

## **CLINICAL STUDY PROTOCOL**

NCT Number: NCT01297309

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

Study Number: PAR-C10-008

Protocol Version: Protocol Amendment 6

Protocol Version Date: 24 October 2016

NPSP558 (rhPTH[1-84])

**A Long-term Open-label Study Investigating the Safety and  
Tolerability of NPSP558, a Recombinant Human  
Parathyroid Hormone (rhPTH[1-84]), for the Treatment of  
Adults with Hypoparathyroidism –  
A Clinical Extension Study (RACE)**

**Phase 3**

**Clinical Protocol PAR-C10-008**

US IND Number: 76,514

**Shire\***

**300 Shire Way**

**Lexington, MA 02421**

\*NPS Pharmaceuticals was acquired by Shire on 21 February 2015

**ISSUED:**

<b>Original Protocol Version 1.0:</b>	<b>30 December 2010</b>
<b>Amendment 1 Version 2.0:</b>	<b>29 June 2011</b>
<b>Amendment 2 Version 3.0:</b>	<b>05 October 2011</b>
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<b>Amendment 5 Version 6.0:</b>	<b>3 May 2016</b>
<b>Amendment 6:</b>	<b>24 October 2016</b>

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## PROTOCOL SIGNATURE PAGE

### Sponsor's (Shire) Approval

Signature: PPD [redacted]	Date: PPD [redacted]
PPD [redacted], MD	

### Investigator's Acknowledgement

I have read this protocol for Shire Study PAR-C10-008.

**Title:** A Long-term Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH[1-84]), for the Treatment of Adults with Hypoparathyroidism – A Clinical Extension Study (RACE)

I have fully discussed the objective(s) of this study and the contents of this protocol with the sponsor's representative.

I understand that the information in this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the scientific/ethical review of the study, without written authorization from the sponsor. It is, however, permissible to provide the information contained herein to a subject in order to obtain their consent to participate.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with International Conference on Harmonisation guidelines on Good Clinical Practice and with the applicable regulatory requirements.

I understand that failure to comply with the requirements of the protocol may lead to the termination of my participation as an investigator for this study.

I understand that the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study I will communicate my intention immediately in writing to the sponsor.

Investigator Name and Address: (please hand print or type)	<i>{The investigator completes the bottom section of the protocol signature page}</i>

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

## SUMMARY OF CHANGES FROM PREVIOUS VERSION

The table and the summary below provide an overview of the changes from the previously implemented version of this protocol (Amendment 5) dated 03 May 2016 to the current version of the protocol (Amendment 6). Please see [Appendix 4](#) for the protocol history.

The primary purpose of this amendment is to extend the study through January 2018, or after the last patient completes his or her Month 72 visit (whichever comes last), to continue to collect long-term data; since rhPTH[1-84] is intended for life-long use, additional long-term safety data will help in evaluating the benefit/risk profile. The benefits and risks of extending the study, with specific consideration given to patient safety, have been evaluated and it is Shire's position that the benefits of longer-term monitoring under expert clinical supervision by study investigators outweigh potential risks.

A description of the changes are described in the table below; however, minor changes to wording, style, and formatting that do not affect the study design and operations are not described.

Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 6	Amendment Date 24 October 2016	Global
Description of Change	Rationale for Change	Section(s) Affected by Change
Formatting change: Pages 2-5 were replaced with the current Shire Protocol Signature Page (Shire MM/investigator approvals, (page 2), Summary of Changes (page 3), Emergency Contact Info (page 4), and the Product Quality Complaint (page 5).	<ul style="list-style-type: none"> <li>Changing key pages aligns with current Shire standards and expectations regarding product complaints and internal approval practices</li> <li>No changes in SAE reporting contacts were made; however, the formatting was changed from the cover page to the Emergency Contact Page (page 4).</li> </ul>	<ul style="list-style-type: none"> <li><a href="#">Protocol Signature Page</a>, (page 2)</li> <li><a href="#">Summary of Changes</a> (page 3),</li> <li><a href="#">Emergency Contact Info</a> (page 4),</li> <li><a href="#">Product Quality Complaint</a> (page 5).</li> </ul>
Formatting change: refined the summary of changes to protocol from the longer, track-changes style to currently used style (more descriptive and less detailed). Also, as mentioned above, the summary of changes has been moved from Appendix 4 to the new location on Page 3. The former Appendix 4 summary of changes has now been revised to be the Shire standard Protocol History.	<p>Allows reader to better comprehend the actual changes to the protocol.</p> <p>Aligns with current Shire documentation practices and format.</p>	Summary of Changes from Previous Version, <a href="#">Appendix 4</a>
Changed text throughout the protocol that stated to record content in the CRF or eCRF to record content in the "source document."	Specific instructions for CRFs are provided in the CRF completion guidelines or other study-related manuals. This	Section 3, Section 4.4, Section 5.4.1, Section 5.4.2, Section 6.2.1.3, Section 6.2.5, Section



