table B-14.3.3.2.1

Changes in lipid parameters were unremarkable.

7.4.3 Vital Signs

Overall, mean values of vital signs during the trial were unremarkable in both groups.

Table 46 summarizes the markedly abnormal vital signs during the pivotal trial. The criteria are including in the table. Overall, there were few subjects with observed abnormalities. There was one subject with 7 separate incidences of hypotension. He was a 46 year old man with hypertension on enalapril 20 mg daily. Although his baseline BP was normal, BP was low (lowest 80/55) on multiple visits beginning with Visit 12. Enalapril was reduced to 10 mg daily. It is notable that he also had repeated low calcium measurements (with symptoms). He was a non-responder in the trial.

Table 46 Summary of Post-baseline Abnormal Vital Sign Results, Excluding Site 1002

Parameter (unit)	Placebo N=40 n/m (%)	NPSP558 N=84 n/m (%)
Sitting systolic blood pressure (mmHg)		
Decrease from baseline of ≥20 to a value ≤90	1/40 (2.5)	1/84 (1.2)
Increase from baseline of ≥20 to a value ≥180	0/40	1/84 (1.2)

Sitting diastolic blood pressure (mmHg) Decrease from baseline of ≥15 to a value ≤50 Increase from baseline of ≥15 to a value ≥105	 1/40 (2.5) 0/44	 1/84 (1.2) 0/84
Sitting pulse rate (beats/min) Decrease from baseline of ≥15 to a value ≤50 Increase from baseline of ≥15 to a value ≥105	 1/40 (2.5) 0/40	 1/84 (1.2) 0/84
Temperature (C) Value ≥38.3ºC and ≥0.8ºC increase from baseline	 0/40	 0/90

Applicant's Submission dated May 28, 2014, Table B-14.3.5.2

7.4.4 Electrocardiograms (ECGs)

Two of 80 subjects in to the NPSP558 group had clinically significant abnormal ECG findings at Week 24, based on investigator and/or central ECG reader assessment (both had first degree AV block). There was one subject in the placebo group who had clinically significant ECG findings at Week 2 and at Week 6 (ectopic supraventricular rhythm).

Clinically significant abnormal QT results were observed more frequently in the placebo group and are not detailed here.

The Division consulted the QT Interdisciplinary Review Team for input regarding QT results. The Team has previously recommended that the Applicant summarize QT and other cardiovascular safety data from clinical trials rather than conduct a specific QT study. Conclusions from the team were:

- The best data were obtained in the pivotal trial and this trial ruled out clinically relevant effects on vital signs as well as PR and QRS intervals.
- QTc declined by about 10 ms, paralleling the rise in calcium that was observed. This is not clinically relevant.
- The other trials also showed no concerning signals.
- Overall, Natpara has a reassuring cardiovascular safety profile.

7.4.5 Special Safety Studies/Clinical Trials

None

7.4.6 Immunogenicity

Refer to Dr. Puig's Review for details of this program's complicated immunogenicity program. This section covers immunogenicity results for all trials, including extensions, in this program and includes data from the 4-month safety update.

Because rhPTH(1-84) is a therapeutic protein, there is potential to develop anti-rhPTH antibodies (anti-drug antibodies, or ADA). These could lead to neutralization of native PTH or other potentially homologous proteins. Neutralizing antibody (Nab) can also lead to decreased drug efficacy.

As reference, 3-5% of subjects were ADA positive in the osteoporosis development program for rhPTH(1-84).

The Applicant reports that a total of 140 subjects were tested for ADA: 132 subjects from NPS-sponsored trials and eight subjects from the Bilezikian trial (who were all screened negative and are not discussed because of the exclusion of data from his site). In the pivotal clinical trial, the Applicant assessed immunogenicity at baseline (prior to treatment), Week 24 (end-of-treatment), and Week 28 (follow-up) visits. Initially, a radioimmunoassay (RIA, (b) (4)) was used to test for ADA positive samples. However, since (b) (4) was unwilling to provide the validation of the RIA assay, the Applicant switched to a new and validated electrochemiluminescence ((b) (4) MDS-ECL) screening assay. Less than half of the samples from the pivotal trial were retested with the ECL assay (corresponding to samples of only 70 out of 132 subjects). Unfortunately, baseline samples were not available for retesting. None of the RIA-positive samples could be confirmed by the (b) (4) MSD-ECL assay.

All subjects were ADA-negative at baseline in the pivotal trial (by RIA). Looking at the pivotal trial alone, for the RIA assay, there were 80 subjects tested, and one was found to be ADA-positive. For the ECL assay, there were 30 subjects tested, and 3 were found to be ADA-positive. If the ECL assay is more sensitive, it is possible that these subjects had antibodies at baseline, but this remains unknown. The Applicant conducted the immunogenicity assessment based on results obtained only by the (b) (4) MSD-ECL test.

Overall, post-treatment ADA evaluations from all NPS-sponsored trials showed that 14 out of 87 (16%) subjects had confirmed ADA, from which 8/14 were positive at the first trial in which they received treatment and 6/14 became positive at a second trial in which they were treated with rhPTH again (all 14 were enrolled in the pivotal trial). As a reference, 3-5% of subjects were ADA positive in the osteoporosis development program for rhPTH(1-84).

NAb was not measured in the pivotal trial. One subject (8002-001) had confirmed Nab at Week 24 of the second study (Trial 009) although the ADA titers were negative. All the assays used to assess immunogenicity were adequately validated.

Reviewer comment: The Applicant bases the immunogenicity assessment on a small number of samples, which were tested using the validated methods. However, since the presence of ADA does not appear to be associated with clinical adverse events or loss of efficacy, safety concerns associated with the

development of ADA are low. The Applicant was asked to report separately the rate of immunogenicity observed in the hypoparathyroidism program and the osteoporosis program, since the immune mechanisms involved in ADA development might be different for the two populations and are not currently well-understood.

The 14 subjects who were treated with rhPTH(1-84) who developed ADA positivity at some point are summarized below. The first four developed ADA positivity during the pivotal trial. Only one subject was found to have neutralizing antibodies.

Table 47 Subjects who developed ADA positivity during the development program

Subject	Time point for ADA positivity	Neutralizing Ab?	Responder/ Non-responder in the pivotal trial	Adverse events?
1001-0004	• Week 28 REPLACE • Week 52 RACE	REPLACE: not done RACE: negative	Responder	Moderate injection site hematoma 2 weeks after study drug initiated, which persisted until the end of treatment. No injection site or hypersensitivity reactions in RACE
8001-0010	• Week 24 REPLACE • Baseline REPEAT	REPLACE: not done REPEAT: negative	Non-responder	No hypersensitivity or injection site reactions
8002-0001	• Week 24 REPLACE • Baseline REPEAT	REPLACE: not done REPEAT: **positive**	Responder	No hypersensitivity or injection site reactions
1004-0003	• Baseline and Week 8 RELAY • Week 24, Week 52, and Month 24 RACE	RELAY: negative RACE: negative	Non-responder	No hypersensitivity or injection site reactions
1010-0010	• Week 52 and Month 24 RACE	negative	Non-responder	Had mild hives in REPLACE that resolved; during RACE developed a severe

				anaphylactic reaction to MRI dye that resolved
1015-0001	Baseline and Week 8 RELAY	negative	Responder	No hypersensitivity or injection site reactions
1018-0005	Baseline REPLAY	Not determined	Non-responder	No hypersensitivity or injection site reactions
8001-0005	Week 24 REPEAT	Negative	Non-responder	No hypersensitivity or injection site reactions
8001-0007	Week 24 REPEAT	negative	Non-responder	No hypersensitivity or injection site reactions
1011-0004*	Baseline and Week 8 RELAY	negative	Discontinued before first dose	
1006-0003	Month 24 RACE	negative[1]	Responder	
1010-0004	Month 24 RACE	negative	Responder	
1018-0003	• Week 28 REPLACE (by RIA, not confirmed with ECL) • Baseline RELAY	REPLACE: not done RELAY: not determined	**Placebo**	
8003-0003	Week 24 REPEAT	negative	**Placebo**	No hypersensitivity or injection site reactions

*discontinued from the trial before beginning treatment
[1]initially identified to have Nab+ at Month 24, but negative upon re-testing

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the pivotal trial, doses were titrated up until Week 12, but down-titration could occur at any time during the trial. There was no formal analysis of incidence of adverse events based on the dose during the maintenance period. Trial 007 offers an opportunity to compare stable doses of 25 vs 50 µg during an 8 week period. There was a slight trend

towards higher calcium levels, although not hypercalcemia. There were no other apparent dose-dependent adverse events.

7.5.2 Time Dependency for Adverse Events

In this disease, the time dependency for adverse events is related less to duration of exposure to the drug, but more related to dose titration for both study drug and supplements. In the pivotal trial, hypercalcemia in rhPTH(1-84)-treated subjects was observed mostly during the titration period. Hypocalcemia, on the other hand, was seen during the entirety of the trial, and was more frequent in the rhPTH(1-84)-treated subjects during the maintenance period.

Hypocalcemia during the post-treatment phase, following withdrawal of drug and transitioning back to baseline supplements, was not uncommon.

7.5.3 Drug-Demographic Interactions

There are no interactions noted.

7.5.4 Drug-Disease Interactions

There are no interactions noted.

7.5.5 Drug-Drug Interactions

There are no drug interactions noted.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

The issues regarding Forteo and the osteosarcoma signal in rats is discussed in Section 2.4.

7.6.2 Human Reproduction and Pregnancy Data

There are no trials of rhPTH(1-84) in pregnant women. Pregnancy was an exclusion criteria in the trials and there were no reports of women becoming pregnant during the trials. It is unknown whether rhPTH(1-84) is excreted in human milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

This biologic has not been studied in the pediatric population.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In this program, overdosage was assessed by reviewing cases where subjects either received planned dose of rhPTH(1-84) at least twice the recommended daily dose or had TEAEs of overdose or accidental overdose. All trials from this NDA as well as the osteoporosis NDA were considered. There were 17 subjects (both referenced from NDA 21,847 in single and multiple-dose preliminary trials) who received dose of at least twice the recommended (100 µg) daily dose. In these subjects, daily doses ranged from 200.4 µg to 336.5 µg. While there were reported AEs, none were serious or led to discontinuation, and all resolved.

A total of 17 rhPTH(1-84)-treated subjects had a TEAE of overdose or accidental overdose related to study drug. There were 2 rhPTH(1-84)-treated subjects in the hypoparathyroidism program (both in the pivotal trial) who had a TEAE of overdose or accidental overdose, but neither was serious or led to discontinuation. The Applicant states that the cases were the "consequence of misunderstanding that resulted in misuse or misoperation of the injection pen…the Ypsomed pen…" The Applicant also states that there were no cases of overdose with the Natpara pen intended for marketing. There narratives are included here:

- Subject 1002-0002: This subject injected himself and noted that 5 drops of liquid were ejected from the needle after it was withdrawn from his thigh. He then re-injected himself. His ACSC was 9.3 mg/dL and did not experience any related AE.
- Subject 4002-0003: This subject had multiple complaints about reliability of the Ypsomed device, including lack of reliability, causing loss of study drug during administration, at which time a potential overdose was reported. One day post-treatment, she experienced an AE of hypercalcemia (ACSC 11 mg/dL) that led to study drug discontinuation.

There were 15 subjects in the osteoporosis program who met this definition of overdose, but none of the events were serious or led to discontinuation of study drug.

There is no potential for abuse with rhPTH(1-84).

Post-treatment hypocalcemia following abrupt withdrawal of rhPTH(1-84) was observed in the pivotal trial (and can be expected), but may be carefully managed with close monitoring of serum calcium and restarting of appropriate dosages of calcium and vitamin D supplements.

7.7 Additional Submissions / Safety Issues

The Applicant used two different injections pens in this development program, and the pen used in the pivotal trial (Ypsomed) is not the to-be-marketed pen (Haselmeier).

The Haselmeier pen was used starting approximately half-way into the long-term Trial 008. Because this is the to-be-marketed pen, evaluation of pen-related complaints is focused on the Haselmeier.

In Trial 008, there were a total of 32 injection pen complaints (13 for Ypsomed and 19 for Haselmeier) and these are summarized below by pen type and reason. The percentages listed with each reason below are the percentage of the total number of reported events. To put the data below in perspective, the Ypsomed pen was used for over 9,000 injections (and had 5 medication leakages) while the Haselmeier pen was used for over 12,000 injections (with 4 medication leakages). Therefore, the overall number of reported problems appears low. However, the Division is awaiting additional data regarding these complaints.

Table 48 Injection Pen Complaint by Reason—Safety Population Excluding Site 1002

	Pen Type		
Reason	**Ypsomed N=49 # of Events (%)**	**Haselmeier N=49 # of Events (%)**	**All Subjects N=49 # of events (%)**
Total	13 (100)	19 (100)	32 (100)
Reported Leaking Medication	5 (38.5)	5 (26.3)	10 (31.3)
Dose Activator Problems	5 (38.5)	0	5 (15.6)
Dose Knob Problems	0	3 (15.8)	3 (9.4)
Dose Counter Problems	2 (15.4)	0	2 (6.3)
Injection Button	0	2 (10.5)	2 (6.3)
Recon Device-Related Problems	0	2 (10.5)	2 (6.3)
Piston Rod-Related	0	2 (10.5)	2 (6.3)
Insufficient Details to Evaluate	1 (7.7)	0	1 (3.1)
Needle-Related Problems	0	1 (5.3)	1 (3.1)
Cartridge Problems	0	1 (5.3)	1 (3.1)
Stability or Form Change	0	1 (5.3)	1 (3.1)
Difficulty Attaching Cartridge to Pen/Injector Base	0	1 (5.3)	1 (3.1)
Stoppers Resist Meeting (push apart)	0	1 (5.3)	1 (3.1)
CMO/Packaging	0	0	0

CMO=contract manufacturing organization
From Applicant's Submission dated May 31, 2014, Table B-14.3.9.1

The Applicant submitted a 4-month safety update and this was reviewed. The document included updated information from the 2 ongoing trials--Trial 008 and the Bilezikian IIT—and reflected 6 months of additional safety data for the former and 17 additional months for the latter. The focus of the update was on AEs of interest.

There were 11 additional subjects enrolled, all of the Bilezikian ITT. Because data from his site are being excluded, these are not reviewed.

There were no deaths reported in the update. For Trial 008, there were 2 additional SAEs since data cutoff: one subject with fracture and a second subject with dyspnea, chest discomfort, throat tightness. Narratives were reviewed and in both cases, the events appeared to be unrelated to Natpara.

Since the prior data cutoff, there was one additional subject who discontinued in 008. This was a subject with metastatic lung adenocarcinoma, and although this subject was reported as discontinuing in the original BLA, the subject only formally discontinued in the time frame reflected in the safety update. This subject was a 41 year old woman who completed trials 040 and 007 and then continued with 008. Approximately 920 days after initially starting Natpara (in Trial 040), she was diagnosed with metastatic lung adenocarcinoma, with brain metastases. Natpara (on 100 µg at the time of the SAE) was permanently discontinued. Treatment for the cancer was ongoing at the time of the report.

There were 6 additional events of hypocalcemia in 5 subjects while receiving study drug. Two of these subjects were from site 1002. The following are brief narratives of the other 3 subjects:

- Subject 1003-0006 had mild hypocalcemia starting on Study Day 638 that was ongoing at the time of data cutoff. This subject was on 50 µg of Natpara and 1250mg of calcium daily. Serum calcium was 7.5 mg/dl.
- Subject 1006-0001 had hypocalcemia starting on Study Day 546 lasting 6 days (serum calcium was 6.5 mg/dL). At the time of the event, the subject was on Natpara 100 µg and 0.50 µg of active vitamin D.
- Subject 1006-0006 had 2 events of hypocalcemia starting on Study Days 791 and 797 (serum calcium was 7.4 mg/dL at the time of the first event). This subject had 2 prior events of hypocalcemia as well. Although the first event resolved, the second event was ongoing at the time of data cutoff.

There was one additional report of hypercalcemia in Trial 008. The event was characterized as mild and transient (2-days duration).

There were no additional events of hypercalciuria reported in the safety update.

8 Postmarket Experience

This drug is not approved in the US. It is approved in the EU for the treatment of osteoporosis in postmenopausal women at high risk of fractures, a PTH-sufficient population that is very different than the PTH-deficient population of hypoparathyroid subjects.

9 Appendices

Table 49 Schedule of Study Evaluations and Procedures

Visit Number	1	2*	3*	4*	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	Optimization				R***											Follow Up		
Study Week	-8	-6	-4	-2	0	1	2	3	4	5	6	8	12	16	20	24	25	28
Visit Windows**		± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
Informed consent	X																	
Inclusion/Exclusion criteria review	X																	
Medical history and demography[a]	X																	
Review of prior[b, c]/concomitant medications[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Physical examination[d]	X															X		
Vital signs[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ECG (12-lead)[f]	X						X		X		X		X			X		
Hematology[g]	X															X		
Serum chemistry (24-panel)[h]	X				X											X		
Serum thyroid function tests[i]	X															X		
Serum pregnancy test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy Test					X													
FSH levels	X																	
Serum PTH (1-84)[j]	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis (dipstick)[k]					X											X		
24-hour urine creatinine clearance	X				X			X		X	X	X	X	X		X		
24-hour urine calcium	X				X			X		X	X	X	X	X		X		
24-hour urine phosphate	X				X			X		X	X	X	X	X		X		
24-hour urine sodium	X				X			X		X	X	X	X	X		X		
Serum albumin****	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum calcium****	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum phosphate****	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum magnesium	X				X		X		X		X	X	X	X		X		X
Serum 25-hydroxyvitamin D	X				X		X		X		X		X			X		
Serum 1,25-dihydroxyvitamin D	X				X								X			X		

Visit Number	1	2*	3*	4*	5	6	7	8	9	10	11	12	13	14	15	16	17	18
	Optimization				R***											Follow Up		
Study Week	-8	-6	-4	-2	0	1	2	3	4	5	6	8	12	16	20	24	25	28
Visit Windows**		± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 2 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days	± 3 days
Serum bone turnover markers[j]	X				X				X			X	X		X	X		
BMD by DXA[m]	X															X		
QoL (SF-36)					X				X				X			X		
AE/SAE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SAE follow up[n]																		X
Assessment of clinical episodes of hypocalcemia and tetany °	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization[p]					X													
eDiary training/review/ study drug compliance check[q]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Study drug self-administration training and initiation[r]					X													
Dispense/administration/accountability of Study Drug[s]					X	X	X	X	X	X	X	X	X	X	X	X		
Collection of unused study drug and injection pen																X		
Subject collection of eDiary data	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Dispense/accountability/assessment of Supplemental medications[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Calcium supplement (per guideline)[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Active vitamin D metabolite/analog supplement (per guideline)[t]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
PTH antibodies					X											X		X
Serum calcium[u]													X					

AE = adverse event; ALT = alanine transaminase; AST = aspartate transaminase; BMD = bone mineral density; BMI = body mass index; BSAP = blood-specific alkaline phosphatase; BUN = blood urea nitrogen; CO_2 = carbon dioxide; CPK = creatinine phosphokinase; CTx = C-terminal telopeptide of type 1 collagen; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; FSH = follicle stimulating hormone; IV = intravenous; LDH = lactate dehydrogenase; PTH = parathyroid hormone; QoL = quality of life; SAE = serious adverse event; SC = subcutaneous; SF-36 = Short Form-36 questionnaire; TSH = thyroid-stimulating hormone;

* Visits 2, 3 and 4 were combined if the subject was determined by the investigator to have received optimal treatment.

** Study Visits up to Week 6 were to occur within +/-2 days of the designated visit date; visits after and including Week 6 were to occur within +/-3days of designated visit date.

*** Randomization.

**** Step-down protocol for supplemental calcium and active vitamin D metabolite/analog doses could have necessitated testing of albumin-corrected total serum calcium and phosphate concentrations at interim time-points from Week 1 onwards until a stable supplemental dose was reached.

[a] Demography included age (years), gender (male or female), and race. Medical history included hypoparathyroidism, date of diagnosis, etiology of hypoparathyroidism, and history of clinically significant tetany episodes.

[b] Within 6 months prior to screening, with the exception of IV bisphosphonates (excluded within the previous 12 months).

[c] Drug name, dose, route, reason for use, and therapy dates.

[d] Subjects, height, body weight (kg), BMI (derived), and qualitative (normal or abnormal) assessment of general appearance, abdominal and mental assessments, and qualitative assessments of the integumentary, HEENT (head, ears, eyes, nose, and throat), pulmonary, cardiovascular, musculoskeletal, and neurological systems. Abnormalities determined by the investigator to be clinically significant and were detected at the baseline screening visit (Week -8) and any subsequent visits were recorded as medical history and as an AE, respectively.

[e] Vital signs (blood pressure [mmHg], pulse [beats/minute], body temperature [°C], and respiration rate (breaths/min.).

[f] Includes general findings, atrial and ventricular rates (beats/minute), and PR, QRS, and QTc intervals (seconds). Abnormalities determined by the investigator to be clinically significant that are detected at the baseline screening visit (Week -8) and any subsequent visits were recorded as medical history and as an AE, respectively. Postdose ECG was completed 3-4 hours postdose at Week 12.

[g] Included the following analytes: complete blood count, hemoglobin, hematocrit, and total white blood count.

[h] Fasting for at least 8 hours prior to test. Chem-24 included serum sodium, potassium, chloride, magnesium, glucose, phosphate, calcium. acid phosphatase, ALT, AST, alkaline phosphatase, amylase, LDH, lipase, bilirubin (total), BUN, CO_2, cholesterol (total), CPK (total), creatinine, lactic acid, protein (total), triglycerides, and uric acid.

[i] Included the following analytes: thyroxine (T4) and TSH.

[j] If historical Serum i-PTH was not available prior to study entry, a i-PTH was collected at screening in addition to drawing a 2nd i-PTH at any visit using an unscheduled laboratory visit during the optimization period to satisfy Inclusion/Exclusion randomization criteria. Serum PTH was collected at Week12 at predose (0-1 hour before daily dose administered), at 1-2 hours post dose, and at 6-10 hours post dose.

[k] Included the following analytes: pH, bilirubin, blood, glucose, ketone, leukocytes, nitrite, protein, specific gravity, and urobilinogen.

[l] Included the following analytes: BSAP, CTx, serum procollagen type 1 amino-terminal propeptide (P1NP), and osteocalcin.

[m] BMD of the lumbar vertebra (L1-L4), hip (total, trochanter, intertrochanter, Ward's triangle, and femoral neck), and ⅓ distal radius (arm). DXA following screening was performed at any time during the optimization period at least 1 week prior to randomization visit. Any repeat scans were acquired within 2 weeks from the site being notified via a Data Clarification Form that a repeat DXA was required. If a subject could not withhold the calcium supplements 24 hours prior to having the scan due to safety concern, the DXA was performed 2 hours after the last calcium tablet had been ingested.

[n] Clinical study site visit. Serious adverse events or pregnancy only.

° Included symptoms of muscular hypertonia (tremor, twitching, paresthesia, and spasm [muscular or bronchial]), dysphagia, convulsions, cardiac symptoms (arrhythmias, prolonged QT interval, hypotension, or cardiac insufficiency), psychological symptoms (anxiety, irritability, or delirium), Chvostek's Sign, Trousseau's Sign, and corrective treatment administered.

[p] Note: See Protocol CL1-11-040 Section 5.4.2, Calcium, Native Vitamin D, and Active Vitamin D Metabolite/Analog, Magnesium Supplementation. Subjects returned to the site for qualifying blood work drawn 3 days prior to randomization, as these labs were analyzed by the central laboratory. Unscheduled labs inclusive of serum magnesium, 25-hydroxyvitamin D, albumin-corrected total serum calcium levels and 24-hour urine collection, and if not completed, a 2nd qualifying i-PTH was completed at this time also. All laboratory results were available the morning of the baseline/randomization visit (Week 0) for physician review of qualifying laboratory criteria.
[q] eDiary data (inclusive of study drug and concomitant calcium and active vitamin D supplements, study drug administration [including injection site] were reviewed by the investigator at each visit).
[r] Initial, self-administered dose was monitored by investigator to confirm subject competency. Self-administered (or designee-administered) in the morning. Injection sites were rotated.
[s] Subject returned unused and used cartridges at each visit. Amounts self-administered (or designee-administered), wasted, and returned were recorded in the subject's source document.
[t] See Protocol CL1-11-040 Section 5.4.2, Calcium, Native Vitamin D, and Active Vitamin D Metabolite/Analog, Magnesium.
[u] Serum calcium tested 1 hour and 6-10 hours post study drug dosing once the final dose of study drug had been reached in order to assess for the presence of hypercalcemia at peak study drug levels.

Table 50 Markedly Abnormal Laboratory Criteria

Lab parameter	Unit	Lower Limit	Upper Limit
Chemistry			
Albumin	g/L	<=20	>=90
Alkaline Phosphatase	U/L	NA	>2*ULN
ALT	U/L	NA	>3*ULN
Amylase	U/L	<=15	>=350
AST	U/L	NA	>3*ULN
Bilirubin	µmol/L	NA	>2*ULN
BUN	mmol/L	NA	>=10.7
Chloride	mmol/L	<=80	>=125
Cholesterol (total)	mmol/L	NA	>=12.9
Creatinine	µmol/L	NA	>=177
Glucose	mmol/L	<=1.7	>=13.9
Phosphate	mmol/L	NA	>=2
Potassium	mmol/L	<=2.5	>=6.5
Sodium	mmol/L	<=120	>=165
Triglycerides	mmol/L	NA	>=5.6
Uric acid	µmol/L	NA	>=624 (males) >=505 (females)
Hematology			
Hematocrit	L/L	<=0.37 (males) <=0.32 (females)	>0.54 (males) NA (females)
Hemoglobin	g/L	<=115 (males) <=95 (females)	NA
Platelets	10^9/L	<=75	>=700
WBC count	10^9/L	<=2.8	>=16.0
Basophils	L/L	NA	>=0.15
Eosinophils	L/L	NA	>=0.10
Lymphocytes	L/L	NA	>=0.80
Monocytes	L/L	NA	>=0.40
Neutrophils	L/L	<=0.15	NA

NA=Not Applicable; ULN = Upper Limit of Normal

From Applicant's CSR, Appendix 16.1.9

9.1 Literature Review/References

References are included as footnotes throughout the Review.

9.2 Labeling Recommendations

At the time this Review was finalized, labeling negotiations had not commenced. A separate labeling review will be submitted.

9.3 Advisory Committee Meeting

This NDA is scheduled to be presented at an advisory committee meeting on September 2014.

9.4 Individual Study Reviews

PAR-C10-007: A Randomized, Dose-blinded Study to Investigate the Safety and Efficacy of NPSP558, a Recombinant Human Parathyroid Hormone [rhPTH(1-84)], at Fixed Doses of 25 µg and 50 µg for the Treatment of Adults with Hypoparathyroidism (RELAY)

Because the lowest dose in the pivotal trial was 50 µg, the Applicant conducted this 8-week trial using fixed doses of either 25 or 50 µg to explore additional dosing options. The Applicant also sought to gather additional safety data.

This was a randomized, dose-blinded study of NPSP558 for the treatment of adult male and female subjects with hypoparathyroidism. The study included subjects from previous NPSP558 studies. All references to “baseline” in this study report refer to the baseline of Trial 007.

Objectives
The primary objective of this trial was to evaluate the efficacy and tolerability of subcutaneous (SC) NPSP558 [rhPTH(1-84)] doses of 25 µg and 50 µg as replacement therapy for the treatment of adult patients with hypoparathyroidism.
The secondary objectives were:
• To evaluate the effect of NPSP558 at 25 µg and 50 µg SC on oral calcium and calcitriol supplementation and
• To compare response rates and tolerability of dosing with NPSP558 25 µg and 50 µg SC.

Endpoints
The primary efficacy endpoint was the proportion of subjects in the NPSP558 25 µg and NPSP558 50 µg dosage groups that by Week 8 (Visit 4) achieved each of the following:
• A reduction in oral calcium supplementation to ≤ 500 mg/day and

• A reduction in calcitriol dose to ≤ 0.25 µg/day and
• An albumin-corrected total serum calcium level between 7.5 mg/dL and the upper limit of normal (ULN) for the central laboratory

The components of this endpoint were somewhat different than those in the pivotal trial, which focused on reductions of 50% for calcium and vitamin D supplements.

There was also a secondary efficacy endpoint, which was achieved if the following 3 criteria were met:
• A ≥ 50% reduction from baseline (prior to randomization) in dose of oral calcium supplementation and
• A ≥ 50% reduction from baseline (prior to randomization) in dose of oral calcitriol supplementation and
• An albumin-corrected total serum calcium concentration that was normalized or maintained compared to the baseline value (≥ 7.5 mg/dL) and did not exceed the ULN for the central laboratory

Investigator data were primarily used for both primary and secondary endpoints.

There were multiple exploratory endpoints, which are not discussed in this Review.

Safety endpoints included: adverse events, incidence of clinical episodes of hypocalcemia and hypercalcemia, laboratory test results (including 24-hour urinary calcium and PTH antibody), and EKG.

Study Design
Subjects were randomized to receive either NPSP558 25 µg SC once daily (QD) or 50 µg SC QD in a dose-blinded and fixed-dose fashion. Subjects recruited into this trial could have previously completed either the pivotal trial, or Study C09-002, which included 2 single doses of NPSP558 followed by a 4-week washout period. There was no maximum time from completion of either previous trial to entry into this trial. Also, the following categories of subjects were permitted to enroll in this trial:

- Subjects who were enrolled and in the optimization phase of the pivotal trial when randomization was closed
- Subjects new to the NPSP558 program and fulfilled the inclusion and exclusion criteria

Subject randomization was stratified by the subject's current calcium source (carbonate or citrate). Subjects who did not meet the calcium and 25 (OH) vitamin D criteria (normal ranges) could be reconsidered for study entry following attainment of appropriate levels, within the following 4 weeks.

There were 4 scheduled study visits: baseline, Weeks 2, 4, and 8. Total serum calcium levels were determined by a local laboratory for all subjects 3 to 5 days following the

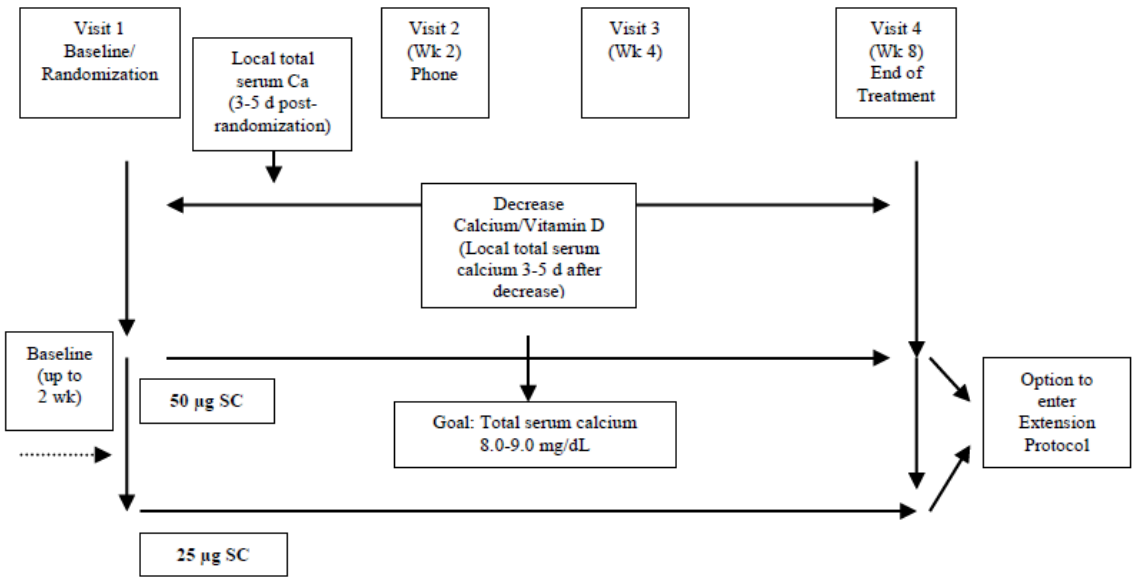
baseline visit. The Week 2 visit consisted of a local laboratory assessment and a telephone contact, in order to assess safety parameters. Subjects also had interim blood draws for determination of total serum calcium levels following any titration of calcium and/or calcitriol.

The goal of supplement titration was to reduce the need for calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible, while maintaining total serum calcium ideally between 8.0 and 9.0 mg/dL. Down-titration of calcitriol and calcium was undertaken by the investigator based on total serum calcium concentrations using an algorithm described in the Titration Guideline in which it was recommended that calcitriol be reduced first by up to 50%, followed by a reduction of up to 50% in oral calcium supplementation. The order and magnitude of subsequent reductions in either calcitriol or oral calcium supplementation was left to the investigator's discretion, based on individual subject response. Titration was performed while assessing symptoms and following calcium levels, which were measured 3 to 5 days after each adjustment of supplements.

Study drug was to be stopped of the pre-dose calcium level remained above the ULN for 2 more consecutive safety assessments (no more than 5 days apart), following withdrawal of all supplements. If any calcium level was above 1..9 mg/dL, treatment with study drug was to be stopped immediately. When calcium levels returned to normal, the decision to restart NPSP558 was done in consultation with the medical monitor.

The study design is shown here:

Study Design



From Applicant's CSR, Figure 9-1

At the end of the 8-week treatment period, subjects had the option of enrolling in PAR-C10-008 (RACE), a 12-month extension trial that is also reviewed in this document.

Inclusion and Exclusion Criteria:
For subjects previously enrolled in an NPSP558 trial, the following were key inclusion criteria:

- Total serum calcium ≤ ULN based on local laboratory results prior to randomization
- Serum 25(OH) vitamin D ≤ 1.5 times the ULN within approximately 16 weeks prior to Randomization

Subjects new to the NPSP558 program had to meet the following criteria:

- Males or females 18 to 85 years of age
- History of hypoparathyroidism for ≥ 18 months post-diagnosis, inclusive of historical biochemical evidence of hypocalcemia and concomitant serum intact PTH concentrations below the lower limit of the laboratory normal range on 2 test dates at least 21 days apart within 12 months prior to randomization
- Requirement for calcitriol ≥ 0.25 µg per day prior to randomization
- Requirement for supplemental oral calcium treatment ≥ 1000 mg per day over and above normal dietary calcium intake prior to randomization
- Serum thyroid function tests WNL at baseline for all subjects not receiving thyroid hormone replacement therapy. For subjects receiving thyroid hormone replacement therapy, the dose must have been stable for at least 3 months prior to baseline (i.e., changes < 25% of the total weekly dose) and the levothyroxine value could be outside the laboratory limits of normal.

Exclusion criteria were generally similar to those in the pivotal trial.

Efficacy
Forty-seven subjects were enrolled and randomized in a 1:1 ratio into 1 of the 2 fixed-dosage groups (23 subjects were randomized to NPSP558 25 µg and 24 subjects were randomized to NPSP558 50 µg SC QD).

Subject disposition is shown below. While most subjects (44.7%) came from the pivotal trial, approximately 40% were new to the development program. There was one early discontinuation, in the 25 µg group: this subject was discontinued on Day 38 because of arthralgia, which was considered unrelated to study drug.

Subject Disposition—All Randomized Subjects, Excluding Site 1002

Category	NPSP558 25 µg n (%)	NPSP558 50 µg n (%)	Total N=47 n (%)

Randomized	19	23	42
Completed 24 wks of therapy and 4 wks of follow- up in CI-11-040	12 (63.2)	9 (39.1)	21 (50)
Enrolled in CL-11-040 but not randomized	0	4 (17.4)	4 (9.5)
New to NPSP558 program	6 (31.6)	8 (34.8)	14 (33.3)
Enrolled in C09-002	1 (5.3)	2 (8.7)	3 (7.1)
ITT Population	19 (100)	23 (100)	42 (100)
Per-protocol Population	16 (84.2)	23 (100)	39 (92.9)
Safety Population	19 (100)	23 (100)	42 (100)
Completed Study	18 (94.7)	23 (100)	41 (97.6)
Discontinued study early	1 (5.3)	0	1 (2.4)
Adverse event	1 (5.3)		1 (2.4)

From Applicant's Submission dated June 4, 2014

There were 4 significant protocol deviations, all in the 25 µg group. The violations were:

1) Compliance for study drug was outside of 80-120%. No Week 8 visit and efficacy determinations; discontinued Day 71.
2) Baseline vitamin D analog prescription was 0.
3) Baseline vitamin D analog prescription was 0, and baseline calcium prescription was 500 mg.
4) Compliance for study drug was outside of 80-120%. No Week 8 visit and efficacy determinations; discontinued Day 38.

Demographics

The two treatment groups were generally similar in demographic characteristics. Overall, the majority of subjects were female (84.8%) and white (93.5%), and the mean age was 48.2 years. The proportions of subjects requiring higher doses of calcium and calcitriol supplementation were higher in the NPSP558 50 µg group than in the NPSP558 25 µg group.

Treatment compliance was calculated based on the diary data and defined as: (number of doses administered) / last dosing date – first dosing date + 1). Mean compliance was 99% for both treatment groups.

Primary Endpoint

The primary analysis of the primary endpoint was based on the investigator-prescribed data, and those results are shown below. Four subjects in the 25 µg group and six subjects in the 50 µg group met the primary endpoint. There was no statistically significant treatment difference between the two groups.