Protocol Amendments		
Summary of Change(s) Since Last Version of Approved Protocol		
Amendment Number 6	Amendment Date 24 October 2016	Global
Description of Change	Rationale for Change	Section(s) Affected by Change
	change will align the wording in this protocol with standard Shire documentation practices as well as with new rhPTH[1-84] protocols.	6.3.
Secondary objective change: Removed “and calcitriol” from the first secondary objective. Sentence now reads: To evaluate the impact of different preparations of calcium <del>and calcitriol</del> on the response to rhPTH[1-84] replacement therapy	This study was not intended to evaluate different sources of calcitriol. Calcitriol is the only form of active vitamin D available in the US.	Synopsis, Section 2.2
Study design change: the end of study has been changed from December 2016 to January 2018 or after the completion of the last patient’s Month 72 visit, whichever comes last.	To extend the period of safety and efficacy monitoring and data collection.	Synopsis, Section 3.1, Section 3.2
Added in the text that, once the inventory of ancillary kits is depleted, the clinical centers will receive the ancillary kit components separately and not as a kit (injection pen needles and alcohol prep pads).	Change in how the kits are being provided.	Section 5.1.2
Laboratory test change: eliminated calcium-phosphate ratio from the serum phosphate lab test.	Calcium-phosphate ratio is not a useful clinical metric	Synopsis, Section 6.1
Wording was clarified for the schedule of follow up visits and procedures for subjects with PTH-specific antibodies at the final 2 visits (rather than the final visit).	Low levels of detectable antibody tend to be variable and of no known clinical significance.	Table 6-3, Table 6-4
Wording was added to clarify that additional interim analyses may be performed as necessary to support regulatory interactions and/or publications.	Updated information.	Section 8.6.3
Removed ( $\geq 7.5$ mg/dL) from the baseline value of albumin-corrected total serum calcium concentration since this was an inadvertent carryover from the previous study, REPLACE. Sentence now reads: An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value ( <del><math>\geq 7.5</math> mg/dL</del> ) and does not exceed the ULN for the central laboratory	Correction.	Synopsis, Section 2.3.2, Section 8.3

## EMERGENCY CONTACT INFORMATION

**For protocol- or safety-related issues, the investigator must contact the study medical director:**

PPD [REDACTED] MD PPD [REDACTED]  
Phone: PPD [REDACTED]  
Mobile: PPD [REDACTED]  
Email: PPD [REDACTED]

In the event of serious adverse event (SAE), the investigator must complete and electronically sign the electronic SAE EDC CRF within 24 hours of first awareness.

FAX (PPD [REDACTED]) OR EMAIL PPD [REDACTED] the Shire SAE paper form in case EDC is unavailable or down to the Shire Global Pharmacovigilance and Risk Management department.

## PRODUCT QUALITY COMPLAINTS

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Please use the information below as applicable to report the Product Quality Complaint:

Origin of Product Quality Complaint	E-mail Address
North and South America	PPD [REDACTED]
European Union and Rest of World	PPD [REDACTED]

Telephone numbers (provided for reference if needed):

Shire, Lexington, MA (USA)  
PPD [REDACTED]

## SYNOPSIS

**Title:** A Long-term Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH[1-84]), for the Treatment of Adults with Hypoparathyroidism – A Clinical Extension Study (RACE)

**Protocol No:** PAR-C10-008 Amendment 6

**Phase of Development:** Phase 3

### Objectives:

#### Primary Objective:

The objective of this study is to demonstrate the long-term safety and tolerability of subcutaneous (SC) NPSP558 (rhPTH[1-84]) as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.