However, if patient diary data is used, only 1 subject in each group met the primary endpoint.

Primary Response Rate at Week 8 Based on Investigator-prescribed Data –ITT Population, Excluding Site 1002

	rhPTH(1-84) 25 ug (N=19)		rhPTH(1-84) 50 ug (N=23)			
Status	n (%)	(95% CI)[a]	n (%)	(95% CI)[a]	Treatment Difference (95% CI)[b]	p-Value[c]
Responder	4 (21.1)	(6.1, 45.6)	6 (26.1)	(10.2, 48.4)	5.0 (-20.6, 30.7)	>0.999
Non-Responder	15 (78.9)		17 (73.9)			

From Applicant's Submission dated June 5, 2014, Table B-14.2.1.1.1
Percentages are based on the number of ITT subjects in each treatment arm. Responder is defined as subjects whose daily calcium supplementation at Week 8 was ≤500 mg/day and the daily calcitriol dose was ≤0.25 µg/day and the albumin-corrected calcium level at Week 8 was between 7.5 mg/dL and the upper limit of normal. Subjects who terminated early or had missing lab data at Week 8 were considered non-responders.

Although subgroup analyses are not discussed in detail here, it is noteworthy that all subjects who met the primary endpoint criteria in both treatment groups were receiving the lower prescribed calcium dosage at baseline (0-200 mg/day), and all but one subjects were receiving the low or medium calcitriol dosage at baseline.

Secondary Endpoint
Secondary endpoint was the response rate at Week 8 based on the proportion of subjects with ≥50% reductions from baseline in oral calcium and calcitriol supplementation and albumin-corrected total serum calcium concentration that was normalized or maintained compared to the baseline value (≥7.5 mg/dL) and did not excess the ULN. The table below summarizes the secondary endpoint results.

Secondary Response Rate at Week 8 Based on Investigator-prescribed Data—ITT Population, Excluding Site 1002

	rhPTH (1-84) 25 µg N=19		**rhPTH (1-84) 50 µg N=23**			
Status	n (%)	(95% CI)	n (%)	(95% CI)	Treatment Difference (95% CI)	p-value
Responder Non-responder	2 (10.5) 17 (98.5)	(1.3, 33.1)	6 (26.1) 17 (73.9)	(10.2, 48.4)	15.6 (-7.1, 38.2)	0.258

From Applicant's submission dated June 5, 2014, Table B-14.2.2.1.1

Given the small number of subjects and the short duration of the trial, exploratory analyses are not discussed in this review.

Safety
The table below summarizes exposure in the trial. The majority of subjects were exposed to NPSP4558 for at least 8 weeks.

Extent of Exposure—Safety Population, Excluding Site 1002

Extent of Exposure	NPSP558 25 µg N=19	NPSP558 50 µg N=23
Exposure, n (%)		
Any exposure	19 (100)	23 (100)
<1 week	0	0
1 to <4 weeks	0	0
4 to <8 weeks	3 (15.8)	2 (8.7)
≥8 weeks	16 (84.2)	21 (91.3)
Exposure Duration (days)		
n	19	23
Mean	56.2	58
SD	5.2	2.6
Median	57	57
Min, max	37, 64	54, 65

Applicant's Submission to FDA dated June 5, 2014, Table B-14.3.9.2

The table below summarizes adverse events in the trial. The majority of subjects in both groups experienced an adverse event. There was one subject who discontinued due to an adverse event. This was a 71 year old man who was randomized to the 25 µg group (had not participated in the pivotal trial) who experience joint pain 10-34 days after initiating study drug. The event was considered unrelated to study drug.

Summary of Treatment-emergent Adverse Events, Excluding Site 1002

Category	NPSP558 25 µg N=19		NPSP558 50 µg N=23	
	n (%)	events	n (%)	events
Any TEAE				
No	8 (42.1)		6 (26.1)	
Yes	11 (57.9)	43	17 (73.9)	54
Any TEAE leading to discontinuation	1 (5.3)	1	0	0
Any TESAE	0	0	0	0
Deaths	0	0	0	0

Applicant's Submission to FDA dated June 5, 2014, Table B-14.3.1.1.2
TEAE=treatment-emergent adverse event
TESAE=treatment-emergent serious adverse event

The table below summarizes AEs occurring in at least 10% of subjects in either treatment group.

Treatment-emergent Adverse Events Occurring in ≥ 10% of Subjects in Either Treatment Group

	NPSP558 25 µg N=23	NPSP558 50 µg N=24

	n (%)	events	n (%)	events
Paresthesia	4 (21.1)	8	5 (21.7)	6
Headache	1 (5.3)	1	3 (13)	3
Nausea	2 (10.5)	2	3 (13)	4
Fatigue	3 (13)	5	2 (8.3)	2
Arthralgia	2 (10.5)	3	1 (4.3)	1
Muscle spasms	3 (15.8)	5	3 (13)	4
Hypercalcemia	2 (10.5)	2	1 (4.3)	1
Pollakiuria	2 (10.5)	2	1 (4.3)	1

Applicant's Submission to FDA dated June 5, 2014, Table B-14.3.1.1.3

For this trial, the Applicant combined the following terms: hypocalcemia, hypercalcemia, hypercalciuria, blood calcium increased, blood calcium decreased, and urine calcium decreased. Based on this, 3 subjects in the 25 µg group and 3 subjects in the 50 µg group experienced such an event during the treatment period.

In the 25 µg group, there was one subject with hypocalcemia and two subjects with hypercalcemia, one noted as severe (Subject 1007-0006). This one subject was a 60 year old woman who had a baseline calcium level of 9.3 mg/dL who had severe hypercalcemia at Week 4 (maximum value of 12.3 mg/dL). She experienced no symptoms. Calcium supplementation was discontinued and study drug was interrupted on Days 30 through 32. Serum calcium returned to normal and study drug was resumed with a calcium level of 10.8 mg/dL at Week 8.

In the 50 µg group, there was one subject with hypercalcemia, one with hypocalcemia, and one with hypercalciuria.

Laboratory Results

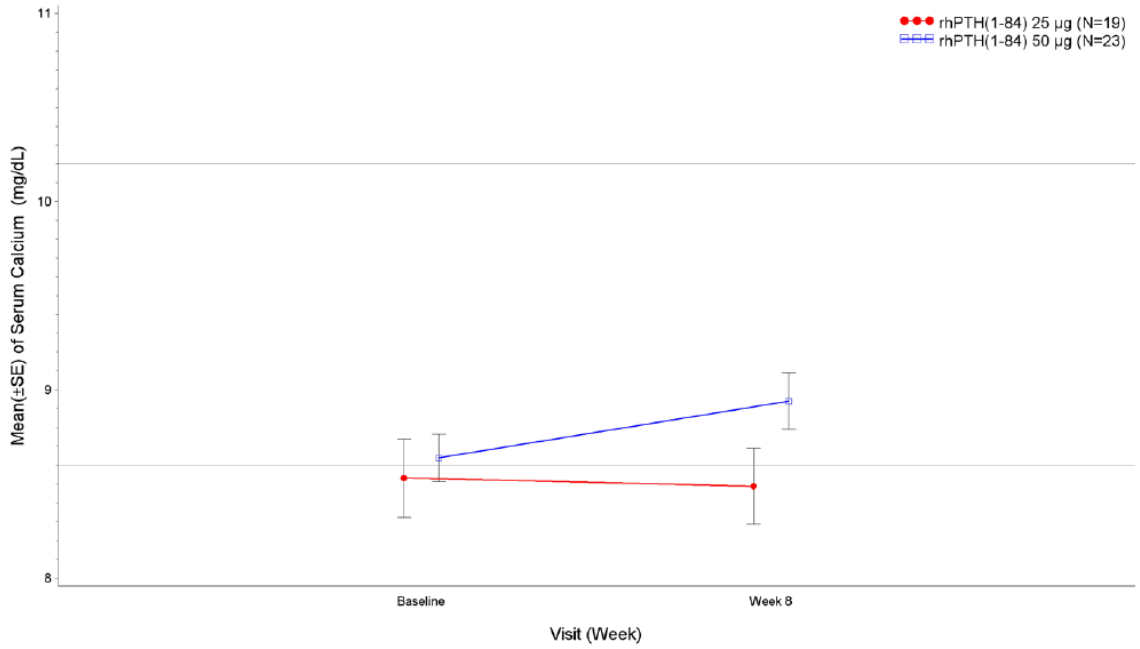
For hematology, there was one subject, in the 50 µg group, with a markedly abnormal post-baseline value. This subject had a WBC count of 2.3 x 10^9/L at Week 8.

For chemistry parameters, one subject in the 25 µg group and 2 subjects in the 50 µg group had 1 or more markedly abnormal values. The subject in the 25 µg group had an elevated uric acid at baseline an again at Week 8. In the 50 µg group, one subjects developed elevated AST and ALT at Week 8 (peak levels of ALT 335 and 299, respectively). The second subject in the 50 µg group who had an elevated baseline phosphate 5 mg/dL) also had an elevated level at Week 8 (6.4 mg/dL).

Calcium Levels

The figure below depicts the mean change in calcium levels for both groups. The 50 µg group remained close to the lower limit of normal, while the 25 µg group was just below or at the lower limit.

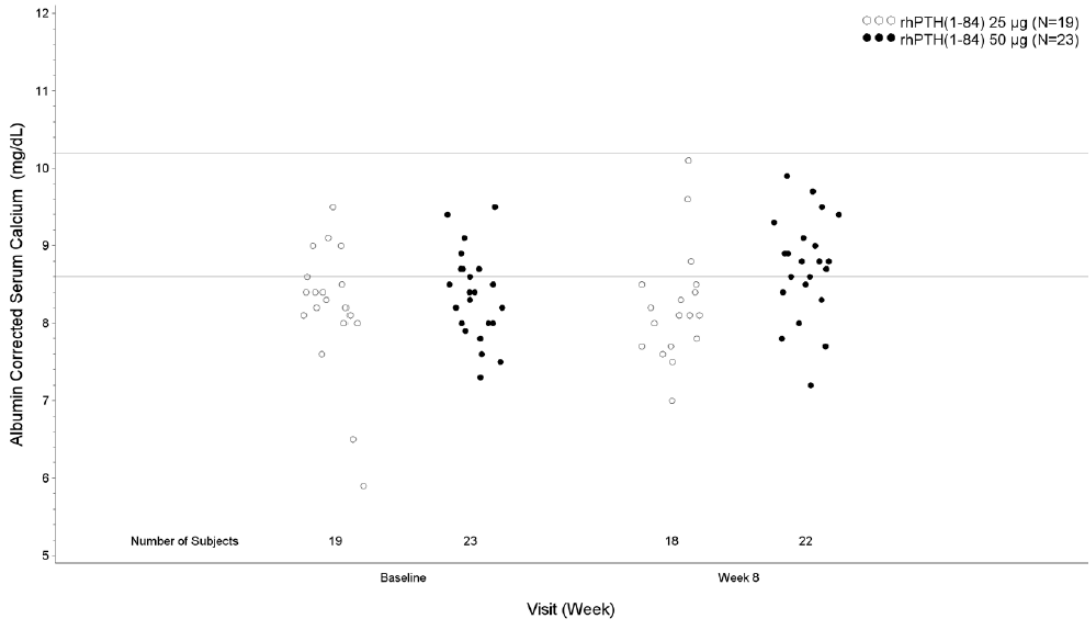
Mean (±SE) of Serum Calcium (mg/dL) by Visit, Excluding Site 1002



From Applicant's Submission dated June 2, 2014, Figure 1b

The figure below is a scatterplot of serum calcium at baseline and at Week 8 for both dose groups. Consistent with the figure above, there is a tendency for more hypocalcemia in the lower dose group at Week 8.

Scatterplot of Albumin-corrected Serum Calcium (mg/dL) at baseline and at Week 8-ITT Population, Excluding Site 1002



From Applicant's Submission dated June 2, 2014, Figure 2b

Study 009: A 6-Month Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH [1-84]), for the Treatment of Adults with Hypoparathyroidism – A Clinical Extension Study (REPEAT)

This was a 6-month open-label trial that involved Hungarian subjects who previously completed Study 040 (REPLACE) or who qualified for and enrolled in REPLACE, but dropped out during optimization. The goal of this trial was to optimize NPSP558 dosing while reducing calcitriol or alfacalcidol and oral calcium citrate supplementation to as low as safely possible while maintaining total serum calcium levels. There was no comparator in this trial. The Applicant states that in this trial they also sought to better mimic usual clinical practice, thereby reducing the frequency and intensity of the medical investigations after drug titration was complete.

The primary objective was to demonstrate safety and tolerability of NPSP558 as hormone replacement therapy administered for 6 months for the treatment of hypoparathyroidism in adult subjects.

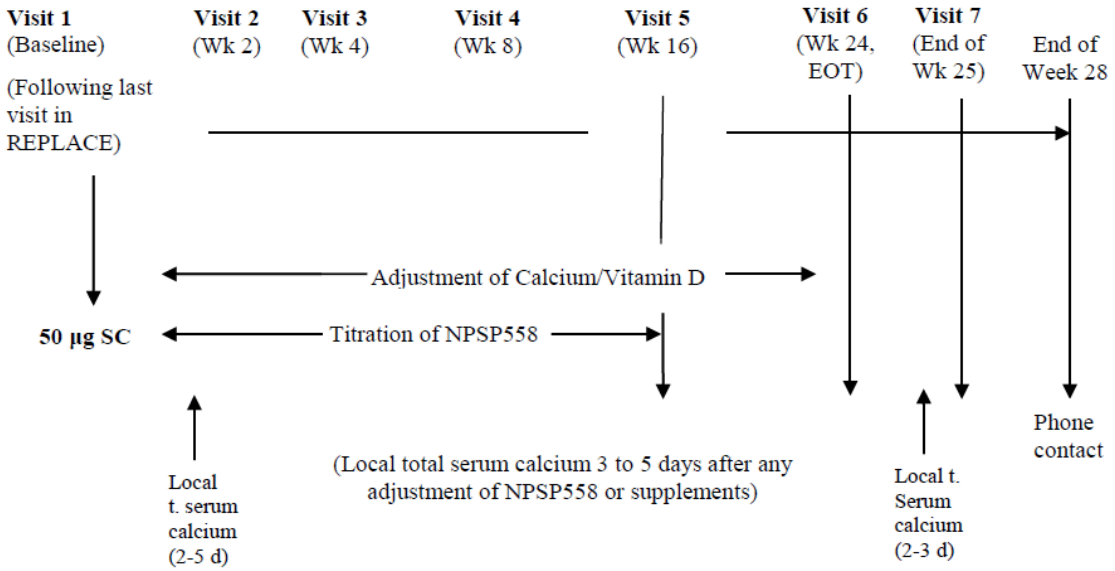
The secondary objective of the trial was to demonstrate that dosing with NPSP558 across a dose range of 50 to 100 µg could be implemented in a safe and effective manner and could be maintained throughout 24 weeks of treatment.

The starting dose of NPSP558 for all subjects was 50 µg daily. Up-titration up to 100 µg was allowed in increments of 25 µg at each visit through Week 16, with the goal of achieving normal calcium levels (8-9 mg/dL). Study visits were conducted at baseline and Weeks 2, 4, 8, 16, and 24, with a follow-up visit at Week 25 and a follow-up telephone contact at Week 28. Down-titration was possible at any point.

Serum calcium levels were tested 3-5 days after any NPSP558 dose adjustment, after any significant changes in doses of calcium and/or calcitriol/alfacalcidol supplements, or at any other time at the discretion of the investigator. If any total serum calcium level exceeded 11.92 mg/dL, study drug was stopped and appropriate dosing changes were made to calcium, calcitriol, and study drug doses before restarting. Once a subject achieved a stable serum calcium with the minimum doses of supplements possible, they were maintained on that dose of NPSP5558.

The trial design is summarized in the figure below:

Trial Design



From Clinical Study Report, Study 009

A total of 24 subjects were enrolled at 3 sites.

Main Inclusion Criteria: All subjects must have completed 24 weeks of therapy and 4 weeks of follow-up in REPLACE or most have enrolled in REPLACE and discontinued during optimization. Any subjects in the latter category had to meet inclusion/exclusion criteria for REPLACE at the time they enrolled in the current trial. In addition, subjects could not have:

- Received NPSP558 of Forteo therapy within 1 week prior to baseline

- Total serum calcium ≤ ULN prior to randomization
- Serum 25-hydroxyvitamin D ≤ 1.5 times the ULN within approximately 16 weeks prior to randomization
- Serum creatinine <1.5 mg/dL at baseline

The primary endpoint was comparable to that in the pivotal trial, with the exception of the italicized wording below. Specifically, the primary endpoint was the proportion of subjects in whom the following three conditions were fulfilled at Week 24 (Visit 6)

- A ≥50% reduction from baseline in dose of oral calcium supplementation *or an oral calcium dose of ≤500 mg/day*
  AND
- A ≥50% reduction from baseline in dose of oral calcitriol/alfacalcidol dose *or an oral calcitriol dose of ≤ 0.25 µg or alfacalcidol dose of ≤ 0.50 µg*
  AND
- A total serum calcium concentration that was normalized or maintained compared to the baseline value and did not exceed the ULN of the central laboratory

Because of the italicized additions, it is possible that subjects who initiated the trial at lower doses of calcium and vitamin D analogs and maintained those doses could be considered a responder (rather than having to prove a 50% reduction). Nevertheless, the Applicant states that this composite endpoint was chosen to match that of the pivotal trial.

There were multiple secondary and exploratory endpoints. The ones discussed here are:

- Mean change from baseline in 24-hour urine calcium excretion
- Proportion of subjects who maintain a calcium phosphate product in the range of 35 to 55 mg^2/dl^2
- Changes in calcium levels
- Distribution of Subjects by NPSP558 Dose at the End of Treatment Visit
- Changes from baseline in bone turnover markers, PTH antibodies, and bone mineral density

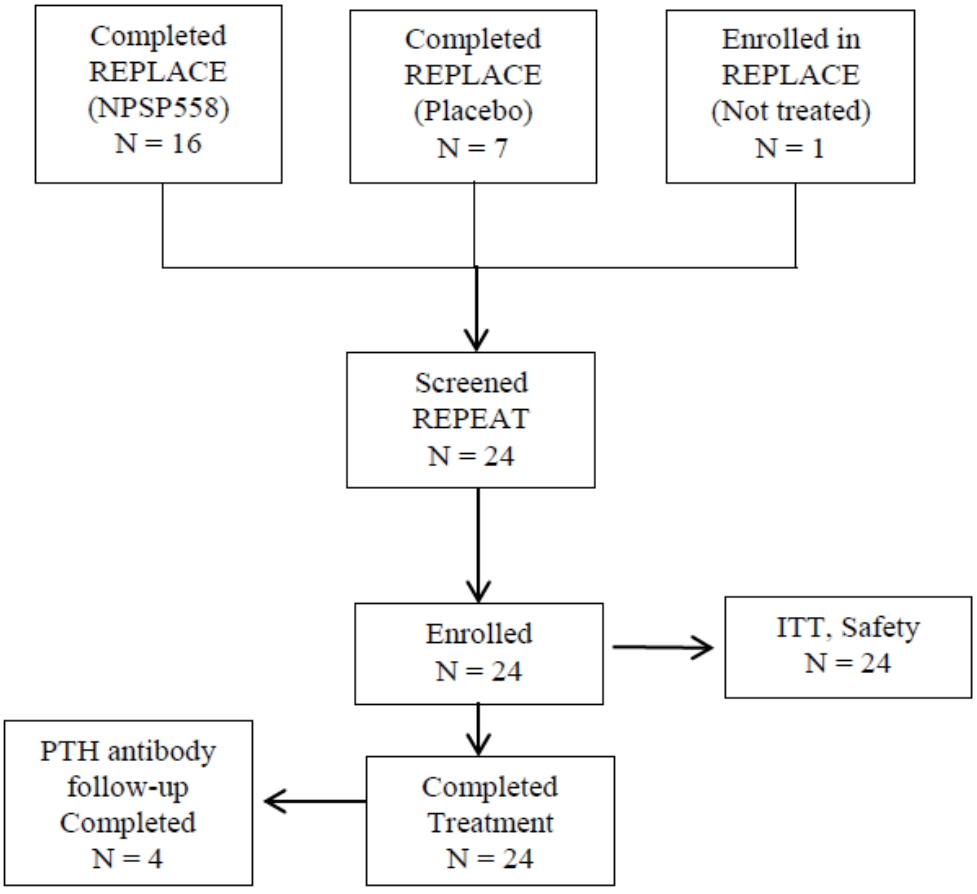
One of the secondary endpoints was ‘mean percentage changes from baseline in supplemental oral calcium and supplemental calcitriol/alfacalcidol dosages at each visit’. While this review will not detail percentage decreases, the observed decreases in dosage for supplements is discussed generally under secondary endpoints below. In particular, emphasis is placed on those subjects who were able to completely come off one or both supplements.

Safety Evaluations: adverse events, incidence of hypocalcemia and hypercalcemia, laboratory tests, DXA scans, ECG

Protocol Amendments: Approximately 4 months into the trial, a clarification was added indicating that final REPLACE parameters could be used as baseline for the REPEAT trial if they were collected within 4 weeks of the baseline for REPEAT.

Disposition: Of the 24 subjects enrolled, 23 had completed REPLACE. An average duration of 10.4 weeks elapsed between the completion of REPLACE and enrollment into this trial. Seven subjects enrolled in this trial received placebo in REPLACE and 16 had received NNPSP558 at doses of 50 to 100 µg daily. One additional subject was in the optimization phase of REPLACE when randomization closed and enrolled in the trial having no prior exposure to NPSP558. There were no significant protocol violations. Subjects who tested positive and/or specific for antibodies to PTH were followed for an additional 6 months to ascertain antibody sensitivity following withdrawal of study drug. While all 24 subjects completed, treatment, only 4 subjects completed the follow-up period for PTH-antibody measurements. This is summarized below:

Subject Disposition



From Applicant's CSR Trial 009, Figure 10-1

Protocol Deviations:
The majority (75%) of subjects had at least one protocol deviation, the majority of which were considered minor. They are summarized below. The one inclusion/exclusion violation involved a woman with an FSH below 40; however, she had not had menses in the 19 years prior to enrollment. There were 3 study drug dosing violations, all due to a reduction in study drug to 50 µg every other day in response to safety concerns over persistent hypercalcemia.

Summary of Reported Protocol Deviations by Categories—ITT Population

Protocol Deviation Category[a]	All Subjects N = 24 n (%)	Number of Deviations per Category
Subjects with at Least One of the Listed Deviations	18 (75)	
Inclusion/exclusion criteria	1 (4.2)	1
Study drug dosing	3 (12.5)	5
Compliance, supplements	3 (12.5)	3
Missed procedures	14 (58.3)	33
IP dispensing/return	8 (33.3)	10

Applicant's CSR Trial 009, Table 10-2

Demographics: All subjects were from 3 centers in Hungary. The mean age of subjects was 52.7 (±10.87 years), primary female (21/24), and all white. The mean duration of hypoparathyroidism was 15.1 (±12.56 years). Most subjects (22/24) were on a calcitriol/alfacalcidol dose of greater than 0.5 µg/day (high dose), but the same number of subjects (22.24) were on a calcium dose of less than 2000 mg/day.

Compliance
Study drug dosing was recorded in subject diaries. Subjects were considered compliant if they took ≥80% to ≤120% of their total expected regimen. Mean compliance was 98.4% (±3.86) with all subjects having greater than 80% compliance.

Efficacy
Primary Efficacy Endpoint
Based on investigator-prescribed data, 18/24 (75%) of subjects were responders at Week 24. Results were identical when using subject diary data.

Analysis of Responder Rate at Week 24 (EOT) Based on Investigator-prescribed Data—ITT Population

	NPSP558 N=24	
Status	n (%)	(95% CI)

Responder	18 (75)	(53.3.3, 90.2)
Non-Responder	6 (25)	

Applicant's CSR, Table 11-3

The Applicant was asked to re-analyze the primary efficacy data, using the identical primary endpoint criteria as the pivotal trial. This analysis, shown below, was similar.

Analysis of Responder Rate at Week 24 Using Primary Endpoint Criteria from Study 040—ITT Population

	NPSP558 N=24	
Status	**n (%)**	**(95% CI)**
Responder	17 (70.8)	(48.9, 87.4)
Non-Responder	7 (29.2)	

Because of the low numbers of subjects involved, subgroup analyses are not presented.

Secondary Efficacy Endpoints

Because the small number of subjects enrolled in this trial, actual values rather than percentages are presented here. There were steep recorded decreases in use of supplements. At baseline, the mean calcitriol dose was 1.13 (±0.42) µg/day and the Week 24 mean dose was 0.02 (±0.1) µg/day. The majority of subjects (23/24) came off all vitamin D analogs by Week 24.

At baseline, the mean dose of oral calcium supplementation was 1688 (±548) mg/day and the Week 24 mean dose was 333 (±540) mg/day. By Week 24, 14 subjects had discontinued taking oral calcium supplementation altogether.

Mean Change from Baseline in 24-Hour Urinary Calcium Excretion

Changes in 24-hour urinary calcium are summarized below for the 24 enrolled subjects. There was one outlier at Week 24, a subject who had a value of 1114 mg/24 hr. Therefore the median value at Week 24 shows a steeper decrease.

Change from Baseline in 24-Hour Urine Calcium Excretion—ITT Population

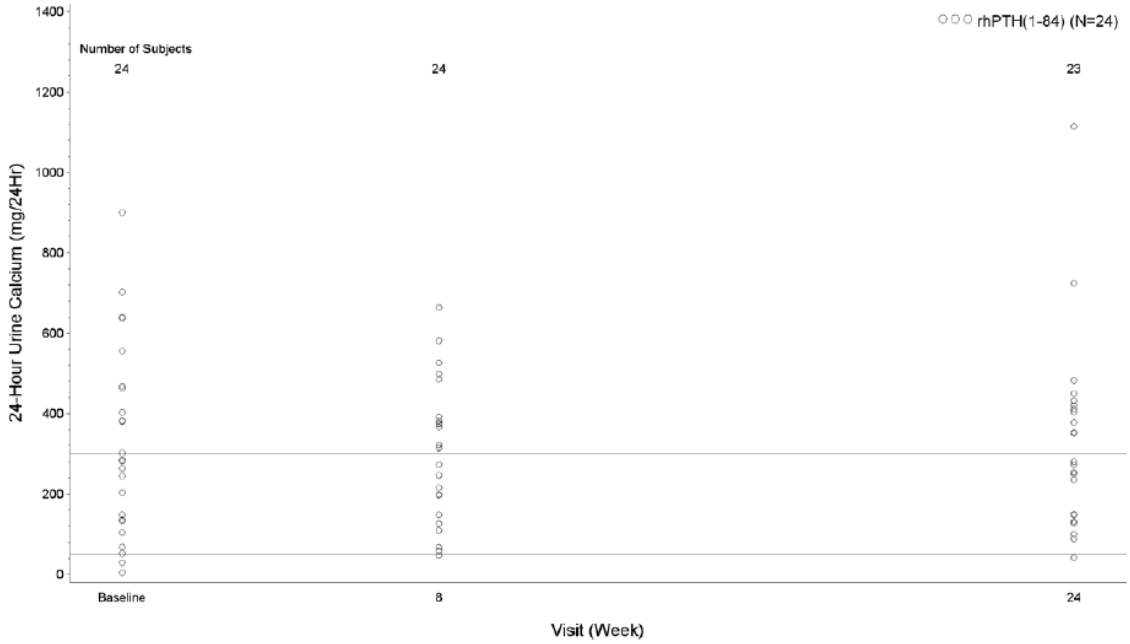
	NPSP558 (N=24)	
24-Hour Urine Calcium (mg/24 hr)	**Actual Value**	**Change from Baseline**
Baseline		
n	24	
Mean (SD)	368 (198)	
Median	329	
Min, Max	49, 872	
Week 8		
n	24	24

Mean (SD)	304 (170)	-65 (188)
Median	315	-37
Min, Max	48, 664	-490, 232
Week 24		
n	23	23
Mean (SD)	331 (234)	-52 (183)
Median	281	-100
Min, Max	42, 1114	-382, 292
End of Treatment		
n	24	24
Mean (SD)	321 (234)	-47 (180)
Median	277	-93
Min, Max	42, 1114	-382, 292

Applicant's CSR Trial 009, Table 11-5

The plot below shows 24-hour urine calcium levels for all subjects at baseline, Week 8, and Week 24. Elevated urine calcium remained an issue at Week 24.

Scatterplot of 24-hour urine calcium (mg/24 hr) by Visit—ITT Population



Applicant's Response to IR 21, May 20, 2014

Proportion of subjects who maintain a calcium phosphate product in the range of 35 to 55 mg^2/dl^2

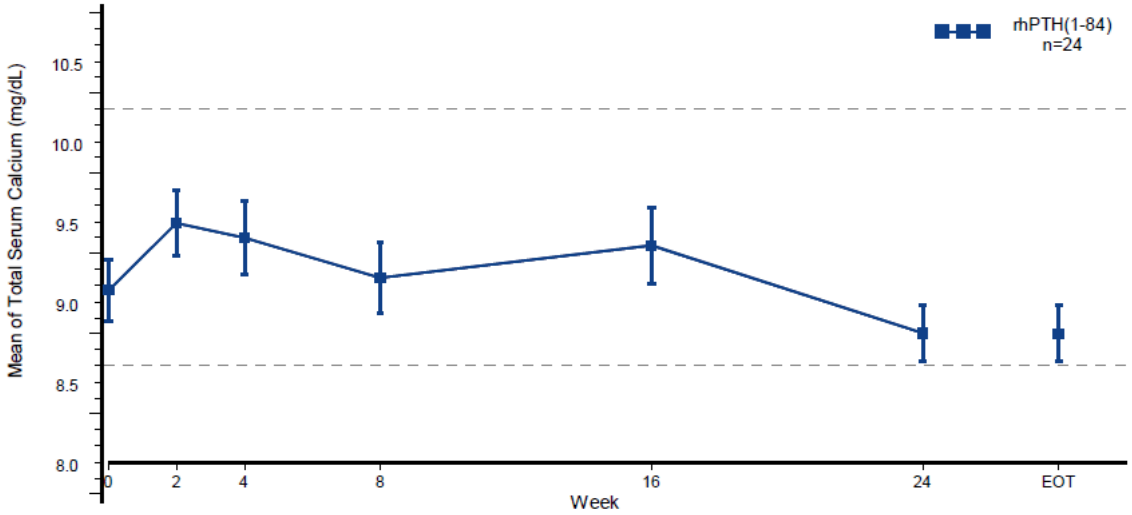
There were only 2 total instances of calcium phosphate product above the acceptable range. The first was a subject at baseline. The second subject had an elevated level at Week 2. Both increased levels were transient, and both of the subjects were considered responders.

Changes in calcium levels

The figure below summarizes changes in total serum calcium by week. The target range was 8-9 mg/dL, therefore the mean at baseline slightly exceeded this (9.07 [0.93] mg/dL) and remained above the target range until Week 24, when the mean value was 8.80 (±0.86) mg/dL.

At Week 24, 10 subjects had total serum calcium values between 8 to 9 mg/dL.

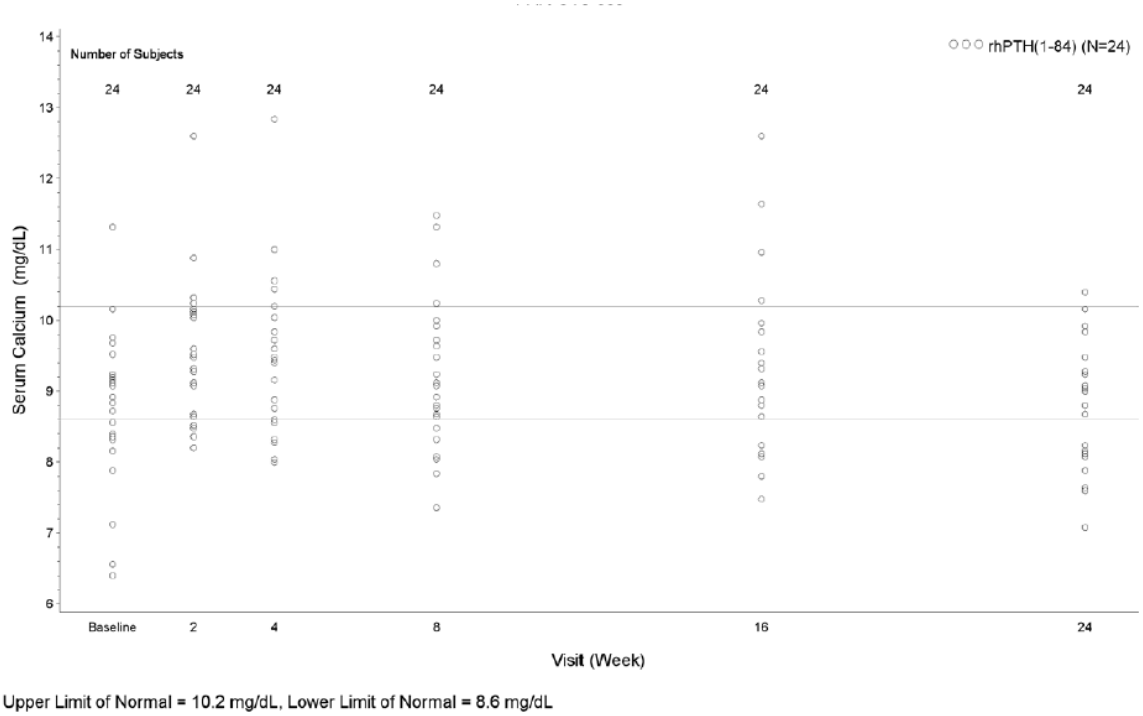
Change in serum calcium—ITT Population



EOT = end of treatment; ITT = Intent-to-Treat; n = number; SE = standard error
Note: EOT is the last observation during the treatment period.
Note: The reference lines indicate the normal range of total serum calcium (ie, 8.6 to 10.2 mg/dL).

The plot below shows calcium levels for all subjects by trial visit. At Week 24, most subjects were within normal or just below normal range.

Scatterplot of Serum Calcium (mg/dL) by Visit-ITT Population



Upper Limit of Normal = 10.2 mg/dL, Lower Limit of Normal = 8.6 mg/dL
Applicant's Response to IR 21, Figure 2.1, May 20, 2014

Distribution of Subjects by NPSP558 Dose at the End of Treatment Visit
Up-titration was allowed until Week 16. As in the pivotal trial, the majority of subjects required titration to the highest dose. Of the 5 subjects finishing the trial at 75 µg, 3 had down-titrated from 100 µg daily. Of the 4 subjects completing the trial on a 50 µg dose, one subject was being dose at 50 µg every other day due to persistent hypercalcemia. Two other subjects (of the 4) had interim reductions to every other day dosing, but completed the trial on a daily 50 µg regimen. One of the 4 subjects had been down-titrated from 75 µg.