#### Secondary Objectives:

- To evaluate the impact of different preparations of calcium on the response to rhPTH[1-84] replacement therapy
- To demonstrate that dosing with rhPTH[1-84] 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

### Study Rationale

This study is designed to evaluate long-term treatment with rhPTH[1-84].

### Study Design

This study is a long-term, open-label study using rhPTH[1-84] for the treatment of adult male and female subjects with hypoparathyroidism. Subjects can enroll if they either previously completed the rhPTH[1-84] RELAY study (PAR-C10-007) (8 weeks of active therapy) and/or completed the REPLACE study (CL1-11-040) (Visit 18).

The goal of this study is to optimize rhPTH[1-84] dosing while reducing calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible and maintaining total serum calcium levels. Dose adjustments to rhPTH[1-84] and to the calcium/calcitriol supplements and safety monitoring of calcium levels are explained in Appendix 2, rhPTH[1-84] and Supplement Titration Guideline.

- The starting dose of rhPTH[1-84] for this study will be 25 or 50 µg SC once daily (QD).



- Subjects may have their rhPTH[1-84] dose adjusted by the investigator at any time during the study, with the goal of achieving or maintaining total serum calcium levels in the range of 8.0 to 9.0 mg/dL.
- If **ANY** predose (trough) total serum calcium is >11.9 mg/dL study drug will be stopped.
- Subjects will have blood draws to assess total serum calcium levels (which may be performed locally) 3 to 5 days after **ANY** dose adjustment of rhPTH[1-84], after any significant change in doses of calcium and/or calcitriol supplements, or at any other time at the discretion of the investigator.
- Study visits during the first 12 months of the study will be conducted at Weeks 1 (baseline), 4, 8, and then every 8 weeks thereafter up to Week 48 (Visit 8). The Week 52 visit (Visit 9) is scheduled 4 weeks later.
- At any time following the Week 16 (Visit 4), subjects who are on a stable dose of rhPTH[1-84] and have a 24-hour urine calcium >300 mg (males) and >250 mg (females) may be treated for hypercalciuria with calcium-sparing diuretics, if this therapy had not been introduced prior to the study.
- At the end of Week 52, subjects will be invited to extend their study drug regimen until January 2018 or after the completion of the last patient's Month 72 visit, whichever comes last.
- During this time, subjects will return to the clinic for interim visits every 2 months (Months 14, 16, 18, etc).
- After the End of Treatment visit or early termination visit, subjects who will not continue rhPTH[1-84] treatment will have their total serum calcium and phosphate levels measured 3 to 5 days after the last dose of study medication. Doses of calcium and active vitamin D supplements will be adjusted by the Investigator as appropriate. Thereafter, the Investigator will repeat serum calcium/phosphate monitoring and supplement dose adjustments as appropriate to achieve target serum calcium/phosphate concentrations until the follow up phone call 4 weeks  $\pm$  7days after end of treatment visit. After the 4 weeks follow up phone call, further management of hypoparathyroidism will occur as part of the subject's long-term non-study medical care.

**Number of Subjects Planned:** Approximately 50 subjects will be enrolled.

**Diagnosis and Main Criteria for Inclusion:**

**Inclusion Criteria**

Subjects who meet all of the following inclusion criteria may be enrolled in this study:

1. Signed and dated informed consent form before any study-related procedures are performed
2. Previously completed the rhPTH[1-84] RELAY study (8 weeks of active therapy) and/or previously completed the rhPTH[1-84] REPLACE study (Visit 18)
3. Able to perform daily SC self-injections of study medication (or have designee perform injection) via a multidose pen injector into the thigh

4. Willingness and ability to understand and comply with the protocol
5. Women who are: (1) postmenopausal defined as 12 months amenorrhea with appropriate serum follicle stimulating hormone levels ( $> 40$  IU/L); (2) surgically sterilized; OR (3) of childbearing potential with a negative pregnancy test at screening and who consent to use two acceptable methods of contraception for the duration of the study, with pregnancy testing at every scheduled visit. Male subjects who have female partners of childbearing potential together also must use two acceptable forms of contraception during the subject's participation in the study.
6. Serum creatinine  $<1.5$  mg/dL at enrollment
7. Total serum calcium  $\leq$  upper limit of normal (ULN) based on local laboratory result prior to enrollment
8. Serum 25 hydroxy (OH) vitamin D  $\leq 1.5$  times the ULN within approximately 16 weeks prior to enrollment

#### **Exclusion Criteria**

Subjects who meet any of the following exclusion criteria at baseline (Visit 1) are not eligible for enrollment in this study:

1. Any condition that, in the investigator's opinion after consultation with the sponsor, would preclude the safe use of parathyroid hormone (PTH)
2. Any disease or condition, in the opinion of the investigator, which has a high probability of precluding the subject from completing the study or where the subject cannot or will not appropriately comply with study requirements
3. Pregnant or lactating women

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, without prejudice to subsequent care. Withdrawn subjects will not be replaced.

#### **Duration of Study/Treatment:**

The duration of the study was originally intended to be about 1 year. The study has been extended to up to 80 months of treatment with a 4-week follow up call/visit. Therefore, the overall duration of the study is expected to be approximately 81 months.

Study visits will be conducted every 2 months and will continue until the subject voluntarily withdraws or until termination of the study. See Section 6.2 for additional follow-up for subjects who develop antibodies specific to PTH. See Table 6-4 for additional follow-up for subjects who develop antibodies specific to PTH.

### **Test Product, Dose, and Mode of Administration:**

At the beginning of the study, subjects will receive rhPTH[1-84] 25 or 50 µg SC QD in an open-label fashion as described in Section 3.1. Subjects may have their rhPTH[1-84] dose adjusted upwards in increments of 25 µg to a maximum of 100 µg SC QD. rhPTH[1-84] is to be administered into alternating thighs each morning via a multidose pen injector device.

### **Supplements:**

Calcium citrate and calcium carbonate will be supplied by the sponsor throughout the study until approximately May 2014. Following this date, only calcium citrate will be provided. Calcitriol will be supplied by the sponsor through Week 52 only.

### **Criteria for Evaluation:**

#### **Safety:**

Safety variables will be assessed by the following evaluations:

- Adverse events (AEs) and serious adverse events (SAEs)
- Incidence of AEs of hypocalcemia (eg, paresthesia, numbness, tetany) and hypercalcemia (eg, constipation, nausea, poor appetite or vomiting, frequent urination, thirst, and kidney stones)
- Incidence of hypercalciuria
- Immunogenicity analysis (AEs and SAEs related to PTH antibodies)
- Laboratory test results
  - Hematology (hematocrit, hemoglobin, white blood cells, red blood cells, platelets, differential)
  - Serum chemistries (standard Chem-20 panel)
  - Serum 25(OH) vitamin D levels
  - Serum 1,25-dihydroxyvitamin D levels
  - Creatinine clearance
  - Serum bone turnover markers
  - Urinalysis
  - 24-hour urine calcium, phosphate, sodium, and creatinine excretion
  - PTH and *Escherichia coli* protein antibodies
- Bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA)
- Electrocardiogram (ECG) parameters
- Physical examinations (including vital signs)
- Reason for termination from the study

### **Efficacy:**

Efficacy variables will be assessed by one or more of the following evaluations:

- Laboratory test results
  - Total serum calcium
  - 24-hour urinary calcium excretion
  - Serum phosphate
- Supplement usage
  - Concomitant supplemental oral calcium dosage
  - Concomitant supplemental oral calcitriol dosage

### **Statistical Methods:**

Detailed statistical analyses will be conducted as described in the Statistical Analysis Plan (SAP) for this study. Deviations from the SAP (if any) will be described and justified in the Clinical Study Report.

### **Analysis of Demographic and Baseline Variables**

Demographic variables (such as sex, age, race, birthdate, etc.) will be obtained from the REPLACE or RELAY study. Demographic and/or other variables at baseline will be summarized for medical history, demography, physical examination, vital signs, prior medications, ECG, and laboratory test results.

The number and percentage of subjects with specific prior medications will be summarized. The number and percentage of subjects will be summarized by system organ class and by high-level term and preferred term for each medical history condition.