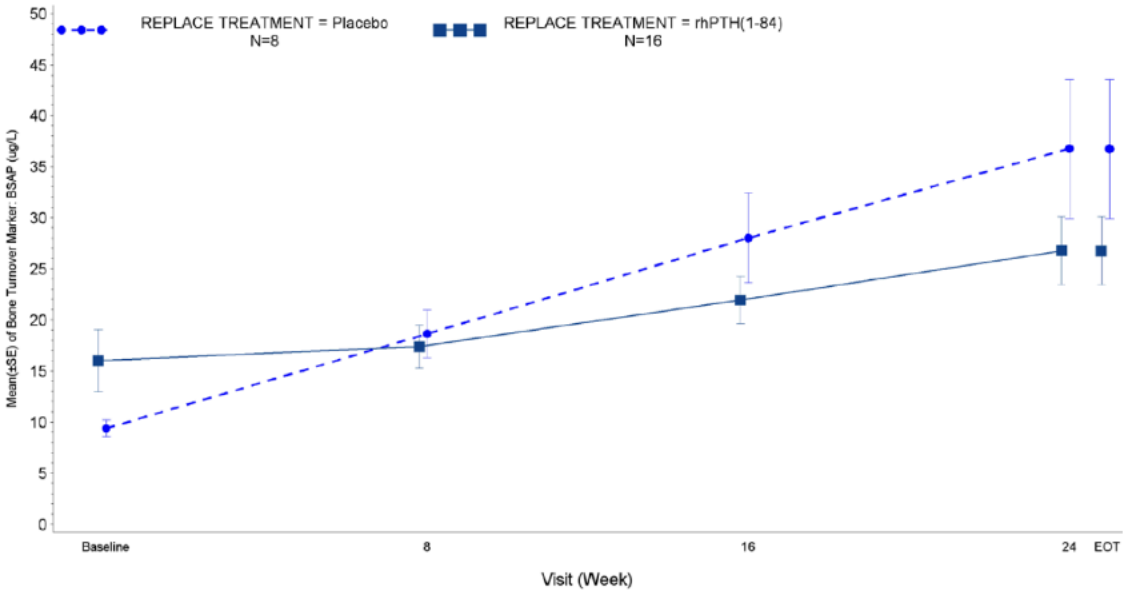
Final NPSP558 Dose Level	**NPSP558 (N=24) n (%)**
100 µg	15 (62.5)
75 µg	5 (20.8)
50 µg	4 (16.7)[a]

[a]Subject 8002-0004 was being dosed every other day from Study Day 114 to the end of treatment.
From Applicant's CSR Study 009, Table 11-6

Changes from baseline in bone turnover markers
Bone turnover markers (BSAP, s-CTx, P1NP, and osteocalcin) were assessed at baseline and every 8 weeks during treatment. It should be noted that 16 of the 24

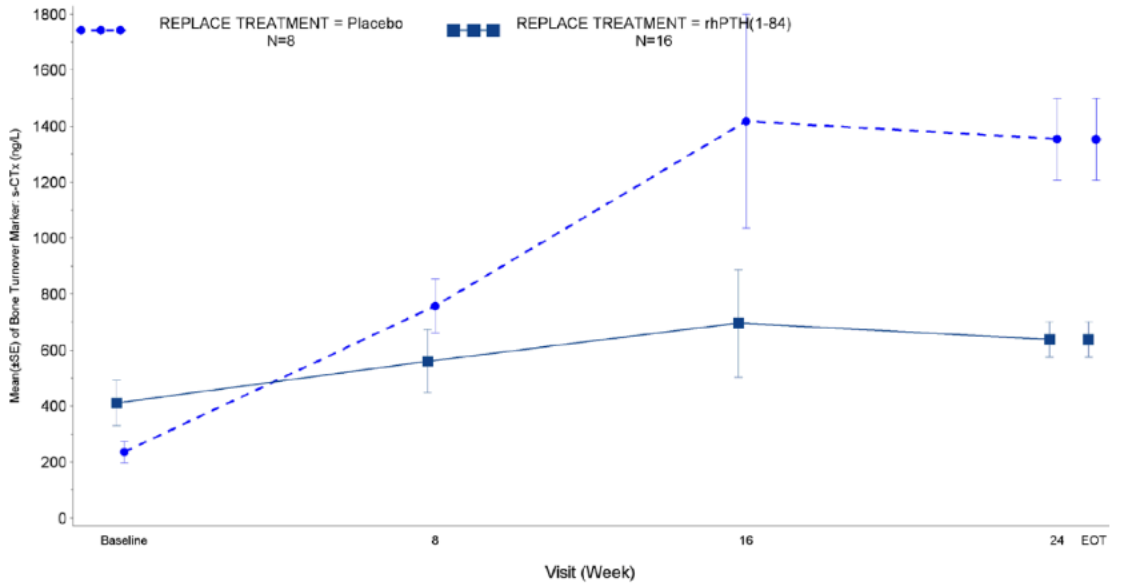
enrolled subjects received NPSP558 during REPLACE, and mean bone markers increased in NPSP558-treated subjects in REPLACE. In this trial, mean increases were seen for each marker, although the increases were more marked for those who had received placebo or were untreated.

Mean (±SE) of BSAP by Week and by Treatment Group in REPLACE Trial

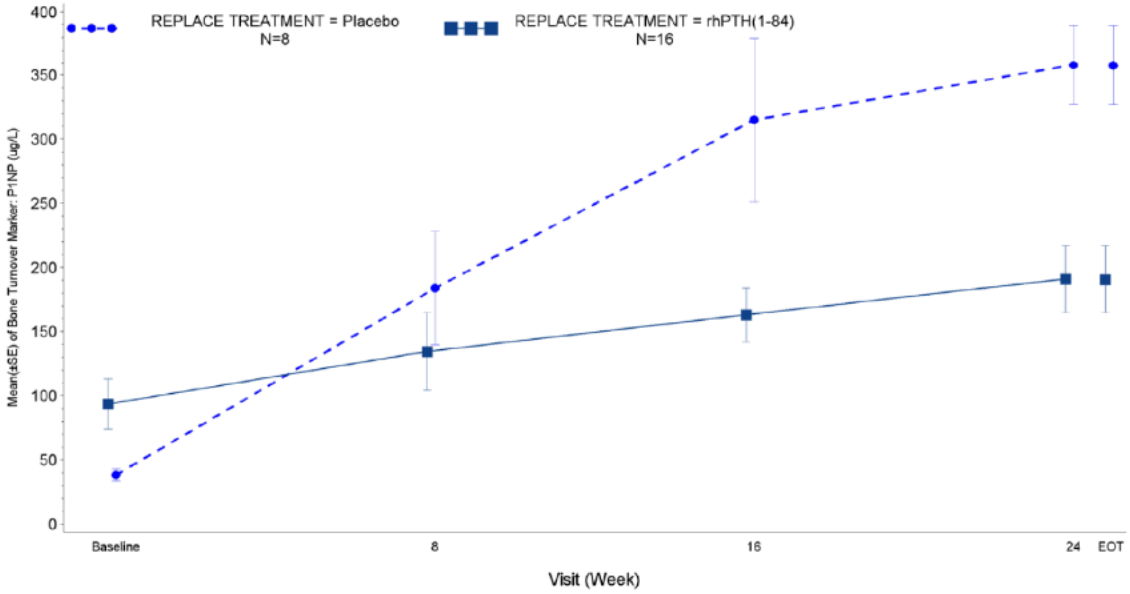


Subjects participating in REPEAT (PAR-C10-009), N = 24, have been divided in 2 groups labeled 'rhPTH(1-84)' (N= 16) if their treatment in the previous REPLACE study was rhPTH(1-84) or 'PLACEBO' (N=8) if their treatment in the previous REPLACE study was placebo (N=7) or not randomized (N=1).
BSAP=bone-specific alkaline phosphatase; SE=standard error
Visit 1 records of PAR-C10-009 are used as Baseline values in the figure.

Mean (±SE) of s-CTx by Week and by Treatment Group in REPLACE Trial

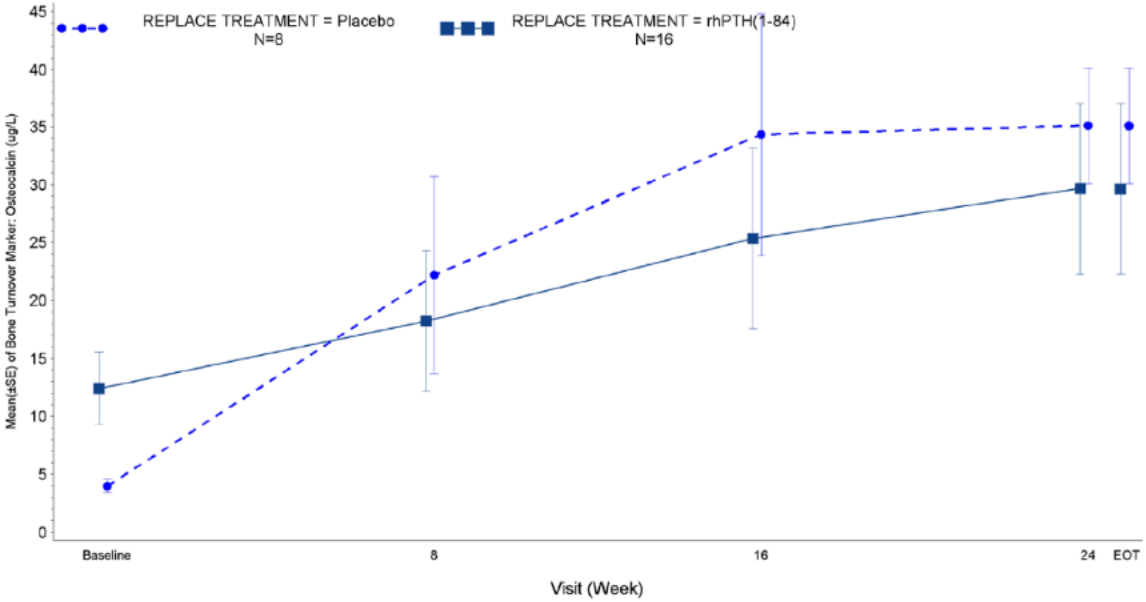


Mean (±SE) of P1NP by Week and by Treatment Group in REPLACE Trial



Subjects participating in REPEAT (PAR-C10-009), N = 24, have been divided in 2 groups labeled 'rhPTH(1-84)' (N= 16) if their treatment in the previous REPLACE study was rhPTH(1-84) or 'PLACEBO' (N=8) if their treatment in the previous REPLACE study was placebo (N=7) or not randomized (N=1).
P1NP=procollagen amino-terminal peptide; SE=standard error

Mean (±SE) of Osteocalcin by Week and by Treatment Group in REPLACE Trial



Subjects participating in REPEAT (PAR-C10-009), N = 24, have been divided in 2 groups labeled 'rhPTH(1-84)' (N= 16) if their treatment in the previous REPLACE study was rhPTH(1-84) or 'PLACEBO' (N=8) if their treatment in the previous REPLACE study was placebo (N=7) or not randomized (N=1).
SE=standard error
Visit 1 records of PAR-C10-009 are used as Baseline values in the figure.

Change from Baseline in Bone Mineral Density

For this trial, the DXA results from the end of the REPLACE trial were used as baseline if it was done within 6 months of this trial. DXA was then done again at Week 24. As in REPLACE, the general trend observed was a decrease in mean absolute DXA values of BMD measurements, with the exception of lumbar spine, hip-Ward's triangle, and distal one-third radius. This decrease was more marked in treatment-naïve subjects. The Z-scores at Week 24 showed minimal differences from baseline for all subjects.
The four figures below depict the mean values of bone markers during the trial. Subjects in this trial came from REPLACE, enrolling both rhPTH(1-84)-treated and placebo subjects. Since rhPTH(1-84)-treated subjects already had changes in bone markers from REPLACE, the figures below separate the 2 groups. As expected, former placebo subjects had steeper changes compared to those already exposed to rhPTH(1-84).

PTH Antibodies
Data regarding PTH antibodies for all trials are discussed under the pivotal trial.

Safety
All 24 subjects had at least 24 weeks of exposure to study drug.

There were no deaths or SAEs and no subjects discontinued due to an AE.

Treatment-emergent AEs were reported by 22/24 (91.7%) of subjects (a total of 112 events). The following table summarizes TEAEs occurring in at least 5% of subjects. Many, if not most, of these AEs are common in the hypoparathyroid population. Interpretation of these data without a comparator is difficult. It should be noted that the table below shows that there were 5 subjects with hypercalcemia, with a total of 7 events. These events relied on Investigator judgment tacking into account symptomatology and/or calcium levels, but were not based on calcium level alone. Therefore, an adverse event of hypercalcemia may or may not have had an associated increased calcium level. This analysis is different than the analyses of specific calcium-related events, further below, which captures only abnormal laboratory calcium values.

Summary of Treatment-Emergent AEs Occurring in ≥5% of Subjects by SOC and PT—Safety Population

Preferred Term	NPSP558 N=24 n (%)	Events
Hypoesthesia	12 (50)	23
Muscle spasms	6 (25)	8
Vitamin D decreased	6 (25)	6
Hypercalcemia	5 (21)	7
Fatigue	4 (17)	6
Hypocalcemia	4 (17)	5
Headache	4 (17)	5
Hypoesthesia oral	3 (13)	4
Arthralgia	3 (13)	3

Tetany	3 (13)	3
Abdominal pain upper	2 (8)	3
Polyuria	2 (8)	3
Hypoesthesia facial	2 (8)	3
Paresthesia	2 (8)	3
Dyspnea	2 (8)	2
Nausea	2 (8)	2

From Applicant's CSR, Table 12-3

In this trial, calcium-associated AEs did not reflect any laboratory-related events. The discussion of hypercalcemia, hypocalcemia, and hypercalciuria below are all related to clinical events.

Hypercalcemia
There were five subjects with a total of 7 hypercalcemia events. All events occurred within the treatment period and 4 of the 7 occurred at or after Week 16. All but one event resulted in an interruption or reduction in study drug dosing. The following are narratives for 3 subjects (of the 5) with notable events:

- One subject had a total serum calcium of 12.6 mg/dL on Day 16 and an level of 12.8 mg/dL on Day 31. At the time of the second event, this subject was completely off supplements. Study drug was then decreased to 50 µg every other day from Day 34 to Day 57, after which 50 µg dosing was resumed.
- The second subject had a total calcium level of 13.6 mg/dL on Study Day 112, which resulted in down-titration of study drug from 100 to 75 µg daily. The subject was off supplements at the time of the event.
- A third subject had a total serum calcium level of 11.5 mg/dL on Day 56 which resulted in a decrease of study drug from 75 to 50 µg daily. Due to persistently elevated calcium levels (range 10 to 11.5 mg/dL), study drug dose was eventually administered every other day, from Day 114 to end of treatment. The subject was off all supplements at the time of the event.

The following table summarizes the incidence of hypercalcemia, by category. The denominator is all calcium laboratory tests available during the trial period. The numerator is the total number of albumin-corrected serum calcium tests with a value that falls in one of the specified categories during the trial period.

Hypercalcemia Incidence—ITT Population

Albumin-corrected Serum Calcium	rhPTH(1-84) N=145 n (%)
>10.6 mg/dL	8 (5.5)
>10.6 and ≤11 mg/dL	2 (1.4)
>11 and ≤12 mg/dL	2 (1.4)
>12 and ≤13 mg/dL	4 (2.8)
>13 and ≤14 mg/dL	0
>14 mg/dL	0

From Applicant's Response to Information Request, May 20, 2014

Below is the same analysis for hypercalcemia, but with the number of total subjects in the denominator and the number of subjects whose calcium fell into one of the specified categories.

Hypercalcemia Incidence—ITT Population

Albumin-corrected Serum Calcium	rhPTH(1-84) N=24 n (%)
>10.6 mg/dL	4 (16.7)
>10.6 and ≤11 mg/dL	1 (4.2)
>11 and ≤12 mg/dL	2 (8.3)
>12 and ≤13 mg/dL	3 (12.5)
>13 and ≤14 mg/dL	0
>14 mg/dL	0

From Applicant's Response to Information Request, May 20, 2014

Hypocalcemia
There were 4 subjects with hypocalcemia (4 events total). Three of the four events occurred during the post-treatment period, which was also a frequent event in the pivotal trial. The one subject with hypocalcemia during the treatment period had a total serum calcium level of 7.6 mg/dL on Day 128. At the time, the subject was on a dose of NPSP558 100 µg daily and taking calcitriol 0.25 µg/day and a calcium dose of 1500 mg/day. The hypocalcemia resolved after changing her doses of oral calcium and calcitriol to 200- mg/day and 0.50 µg/day, respectively.
The following table summarizes the incidence of hypocalcemia, by category.

Hypocalcemia Incidence—ITT Population

Albumin-corrected Serum Calcium	rhPTH(1-84) N=145 n (%)
<8.4 mg/dL	51 (35.2)
>8 and <8.4 mg/dL	19 (13.1)
>7 and ≤8 mg/dL	30 (20.7)
>6 and ≤7 mg/dL	2 (1.4)
>5 and ≤6 mg/dL	0
<5 mg/dL	0

From Applicant's Response to Information Request, May 20, 2014

Below is the same analysis for hypocalcemia, but with the number of total subjects in the denominator and the number of subjects whose calcium fell into one of the specified categories.

Hypocalcemia Incidence—ITT Population

	rhPTH(1-84) N=24

Albumin-corrected Serum Calcium	n (%)
<8.4 mg/dL	19 (79.2)
>8 and <8.4 mg/dL	12 (50)
>7 and ≤8 mg/dL	14 (58.3)
>6 and ≤7 mg/dL	2 (8.3)
>5 and ≤6 mg/dL	0
<5 mg/dL	0

From Applicant's Response to Information Request, May 20, 2014

Hypercalciuria
There were no reported AEs of hypercalciuria.

Laboratory Evaluations
Changes in Mean Values: There were no clinically meaningful changes in mean values for hematology or urinalysis parameters. For chemistry parameters, there were only two parameters—creatine phosphokinase (CPK) and alkaline phosphatase (ALP)--with notable changes, summarized below. The ALP changes could be related to the increase in bone turnover markers. Changes in other lives tests were unremarkable.

The following table summarizes mean changes for chemistry parameters:

Change from Baseline to Week 24 for CPK and ALP

Parameter	**NPSP558 N=24**
CPK (U/L)	-128 (539) -9 (-2646, 77)
ALP	60±32.7 62.5 (2, 150)

Plus-minus values are mean±SD; values with parentheses are median (min, max)

Markedly abnormal values: There were no subjects with markedly abnormal hematology or urinalysis values during the trial. Below is a summary of markedly abnormal values for chemistry parameters. Regarding the abnormal calcium values, all 16 subjects noted below had calcium values ≤8.4 mg/dL (range 7.1 to 8.4 mg/dL). Three subjects also had calcium values above 12 mg/dL (range 12.6 to 13.7 mg/dL).

Markedly Abnormal Laboratory Values—Clinical Chemistry—Safety Population

Laboratory Parameter	**NPSP558 N=24 n/m (%)**
Subjects with at least one abnormal post-baseline value, during treatment period	19/24 (79.2)
Calcium	16/24 (66.7)
Urea	3/24 (12.5)
Phosphate	1/24 (4.2)

N=number

m=represents the number of subjects who have valid measurements at any post-baseline visit and n is the number of subjects having at least one abnormal value

Vital Signs
Changes in mean vital signs over the trial were unremarkable. Markedly abnormal vital signs occurred in 2 subjects: one subjects with a low pulse rate and one with a high pulse rate. There were no clinical sequelae to either of these observations.

EKGs
There were 2 subjects with abnormal EKG findings at baseline: one with first degree AV block and one with ST segment depression. At Week 24, there were 6 subjects with abnormal, but not clinically significant EKG findings (does not include QT findings, discussed further below). These included the two subjects with abnormal baseline findings plus an additional 4 subjects with the following: premature ventricular complexes, T-wave inversion, and two with unspecified findings.

Mean changes at Week 24 for EKG parameters were unremarkable.

QT findings: The Applicant provided a separate EKG report combining data from all NPSP558 hypoparathyroid safety and efficacy studies. The table below summarizes QT findings considered clinically significant. No Subjects had a QT prolongation above 500 ms. Of note, in the pivotal trial, QT abnormalities were observed more frequently in the placebo group. One cannot make conclusions without a comparator in this trial.

Summary of Clinically Significant QTc Results—Safety Population

Parameter	NPSP558 N=24 n/m (%)
QTcB	
Any Post-baseline Clinically Significant Value	8/24 (33.3)
Post-baseline value ≥ 500 ms	0
Post-baseline value > 480 ms	2/24 (8.3)
Post-baseline value > 450 ms	8/24 (33.3)
Post-baseline value ≥ 60 ms	0
Post-baseline value ≥ 30 ms	0
QTcF	
Any Post-baseline Clinically Significant Value	2/24 (8.3)
Post-baseline value ≥ 500 ms	0
Post-baseline value > 480 ms	1/24(4.2)
Post-baseline value > 450 ms	2/24 (8.3)
Post-baseline value ≥ 60 ms	0
Post-baseline value ≥ 30 ms	0

From Applicant's CSR, Table 12-8

Trial 008: A Long-term Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant rhPTH(1-84), for the Treatment of Adults with Hypoparathyroidism—A Clinical Extension Study (RACE)

This is an ongoing, long-term open-label trial in adults with hypoparathyroidism. There is no control group. To be eligible, subjects had to have previously completed Study 007 (RELAY) and/or completed Study 040 (REPLACE). The purpose of the trial was to assess the safety and tolerability of varying doses of NPSP558 during long-term treatment, while reducing requirements for supplemental calcitriol and oral calcium supplementation to as low as safely possible while maintaining total serum calcium levels and controlling hypercalciuria. The starting doses were 25 or 50 µg, depending on an algorithm (further discussed below). The Applicant states that this trial simulated a more real-world setting as up-titration was allowed at any time.

The primary objective of the trial is to demonstrate long-term safety and tolerability of NPSP558 as hormone replacement therapy for the treatment of adults with hypoparathyroidism.

The secondary objectives differed somewhat than the previous trials. They are:

- To evaluate the impact of different preparations of calcium and calcitriol on the response to NPSP558 therapy
- To demonstrate that dosing with NPSP558 across a dose range of 25 to 100 µg SC can be implemented in a safe and effective manner and can be maintained throughout long-term treatment.
- To evaluate the impact of calcium-sparing diuretics on serum and urinary calcium

There were no exploratory objectives.

Given that this trial was open-label without a comparator, only the primary efficacy results will be discussed, unless there are particularly notable findings.

A subject was considered a responder if they met the following 3 criteria at Week 52 (Visit 9) and at End of Treatment:

- A ≥50% reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of ≤500 mg
  AND
- A ≥50% reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of ≤0.25 µg
  AND
- An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value (≥7.5 mg/dL) and does not exceed the ULN of the central laboratory

There were multiple secondary efficacy endpoints.

The baseline parameters for the efficacy variables for RACE were the end of study parameters from RELAY or REPLACE.

Study Dose and Design: Starting dose of NPSP558 was 25 or 50 µg daily. Subjects with total serum calcium of ≤9.5 mg/dL had a starting dose of 50 µg. Subjects with a total serum calcium of >9.5 mg/dL had a starting dose as follows:

- Subjects who were taking supplements (≥ 500 mg calcium and/or any calcitriol) had the supplements reduced or stopped and started at a dose of 50 µg SC QD.
- Subjects who were taking minimal or no supplemental calcium (< 500 mg) and no calcitriol had a starting dose of 25 µg SC QD.

During the first 12 months, visits were to take place at Weeks 1, 4, 8, and then every 8 weeks up to Week 48 (Visit 8). The Week 52 visit was to be scheduled 4 weeks later.

At the end of Week 52, subjects were invited to enter a second year extension period. During this time, subjects were to return to the clinic every 2 months.

The dose of NPSP558 could be increased in increments of 25 µg to a maximum of 100 µg at any time during the trial, with the goal of achieving or maintaining total serum calcium levels in the range of 8-9 mg/dL. The dose could be down-titrated at any time for efficacy or safety reasons.

Adjustment of calcium and calcitriol was based on serum calcium levels, with the goal to be a reduction or removal of calcitriol treatment to the maximum clinically possible and to decrease calcium supplementation to ≤500 mg daily. Blood draw were performed 3-5 days after any dose adjustment of NSPP558 or after any significant change in supplements.

If any pre-dose calcium level was >11.9 mg/dL, study drug was to be stopped. Once serum calcium was in the normal range again, study drug was reintroduced: at the previous dose level if reductions in supplements took place or at the next lowest dose level if calcium had previously been reduced to ≤500 mg daily and calcitriol was eliminated.

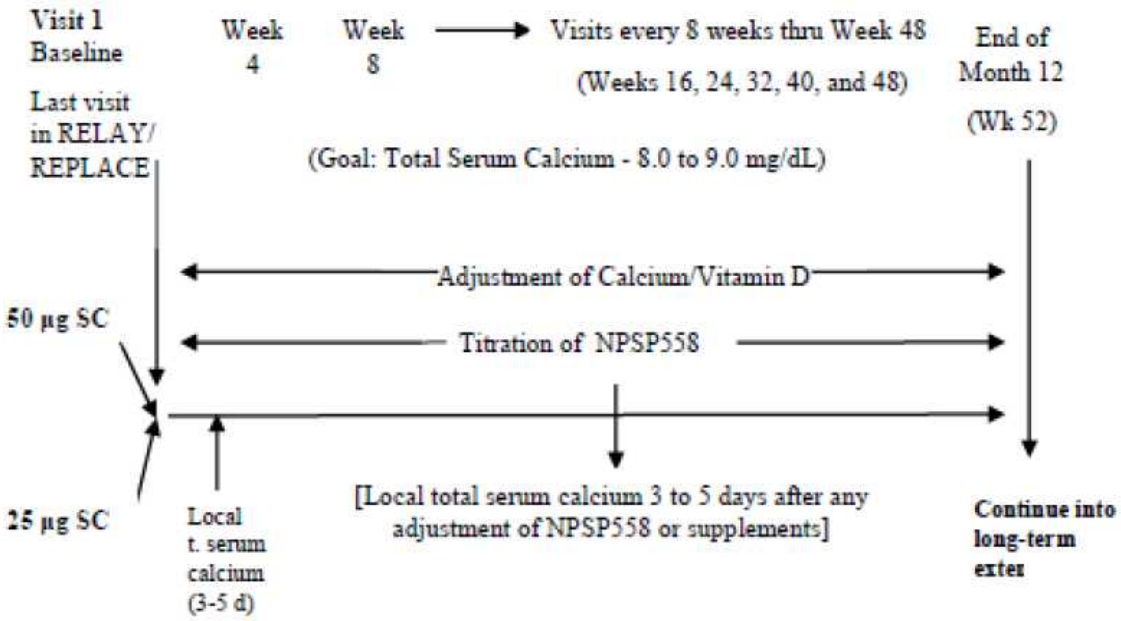
If the pre-dose serum calcium level remained above 10 mg/dL for two or more assessments, the NPSP558 dose was to be reduced at the next lowest dose level. If it remained above the ULN for 2 or more assessments at the lowest dose level, study drug was to be stopped following withdrawal of all supplements.

At any time following Week 16 (Visit 4), subjects who were on a stable dose of NPSP558 and a 24-hour urine calcium >300 mg (males) or >250 mg (females) were allowed to be treated for hypercalciuria with calcium-sparing diuretics, if not already

introduced. The dose of the diuretic could subsequently be adjusted. Monitoring of urine calcium was done at Weeks 16, 32, and 52 and every 4 months thereafter.

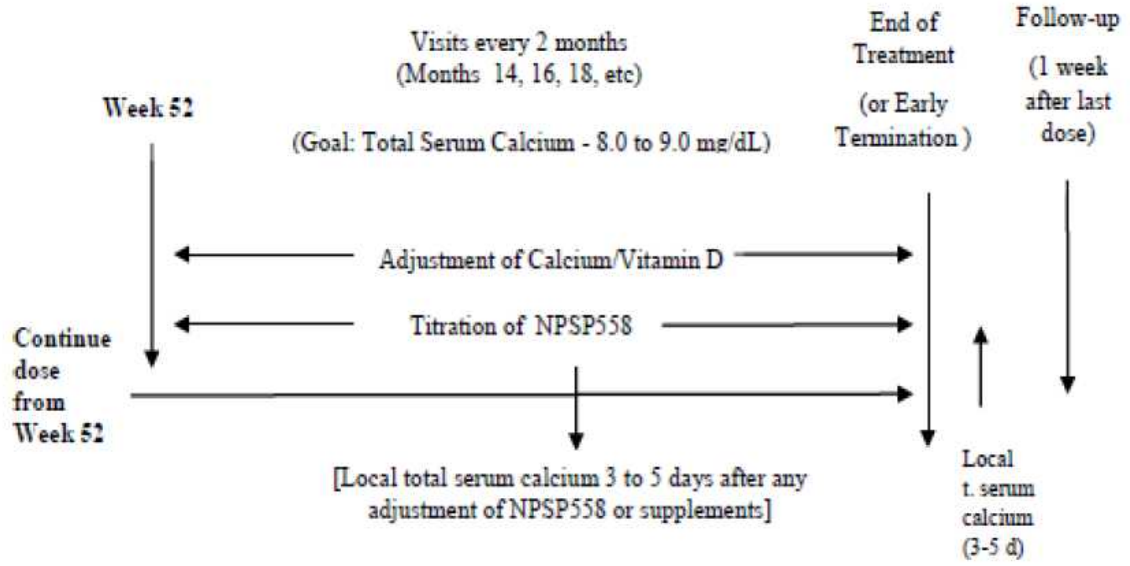
The figure below depicts the overall trial design:

Study design for the initial 12 months



From Applicant's CSR, Figure 9-1

Study design for the long-term extension



From Applicant's CSR, Figure 9-1

Key Inclusion Criteria were:

1) Previously completed RELAY and/or completed REPLACE
2) Women must be postmenopausal, surgically sterilized, or of childbearing potential with a negative pregnancy test at screening and willing to use two acceptable methods of contraception.
3) Serum creatinine <1.5 mg/dL at enrollment
4) Total serum calcium ≤ULN prior to enrollment
5) Serum 25(OH) vitamin D≤1.5 times the ULN within approximately 16 weeks prior to enrollment

Key exclusion criteria were:

1) Any disease or condition that had a high probability of precluding the subjects from completing the trial
2) Pregnant or lactating women
3) Prohibited concomitant medications: raloxifene, bisphosphonates (oral or IV), calcitonin, fluoride tablets

Oral calcitriol was provided by the Applicant for the first 52 weeks of the trial but not for the long-term extension. Oral calcium was provided during the entire trial.

Although the trial was initiated with the Ypsomed pen, this was switched to the Haselmeier pen.

Safety evaluations were similar to those in the pivotal trial.

Disposition:
The table below summarizes subject disposition. The majority of subjects had previously completed RELAY. Also, as of the data cut-off for the report, 89.8% of subjects were on-going with treatment. Two subjects discontinued during the first 12 months, both due to 'subject's decision'. One subject discontinued during the extension due to becoming tired of the daily injections. There was an additional subjects not captured in the table below who did not 'formally' discontinue at the time of data cut-off who did not participate in the trial because of metastatic lung cancer.

Subject Disposition—All Subjects, Excluding Site 1002

Disposition, n (%)	All Subjects N=49 (100)
First 12 months of trial	
Completed	47 (95.9)
Discontinued	2 (4.1)
Extension period	
Entering extension period	46 (93.9)
Discontinued in extension	2 (4.1)
Subject's decision	1 (2)
Adverse event	1 (2)
On-going with treatment	44 (89.8)

Applicant's Submission dated June 2, 2014, Table B-14.1.1.4.1

Protocol Deviations
There were no protocol deviations which excluded subjects from the ITT Population.

Demographics
All study sites were in the US. The table below summarizes baseline characteristics.

Demographic and Baseline Characteristics, Excluding Site 1002

Parameter	**NPSP558 N=49**
Age at screening (yrs) n (%)	
Mean (SD)	48.1 (9.8)
Median	48
Min, Max	26, 66
Age category at screening, n (%)	
<45 years	16 (33)
45 to 64 years	31 (63.3)
≥65 years	2 (4.1)
Gender	
Female	40 (82)
Male	9 (18)
Race	
White	46 (94)

Asian	2 (4.1)
Native Hawaiian/Pacific Islander	1 (2)
Ethnicity	
Hispanic or Latino	1 (2)
Not Hispanic or Latino	48 (98)
Prescribed calcitriol at baseline, n (%)	
Low dose (0 to 0.25 µg/day)	13 (26.5)
Medium dose (>0.25 to 0.5 µg/day)	16 (32.7)
High dose (>0.50 µg/day)	20 (40.8)
Prescribed calcium dose at baseline, n (%)	
0 to 2000 mg/day	31 (63.3)
>2000 mg/day	18 (36.7)
Duration of hypoparathyroidism	
≤5 years	6 (12.2)
>5 to 10 years	19 (38.8)
> 10 years	24 (49)
Duration of hypoparathyroidism (yrs)	
Mean (SD)	15.9 (12.5)
Median	10
Min, Max	2, 47

Applicant's Submission dated June 2, 2014, Table B-14.1.2.1

Medical History and Concomitant Medications were reviewed and are not described in this document.

Treatment compliance was high in the first 12-month period, with a mean (±SD) compliance of 92% (±5.2) with 52/53 subjects having ≥80% compliance.

Efficacy

Efficacy analysis was conducted at two evaluation points: Week 52 and EOT. A subject must have met all 3 criteria to have been considered a responder. The table summarizes the pre-defined responder rates at the two time points. Although this analysis represents data from an open-label without a comparator, the results do suggest sustainability of treatment beyond the 24 weeks seen in the pivotal trial.

Analysis of Responder Rate Based on Investigator-prescribed Data, Excluding Site 1002

	NPSP558 (N=49)	
	n/m (%)	(95% CI)
Week 52		
Responder	34/45 (75.6)	(60.5, 87.1)
Non-responder	11/45 (24.4)	
End of Treatment		
Responder	25/48 (52.1)	(37.2, 66.7)
Non-responder	23/48 (47.9)	

Percentages are based on 'm', the number of ITT subjects with valid responder values available at the visit.
From Applicant's Submission dated June 2, 2014, Table B-14.2.1.1.1

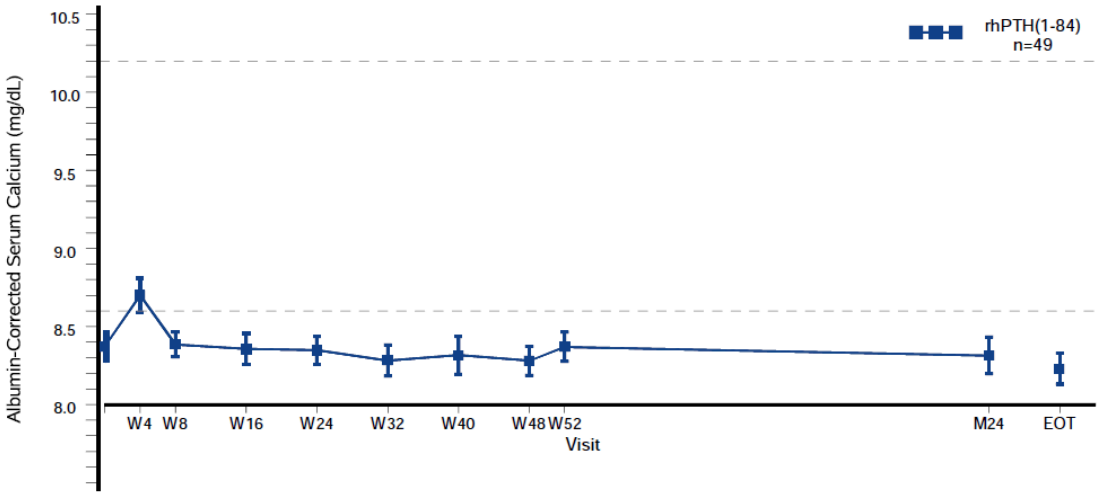
Change from Baseline in 24-hour Urinary Calcium Excretion
At baseline (n=52), the mean (±SD) 24-hour urinary calcium excretion was 354.33 (±196.96) mg/24 hr. At Week 52 (n=48), the mean 24-hour urinary calcium excretion was 317.31 (±174) mg/24 hr.

There were 5 subjects who used calcium-sparing diuretics at baseline, and the mean 24-hour urinary calcium of these subjects was 412.80 (±268.79) mg/24 hr at baseline. At Week 52, the 24-hour urinary calcium in these subjects was still higher compared with subjects not using them (423.60 (±180.65) vs. 304.95 (171.1), respectively).

There were no subjects who had calcium-sparing diuretics added during the trial.

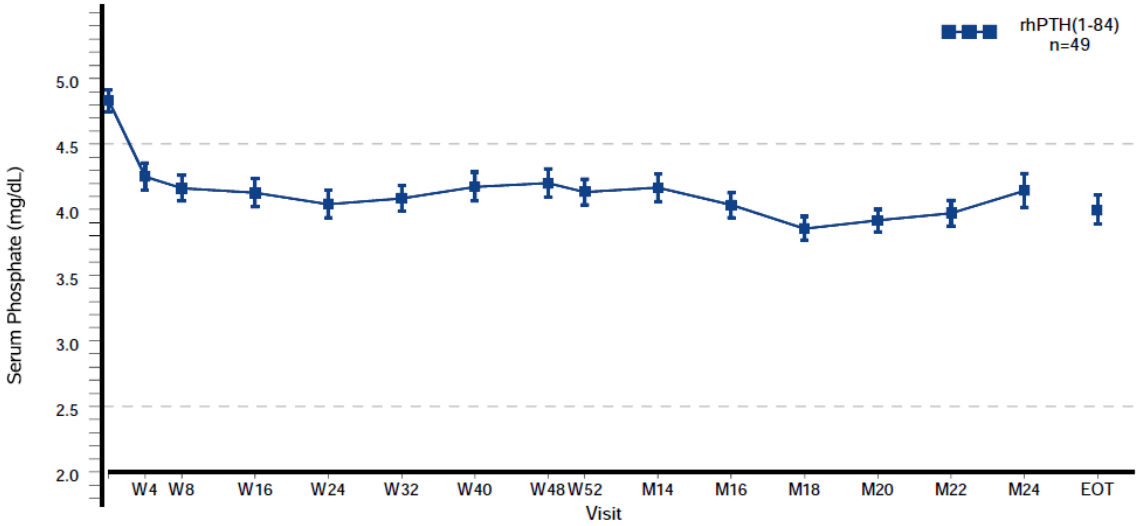
Change from Baseline in Albumin-corrected Total Serum Calcium and Serum Phosphate
Mean calcium levels changed little from baseline to Week 52. Mean levels at both time points were within the target range (8 to 9 mg/dL), which was slightly below the normal range of total serum calcium levels (8.6 to 10.2 mg/dL).

Mean (±SE) of Observed Values in Albumin-Corrected Serum Total Calcium by Visit—ITT Population



Applicant's Submission Dated June 2, 2014, Figure B-14.2.4.2
Mean serum phosphate decreased into the range of normal during the trial.

Mean (±SE) of Observed Values in Serum Phosphate—ITT Population



Applicant's Submission dated June 2, 2014, Figure B-14.2.6.2

The following table summarizes the final dose of NPSP558 as of data cut-off. Similar to the pivotal trial, the majority of subjects required the highest dose.