### **Efficacy Variables Summary**

#### **Efficacy Endpoints:**

The proportion of subjects in whom the following three conditions are fulfilled at Week 52 (Visit 9) and at the End of Treatment will be summarized:

- A  $\geq 50\%$  reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of  $\leq 500$  mg

**AND**

- A  $\geq 50\%$  reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of  $\leq 0.25$   $\mu\text{g}$

**AND**

- An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value and does not exceed the ULN for the central laboratory

**Other Efficacy Endpoints:**

- Mean percentage changes from baseline in supplemental oral calcium and supplemental calcitriol dosages at each visit
- Proportion of subjects achieving the first three conditions of the efficacy endpoints defined above, at each visit
- Mean change from baseline in 24-hour urine calcium excretion
- Impact of calcium source (carbonate vs. citrate) on response
- Impact of calcium-sparing diuretics on serum and urinary calcium
- Proportion of subjects that maintain a calcium phosphate product in the range of 35 to 55 mg<sup>2</sup>/dL<sup>2</sup> (4.4 mmol<sup>2</sup>/L<sup>2</sup>)
- Distribution of subjects by rhPTH[1-84] doses at the End of Treatment Visit
- Change from baseline in bone turnover markers (bone-specific alkaline phosphatase, serum carboxy-terminal telopeptide of type I collagen, serum procollagen type 1 amino-terminal propeptide, osteocalcin), PTH antibodies, and BMD by DXA
- Additional subgroup analyses that are specified in the SAP

**Safety Analysis:**

Safety data including vital signs assessments, physical examinations, AEs, SAEs, the frequency of AEs of hypocalcemia or hypercalcemia, concomitant medications, clinical laboratory tests, ECG monitoring, and termination from study will be summarized by point of time of collection.

Descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.



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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

25(OH) vitamin D	25-hydroxyvitamin D
1,25(OH) <sub>2</sub> vitamin D	1,25-dihydroxyvitamin D
β-HCG	Beta human chorionic gonadotropin
AE	Adverse event
BMD	Bone mineral density
bpm	Beats per minute
BSAP	Bone-specific alkaline phosphatase
CaSR	Calcium-sensing receptor
CSR	Clinical study report
DNA	Deoxyribonucleic acid
DXA	Dual-energy x-ray absorptiometry
E. coli	Escherichia coli
ECG	Electrocardiogram
ECP	E. coli protein
eCRF	Electronic case report form
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GI	Gastrointestinal
hPTH	Human parathyroid hormone
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Institutional Review Board
IV	Intravenous
NPS	NPS Pharmaceuticals, acquired by Shire
NPSP558	Recombinant human parathyroid hormone (1-84)
P1NP	Serum procollagen type 1 amino-terminal propeptide
PMO	Postmenopausal osteoporosis
PTH	Parathyroid hormone
QD	Once daily
QOD	Every other day
RACE	NPSP558 Study PAR-C10-008
REB	Research Ethics Board
RELAY	NPSP558 Study PAR-C10-007
REPLACE	NPSP558 Study CL1-11-040
rhPTH	Recombinant human parathyroid hormone
SAE	Serious adverse event



## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

SAP	Statistical analysis plan
SC	Subcutaneous
s-CTx	Serum carboxy-terminal telopeptide of type I collagen
SMT	Safety Management Team
SUSAR	Suspected, unexpected, serious, adverse reaction
ULN	Upper limit of normal
WMA	World Medical Association
WOCBP	Woman of childbearing potential

## 1 INTRODUCTION

The purpose of this study is to demonstrate the long-term safety and tolerability of subcutaneous (SC) NPSP558 (rhPTH[1-84]) as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.

### 1.1 Background

#### Compound

NPSP558 (rhPTH[1-84]) is the sponsor's designation for recombinant human parathyroid hormone (rhPTH), a single-chain polypeptide consisting of 84 amino acid residues (rhPTH[1-84]). It is identical in structure to endogenous human parathyroid hormone (hPTH), which is the principal regulator of plasma calcium homeostasis through concerted actions on the kidneys and bone. rhPTH[1-84] is manufactured using a strain of *Escherichia coli* (*E. coli*) modified by recombinant deoxyribonucleic acid (DNA) technology.