NPSP558 Dose Level as of data cut-off—ITT Population, Excluding Site 1002

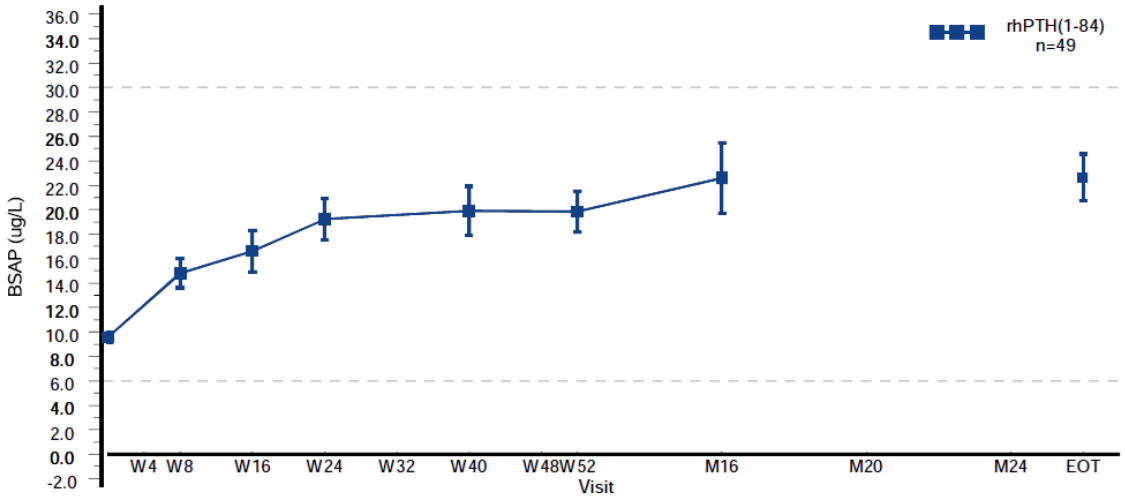
NPSP558 Dose Level	**NPSP558 N=49 n (%)**
25 µg	0
50 µg	10 (20.4)
75 µg	6 (12.2)
100 µg	33 (67.3)

From Applicant's Submission dated June 2, 2014, Table B-14.2.8.1

Change from Baseline in Bone Turnover Markers

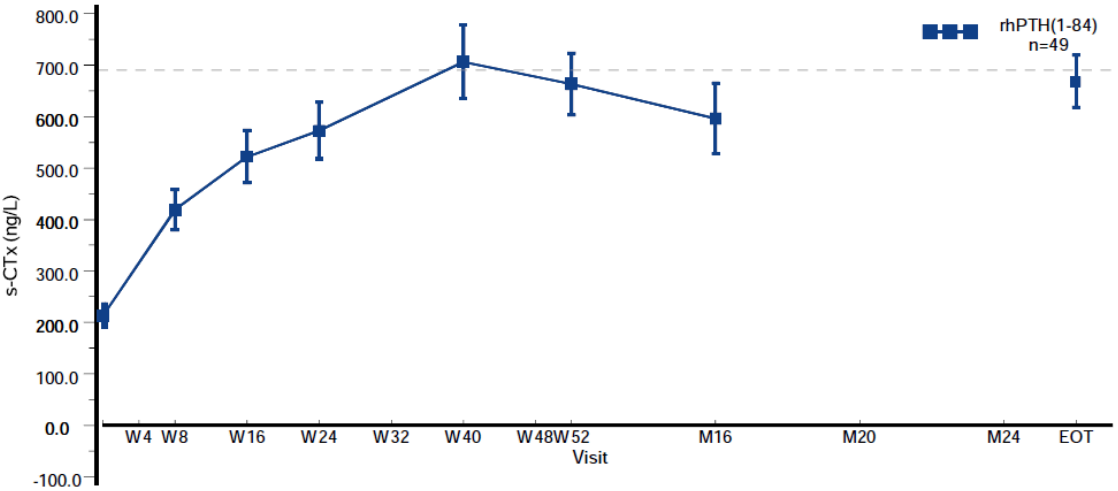
The figures below depict the changes in bone turnover markers during the 52 weeks. It should be noted that the baseline values in this trial reflected the final values from either RELAY or REPLACE, in which increases in subjects' bone markers were observed. With the exception of osteocalcin, levels of other markers appeared to plateau or decrease.

Mean (± SE) of Observed Values in Bone-Specific Alkaline Phosphatase (BSAP) – ITT Population



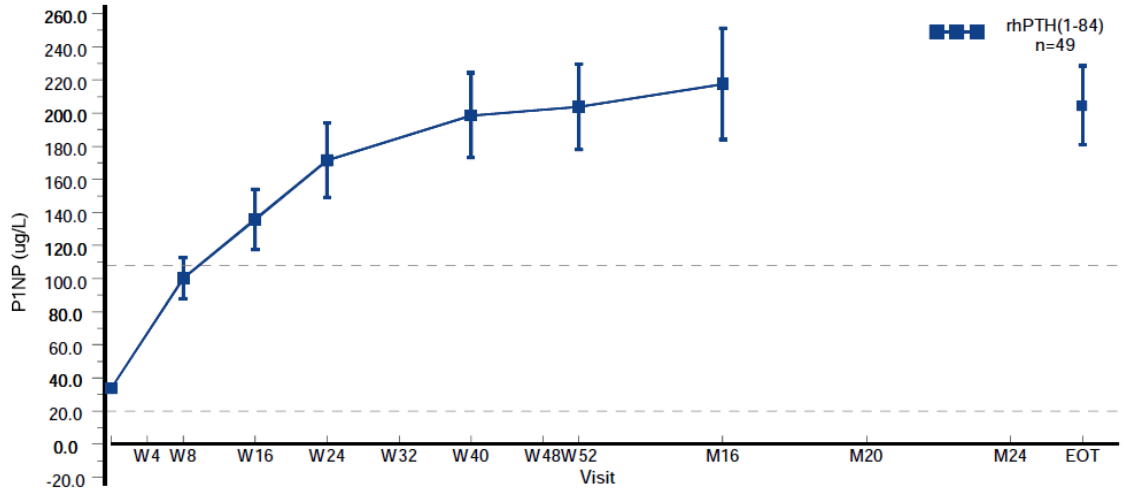
From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.1.2

Mean (± SE) of Observed Values in Serum Carboxy-Terminal Telopeptide of Type I Collagen (s-CTx) – ITT Population



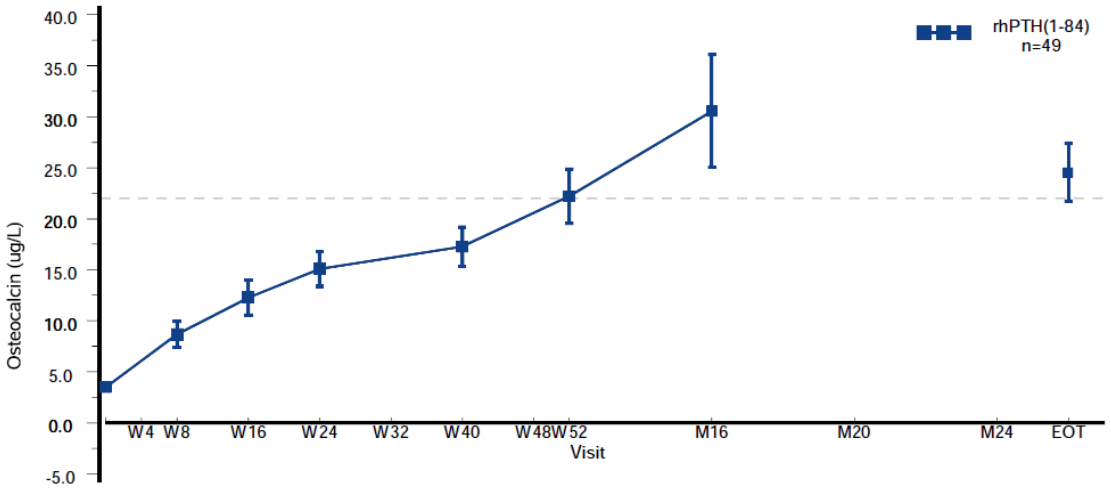
From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.2.2

Mean (± SE) of Observed Values in Serum Procollagen Type 1 Amino-terminal Propeptide (P1NP)—ITT Population



From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.3.2

Mean (± SE) of Observed Values in Osteocalcin—ITT Population



From Applicant's Submission dated June 2, 2014, Figure B-14.2.7.4.2

Change from Baseline in Bone Mineral Density

DXA was done at baseline and at Week 52. Six subjects were excluded from the analysis because different machines were used at the two time points. The data are not presented here as there were minimal mean changes for all measurements.

Calcium-phosphate product

All subjects had a normal calcium-phosphate product at Week 52.

SAFETY

Exposure:

The mean duration of exposure was 576.8 days (±129) days. The minimum time on study drug was 41 days and the maximum was 719 days. Three subjects had an exposure of at least 24 months.

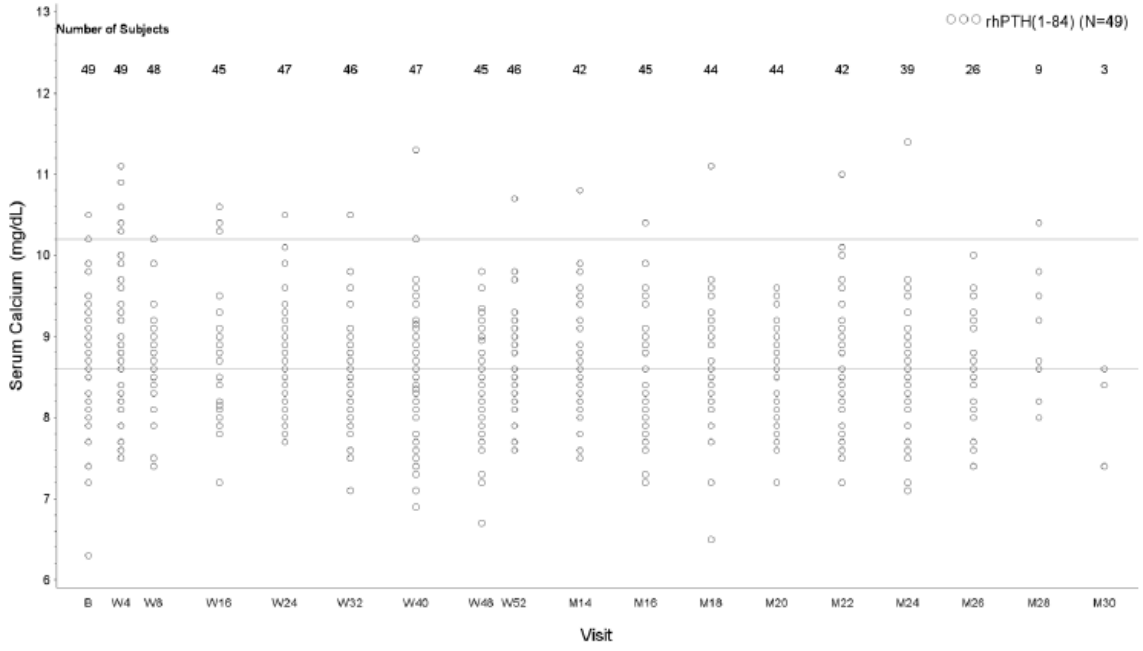
Adverse Events

There were no deaths and no discontinuations due to AEs. There were 4 SAEs during the trial. Overall, 51 (96.2%) subjects experienced at least one AE (total of 507 events). A detailed discussion of all AEs is not included in this review. The following important observations are made:

- Hypocalcemia was observed in 14 (26.4%) subjects (total of 23 events).
- Hypercalcemia was observed in 6 (11.3%) subjects (total of 9 events).
- Hypercalciuria was observed in 4 (7.5%) subjects (total of 6 events).

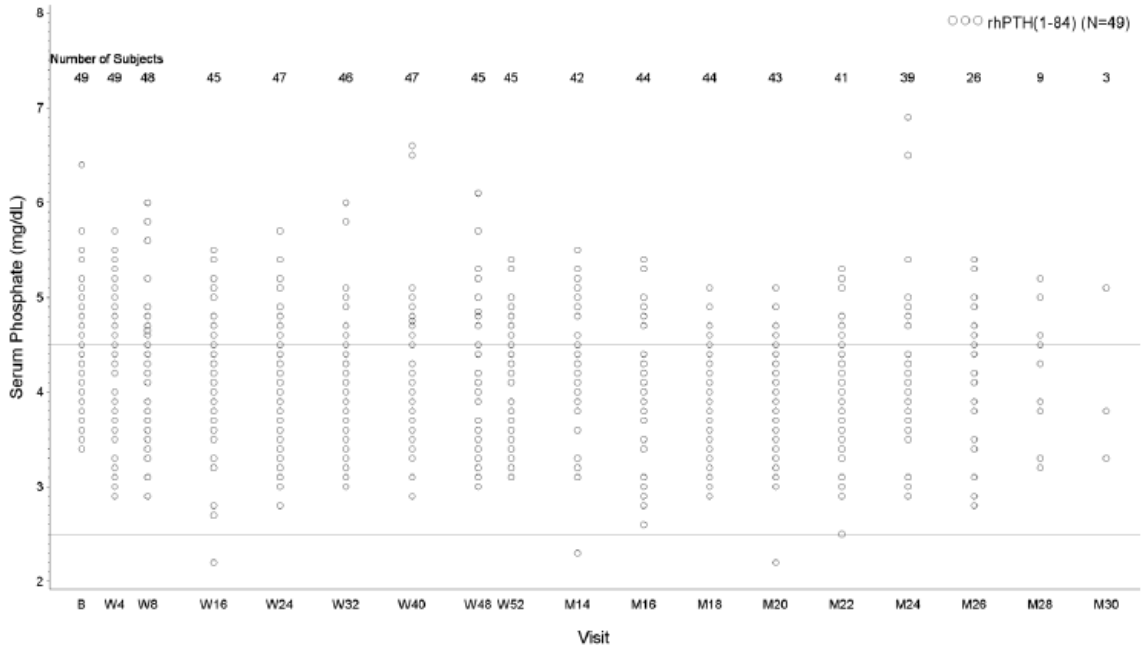
The following are scatterplots of serum calcium, serum phosphorus, and urinary calcium, requested by the Division and submitted by the Applicant. By the end of the extension period, there are few subjects with those measurements.

Scatterplot of Serum Calcium (mg/dL) by Visit—ITT Population, Excluding Site 1002



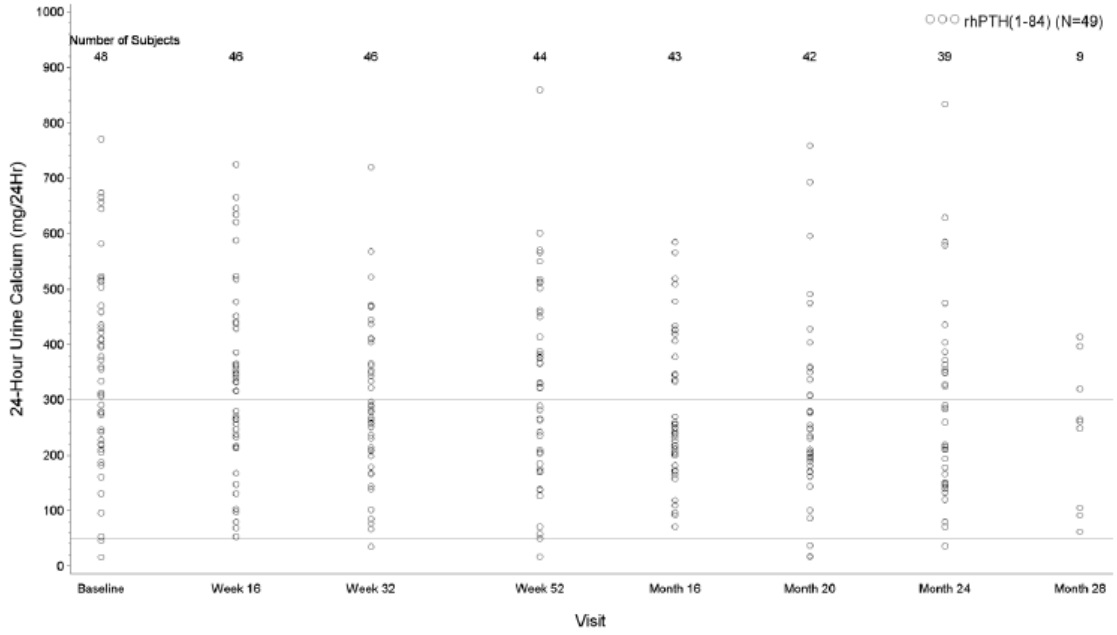
Upper Limit of Normal = 10.2 mg/dL, Lower Limit of Normal = 8.6 mg/dL

Scatterplot of Serum Calcium (mg/dL) by Visit—ITT Population, Excluding Site 1002



Upper Limit of Normal = 4.5 mg/dL, Lower Limit of Normal = 2.5 mg/dL

Scatterplot of 24-huor Urinary Calcium, (mg/24h) by Visit—ITT Population, Excluding Site 1002



Upper Limit of Normal = 300 mg/24Hr, Lower Limit of Normal = 50 mg/24Hr

Hypercalcemia

Six subjects experienced a total of 9 'hypercalcemia' or 'blood calcium increased' events. One event resulted in an interruption of study drug in addition to a reduction in study drug dosing. One of the 9 events was considered unresolved at the time of the report. Here are brief narratives of the six subjects:

- Subject 1002-0021was reported to have moderate hypercalcemia (lab value not reported) on Study Day 4 lasting for 4 days. At the time, the subject was on no calcitriol and 750 mg calcium daily. The drug regimen was changed to every other day dosing (50 µg QOD) and subsequently decreased to 25 µg daily. On Day 333, the subject experienced an intermittent episode of mild hypercalcemia, which lasted 5 days and resolved on Day 338.
- Subject 1003-0003 had two events of hypercalcemia on Days 28 (10.9 mg/dL) and 223 (10.5 mg/dL).The first episode lasted for 10 days and resulted in a decrease in calcium and calcitriol doses. The second episode lasted for 42 days which resulted in the down titration of study drug from 100 to 75 µg.
- Subject 1006-0007 had a continuous episode of hypocalcemia on Study Day 595 lasting 3 days. At the time the subjects was not taking any oral supplements and the dose of study drug was 100 µg. Study drug was briefly interrupted and then resumed. This event was considered unrelated to study drug.
- Subject 1006-0009 had hypercalcemia (10.5 mg/dL) on Day 2 on a dose of 50 µg. On Day 15, serum calcium was 10.6 mg/dL, the dose of study drug was held, and calcitriol was held for 4 days. Study drug was decreased to 25 µg, supplements were re-introduced and hypercalcemia was resolved.
- Subject 1008-0004 was noted to have hypercalcemia on Day 2 which lasted for approximately 2 months and resulted in a decrease of study drug from 50 to 25 µg. The subject appeared to maintain normocalcemia until Day 344, the subject had another episode of mild hypercalcemia but did not required any change in medication.
- Subject 1020-0006 had hypercalcemia on Day 29 which did not result in medication change. The subject discontinued on Day 107 of his own accord ("too many pills").

Hypocalcemia

Eighteen subjects experienced 30 events of 'hypocalcemia' or 'blood calcium decreased'. In only 4 subjects did the event occur prior to Week 24. When the event(s) occurred, 8 subjects were on 100 µg, 5 were on 75 µg, 4 on 50 µg, and 1 on 25 µg. Only 2 cases resulted in up-titration of study drug (from 50 µg to 75 µg and from 75 µg to 100 µg). Below are brief narratives for some of these subjects. Only narratives considered notable (SAEs, change in dose, discontinuations) are included here:

- Subject 1006-1003 had an SAE of hypocalcemia which lasted for 2 days. The calcium level 15 days prior to the event was 7.6 mg/dL. At the time of the event the subjects was on neither oral calcium nor calcitriol. And the dose of study drug was 100 µg. No dose changes were made.

- Subject 1010-0012 had mild hypocalcemia on Day 7 at which time the subjects was on 50 µg study drug and taking 500 mg/day of oral calcium and no calcitriol. Dose was increased to 75 µg.
- Subject 1014-0005 had moderate hypocalcemia on Day 65 while on a dose of 100 µg. The subject discontinued the trial.
- Subject 1020-0006 discontinued had intermittent hypocalcemia. The subject discontinued on Day 107 due to "subject decision" ("too many pills").

Hypercalciuria:

Number (%) of Subjects with Normal of Abnormal Urine Calcium Values (mg/24 hr) by Visit—Safety Population, Excluding Site 1002

	rhPTH (1-84) N=49		
Visit	m	Normal (≤300) n (%)	Abnormal (>300) n (%)
Baseline	48	19 (39.6)	29 (60.4)
Week 16	46	19 (41.3)	27 (58.7)
Week 32	46	28 (60.9)	18 (39.1)
Week 52	44	20 (45.5)	24 (54.5)
Month 16	43	27 (62.8)	17 (37.2)
Month 20	42	28 (66.7)	14 (33.3)
Month 24	39	24 (61.5)	15 (38.5)
Month 28	9	6 (66.7)	3 (33.3)

m is the number of subjects with 24-hour urine calcium excretion tested at each visit

SAEs

Four subjects had at least one SAE during the trial. The following are brief narratives of these events:

- This 48 year old woman completed both REPLACE and RELAY. She initiated this trial at a dose of 50 µg, calcium 500 mg and calcitriol 0.25 µg. Eventually, she was up-titrated to 100 µg and the supplements were discontinued. Approximately 50 weeks into the trial, she awoke with **hypocalcemia** symptoms. Her calcium level in the ER was 6.8 mg/dL. She was treated with IV calcium. There was a question of whether there was a relation of her menses to hypocalcemia episodes in the past, since this episode correlated again with the beginning of her menses. This subject had an unrelated SAE of **gastroenteritis** on Day 388.
- This 39 year old woman was being treated with 100 µg study drug when, approximately 75 weeks after initiating the trial, she was admitted with multiple signs and symptoms suggestive of an infection. Her diagnosis was myocarditis from a **viral infection**. This was not considered to be related to study drug.
- This 35 year old woman, who had a history of a syncopal episode, was up-titrated to 100 µg. On Days 36 and 372 after initiating study drug, she had syncopal events. The etiology of the **syncope** was undetermined, but did not appear to be related to abnormal calcium levels.

- This 41 year old woman had a history of thyroid cancer and cervical cancer and had completed REPLACE and RELAY. Once in this trial, and approximately 131 weeks after initially starting study drug on REPLACE, she was found to have metastatic carcinoma on the lung and underwent a craniotomy of the brain lesions. Study drug was discontinued. She had no history of smoking.

Other AEs

The table summarizes AEs related to calcium occurring in ≥5% of subjects. The other AEs were reviewed and were not notable, especially considering the lack of a comparator arm in this long-term trial.

Summary of Calcium-related AEs Occurring in ≥5% of Subjects—Safety Population, Excluding Site 1002

Preferred Term	NPSP558 N=49 n (%)	Events
Any AE in ≥5% incidence		
Yes	47 (95.9)	
No	2 (4.1)	356
Hypocalcemia	15 (30.6)	26
Hypercalcemia	5 (10.2)	7
Blood calcium decreased	6 (12.2)	7
Urine calcium increased	4 (8.2)	7

From Applicant's Submission dated June 2, 20214, Table B-14.3.1.1.3

Vital signs and EKGs

Mean changes in vital signs were unremarkable. Six subjects had markedly abnormal vital signs. However, they were single instances and not related to any reported AEs. They are not presented here.

EKGs were assessed at baseline, Week 52, and EOT. The EKG data are difficult to interpret without a comparator. The table below summarized clinically significant QT results. The Applicant submitted an Integrated Cardiovascular Safety Report that is being reviewed by the QT-IRT team.

Summary of Clinically Significant QTc Results—Safety Population, Excluding Site 1002

Parameter	NPSP558 N=49 n/m (%)
QTcB	
Any Post-baseline Clinically Significant Value	13/49 (26.5)
Post-baseline value ≥ 500 ms	0
Post-baseline value > 480 ms	0

Post-baseline value > 450 ms	13/49 (26.5)
Post-baseline value ≥ 60 ms	0
Post-baseline value ≥ 30 ms	1/49 (2)
QTcF	
Any Post-baseline Clinically Significant Value	9/49 (18.4)
Post-baseline value ≥ 500 ms	0
Post-baseline value > 480 ms	0
Post-baseline value > 450 ms	8/49 (16.3)
Post-baseline value ≥ 60 ms	0
Post-baseline value ≥ 30 ms	1/49 (2)

Applicant's Submission dated June 2, 2014, Table B-14.3.4.3

DXA results for Trial 040

Table 51 Change in Bone Mineral Density At Week 24—ITT Population, Excluding Site 1002

	Placebo N=40	rhPTH(1-84) N=84
	Actual Value	**Actual Value**
Lumbar Spine (L1-L4)		
Baseline		
n	39	83
Mean (SD)	1.2 (0.27)	1.24 (0.19)
Median	1.2	1.25
Min, Max	0.69, 2.24	0.80, 1.73
Week 24		
n	30	71
Mean (SD)	1.2	1.22 (0.19)
Median	1.13	1.21
Min, Max	0.72, 2.2	0.81, 1.66
EOT		
n	30	73
Mean (SD)	1.19 (0.28)	1.23 (0.12)
Median	1.13	1.21
Min, Max	0.72, 2.20	0.52, 1.66
Hip—Total		
Baseline		
n	39	83
Mean (SD)	1.07 (0.20)	1.09 (0.17)
Median	1.08	1.10
Min, Max	0.71, 1.48	0.69, 1.50
Week 24		
n	30	72
Mean (SD)	1.05 (0.18)	1.07 (0.16)
Median	1.03	1.09
Min, Max	0.75, 1.34	0.70, 1.47
EOT		
n	30	74
Mean (SD)	1.05 (0.18)	1.07 (0.16)

Median	1.03	1.09
Min, Max	0.75, 1.34	0.69, 1.47
Hip—Trochanter		
Baseline		
n	39	83
Mean (SD)	0.84 (0.18)	0.86 (0.15)
Median	0.84	0.87
Min, Max	0.55, 1.23	0.56, 1.26
Week 24		
n	30	72
Mean (SD)	0.83 (0.17)	0.83 (0.14)
Median	0.81	0.83
Min, Max	0.58, 1.19	0.59, 1.19
EOT		
n	30	74
Mean (SD)	0.83 (0.167)	0.83 (0.14)
Median	0.81	0.83
Min, Max	0.58, 1.19	0.59, 1.19
Hip—Intertrochanter		
Baseline		
n	39	83
Mean (SD)	1.26 (0.23)	1.28 (0.20)
Median	1.29	1.28
Min, Max	0.82, 1.76	0.68, 1.78
Week 24		
n	30	72
Mean (SD)	1.24 (0.22)	1.25 (0.20)
Median	1.21	1.25
Min, Max	0.84, 1.76	0.67, 1.78
EOT		
n	30	74
Mean (SD)	4.24 (0.22)	1.25 (0.20)
Median	1.21	1.24
Min, Max	0.84, 1.76	0.67, 1.78
Hip—Ward's Triangle		
Baseline		
n	39	83
Mean (SD)	0.83 (0.25)	0.89 (0.23)
Median	0.85	0.88
Min, Max	0.26, 1.35	0.51, 1.54
Week 24		
n	30	72
Mean (SD)	0.80 (0.23)	0.86 (0.23)
Median	0.78	0.83
Min, Max	0.28, 1.30	0.51, 1.50
EOT		
n	30	74
Mean (SD)	0.80 (0.23)	0.86 (0.22)
Median	0.78	0.83
Min, Max	0.28, 1.30	0.51, 1.5
Hip—Femoral Neck		
Baseline		
n	39	83

Mean (SD)	0.98 (0.23)	1.01 (0.19)
Median	0.96	0.99
Min, Max	0.50, 1.48	0.67, 1.5
Week 24		
n	30	72
Mean (SD)	0.94 (0.20)	0.98 (0.19)
Median	0.88	0.97
Min, Max	0.51, 1.32	0.62, 1.46
EOT		
n	30	74
Mean (SD)	0.94 (10.20)	0.98 (0.19)
Median	0.88	0.97
Min, Max	0.54, 1.32	0.62, 1.46
Distal One Third Radius		
Baseline	40	83
n	0.76 (0.12)	0.79 (0.12)
Mean (SD)	0.74	0.78
Median	0.45, 1.07	0.57, 1.19
Min, Max		
Week 24		
n	29	70
Mean (SD)	0.75 (0.10)	0.78 (0.11)
Median	0.75	0.77
Min, Max	0.44, 0.96	0.55, 1.01
EOT		
n	29	72
Mean (SD)	0.75 (0.10)	0.78
Median	0.75	0.77
Min, Max	0.44, 0.96	0.55, 1.01

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Table 52 Analysis of Change in T-Score at Week 42, ITT Population, Excluding Site 1002

	Placebo N=40	**rhPTH(1-84) N=84**
	Actual Value	**Actual Value**
Lumbar Spine (L1-L4)		
Baseline		
n	39	82
Mean (SD)	0.86 (2.33)	1.16 (1.55)
Median	0.59	1.15
Min, Max	-3.26, 10.87	-2.21, 4.55
Week 24		
n	20	71
Mean (SD)	0.82 (2.42)	0.98
Median	0.36	0.99
Min, Max	-3.0, 10.47	-2.08, 4.45
EOT		
n	30	73
Mean (SD)	0.82 (24.42)	1.03 (1.58)

Median	0.36	0.99
Min, Max	-3.0, 10.47	-2.08, 4.84
Hip—Total		
Baseline		
n	39	82
Mean (SD)	0.68 (1.41)	0.79 (1.22)
Median	0.63	0.73
Min, Max	-2.17, 3.29	-2.11, 3.9
Week 24		
n	30	72
Mean (SD)	0.53 (1.35)	0.61 (1.22)
Median	0.49	0.63
Min, Max	-2.07, 3.29	-2.06, 3.65
EOT		
n	30	74
Mean (SD)	0.53 (1.35)	0.60 (1.2)
Median	0.49	0.58
Min, Max	-2.07, 3.29	-2.06, 3.65
Hip—Trochanter		
Baseline		
n	39	82
Mean (SD)	0.63 (1.47)	0.71 (1.2)
Median	0.53	0.67
Min, Max	-2.2, 3.3.87	-2.56, 3.3
Week 24		
n	30	72
Mean (SD)	0.51 (1.43)	0.50 (1.17)
Median	0.25	0.51
Min, Max	-2.03, 3.97	-2.25, 3.05
EOT		
n	30	74
Mean (SD)	0.51 (1.43)	0.49 (1.15)
Median	0.25	0.51
Min, Max	-2.03, 3.97	-2.25, 3.05
Hip—Intertrochanter		
Baseline		
n	23	49
Mean (SD)	0.6 (1.31)	0.72 (1.09)
Median	0.39	0.58
Min, Max	-1.81, 3.0	-2.74, 2.59
Week 24		
n	18	41
Mean (SD)	0.55 (1.18)	0.59 (1.13)
Median	0.36	0.53
Min, Max	-1.13, 3.06	-2.78, 2.52
EOT		
n	18	45
Mean (SD)	0.55 (1.18)	0.56 (1.12)
Median	0.36	0.51
Min, Max	-1.13, 3.06	-2.78, 2.52
Hip—Ward's Triangle		
Baseline		
n	39	82

Mean (SD)	0.16 (1.77)	0.57 (1.77)
Median	0.12	0.5
Min, Max	-4.07, 2.99	-2.33, 4.86
Week 24		
n	30	72
Mean (SD)	-0.06 (1.67)	0.40 (1.77)
Median	0.11	0.06
Min, Max	-3.85, 2.68	-2.41, 4.55
EOT		
n	30	74
Mean (SD)	-0.06 (1.67)	0.4 (1.75)
Median	0.11	0.06
Min, Max	-3.85, 2.68	-2.41, 4.55
Hip—Femoral Neck		
Baseline		
n	39	82
Mean (SD)	0.38 (1.59)	0.54 (1.37)
Median	0.21	0.53
Min, Max	-3.14, 3.51	-1.92, 3.52
Week 24		
n	30	72
Mean (SD)	0.10 (1.37)	0.34 (1.35)
Median	0.07	0.22
Min, Max	-2.75, 2.66	-2.09, 3.11
EOT		
n	30	74
Mean (SD)	0.10 (1.37)	0.35 (1.34)
Median	0.07	0.29
Min, Max	-2.75, 2.66	-2.09, 3.11
Distal One Third Radius		
Baseline		
n	40	82
Mean (SD)	-0.34 (1.03)	-0.11 (0l99)
Median	-0.13	0.01
Min, Max	-4.08, 1.32	-3.56, 1.84
Week 24		
n	29	70
Mean (SD)	-0.40 (1.13)	-0.16 (1.04)
Median	-0.29	-0.07
Min, Max	-4.18, 1.74	-3.8, 1.84
EOT		
n	29	72
Mean (SD)	-0.40 (1.14)	-0.16 (1.03)
Median	-0.29	-0.07
Min, Max	-4.18, 1.75	-3.8, 1.84

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Table 53 Analysis of Change in Z-Score at Week 24, ITT Population, Excluding Site 1002

	Placebo N=40	**rhPTH(1-84) N=84**
	Actual Value	**Actual Value**

Lumbar Spine (L1-L4)		
Baseline		
n	39	83
Mean (SD)	1.61 (2.24)	1.67 (1.43)
Median	1.35	1.65
Min, Max	-1.63, 12.06	-1.84, 4.99
Week 24		
n	30	71
Mean (SD)	1.68 (2.39)	1.55 (1.38)
Median	1.32	1.58
Min, Max	-1.52, 11.7	-1.21, 4.74
EOT		
n	30	73
Mean (SD)	1.68 (2.39)	1.61 (1.42)
Median	1.33	1.6
Min, Max	-1.51, 11.7	-1.21, 5.19
Hip—Total		
Baseline		
n	39	83
Mean (SD)	1.23 (1.29)	1.22 (1.08)
Median	0.98	1.14
Min, Max	-1.27, 3.82	-1.46, 3.99
Week 24		
n	30	72
Mean (SD)	1.16 (1.29)	1.05 (1.08)
Median	1.01	0.92
Min, Max	-1.13, 3.85	-1.35, 3.75
EOT		
n	30	74
Mean (SD)	1.16 (1.29)	1.05 (1.07)
Median	1.01	0.89
Min, Max	-1.13, 3.85	-1.35, 3.75
Hip—Trochanter		
Baseline		
n	39	82
Mean (SD)	1.15 (1.36)	1.11 (1.08)
Median	1..04	0.98
Min, Max	-1.27, 4.4	-2.06, 3.48
Week 24		
n	30	72
Mean (SD)	1.12	0.92 (1.04)
Median	0.93	0.78
Min, Max	-1.18, 4.53	-1.72, 3.24
EOT		
n	30	74
Mean (SD)	1.12 (1.39)	0.92 (1.03)
Median	0.93	0.78
Min, Max	-1.18, 4.53	--1.72, 3.24
Hip—Intertrochanter		
Baseline		
n	23	49
Mean (SD)	1.0 (1.22)	1.0 (0.97)
Median	0.98	0.97

Min, Max	-1.02, 3.35	-1.56, 2.61
Week 24		
n	18	43
Mean (SD)	1.0 (1.14)	0.87 (1.01)
Median	0.84	0.97
Min, Max	-0.99, 3.42	-1.56, 2.61
EOT		
n	18	45
Mean (SD)	1.0 (1.14)	0.84 (1.0)
Median	0.84	0.93
Min, Max	-0.99, 3.42	-1.56, 2.61
Hip—Ward's Triangle		
Baseline		
n	39	82
Mean (SD)	1.31 (1.47)	1.55 (1.61)
Median	1.54	1.41
Min, Max	-1.88, 3.62	-1.68, 5.49
Week 24		
n	30	72
Mean (SD)	1.26 (1.48)	1.4 (1.58)
Median	1.13	1.34
Min, Max	-1.63, 3.6	-1.71, 4.95
EOT		
n	30	74
Mean (SD)	1.26 (1.48)	1.42 (1.57)
Median	1.13	1.39
Min, Max	-1.63, 3.6	-1.71, 4.95
Hip—Femoral Neck		
Baseline		
n	39	83
Mean (SD)	1.16 (1.34)	1.21 (1.21)
Median	1.04	1.06
Min, Max	-1.69, 4.16	-1.17, 4.34
Week 24		
n	30	72
Mean (SD)	0.99 (1.21)	1.02 (1.20)
Median	1.12	0.86
Min, Max	1.27, 3.81	-1.18, 3.65
EOT		
n	30	74
Mean (SD)	0.99 (1.21)	1.04 (1.19)
Median	1.12	0.92
Min, Max	1.27, 3.81	-1.18, 3.65
Distal One Third Radius		
Baseline		
n	40	83
Mean (SD)	0.36 (1.02)	0.39 (1.03)
Median	0.44	0.39
Min, Max	-2.52, 2.13	-3.56, 2.46
Week 24		
n	29	70
Mean (SD)	0.40 (1.15)	0.37 (1.09)
Median	0.23	0.44

Min, Max	-2.57, 2.58	-3.8, 2.63
EOT		
n	29	72
Mean (SD)	0.4 (1.15)	0.38 (1.08)
Median	0.23	0.44
Min, Max	-2.57, 2.58	-3.8, 2.63

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/s/

NAOMI N LOWY
07/12/2014

DRAGOS G ROMAN
07/13/2014