#### Calcium and Phosphate Absorption, Storage, and Excretion

Dietary calcium is absorbed primarily in the small intestine with an efficiency of 30% to 40%. Up to half of absorbed dietary calcium is returned to the gastrointestinal (GI) tract and is excreted in the stool. Most of the remainder is excreted by the kidneys. The efficiency of absorption of dietary phosphate is greater than that of calcium (about 70%) and most is excreted by the kidneys. Approximately 99% of body calcium (the most abundant body cation) and 85% of phosphorus are found in bone, where they serve not only a structural role, but also as a reservoir for tissue and plasma calcium and phosphate. Most of the remaining phosphorus is intracellular. The majority of the 1% of calcium not found within the skeleton is located in the extracellular fluid. About half of this plasma calcium is ionized and capable of capillary diffusion into the intercellular space; the rest is bound to plasma proteins such as albumin or other substances (citrate, sulfate, and phosphates). Ionized calcium, the physiologically active moiety, plays a vital role in many physiological processes including bone formation, blood coagulation (prothrombin to thrombin conversion), skeletal and smooth muscle function, cardiac automaticity and inotropy, nerve impulse initiation, and a host of other key physiological functions ([Bilezikian et al. 2001](#)).

#### Calcium and Phosphate Regulation

Serum calcium and phosphate levels are regulated principally by parathyroid hormone (PTH), the active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25[OH]<sub>2</sub> vitamin D; calcitriol), and calcitonin. PTH maintains an inverse relationship with serum calcium. Normal total serum calcium levels (generally 8.4 to 10.2 mg/dL) and serum phosphate levels (2.5 to 4.5 mg/dL) are regulated to yield a calcium phosphate product of approximately 35 mg<sup>2</sup>/dL<sup>2</sup>. This product is important because of the potential for calcium phosphate salts to be deposited in soft tissues. Levels of the calcium phosphate product that exceed 50 mg<sup>2</sup>/dL<sup>2</sup> are believed to place patients at risk for ectopic soft tissue calcification. PTH is synthesized and secreted by the parathyroid glands primarily in response to a fall in serum calcium levels. Through concerted actions on the kidney and bone, PTH is the principal regulator of plasma calcium homeostasis. In the kidney,

PTH increases renal tubular reabsorption of calcium (while inversely inhibiting phosphate reabsorption) and increases the synthesis of 1,25(OH)<sub>2</sub> vitamin D from its precursor 25-hydroxyvitamin D (25[OH] vitamin D). Although 1,25(OH)<sub>2</sub> vitamin D has a short in vivo half-life (approximately 6 hours), it directly increases intestinal calcium and phosphate absorption. In bone, PTH increases the efflux of calcium from bone, both from the rapidly exchangeable pool of calcium within bone, and by increasing the number and activity of osteoblasts and osteoclasts, thereby increasing bone turnover. As PTH also acts to inhibit the reabsorption of phosphate in the proximal nephron, it prevents an increase in plasma phosphate levels that could result from increased intestinal phosphate absorption and efflux of phosphate from bone. Calcitonin, secreted by C-cells of the thyroid gland, decreases serum calcium by inhibiting bone resorption and promoting renal tubular calcium excretion, but its effects are relatively minor in comparison to those of PTH and 1,25(OH)<sub>2</sub> vitamin D ([Bilezikian et al. 2001](#)).

## **Disorders of Calcium Homeostasis**

### **Situations Associated With Hypocalcemia**

Hypocalcemia (low serum ionized calcium) may result from abnormally increased calcium binding (rapid blood transfusion due to citrate binding or increased serum free fatty acids due to stress, medications, alcohol, or acute pancreatitis), abnormal calcium losses (impaired phosphate excretion leading to hyperphosphatemia in renal failure), vitamin D deficiency (impaired GI calcium absorption and renal or liver disease with associated vitamin D activation impairment), inadequate calcium intake, or hypoparathyroidism ([Shoback 2008](#)). Hypocalcemia due to deficient protein-bound (non-ionized) calcium may result from decreased serum albumin, but this condition is usually asymptomatic because serum ionized calcium levels are typically normal.

### **Hypoparathyroidism and Hypocalcemia**

The most common cause of chronic hypocalcemia is hypoparathyroidism, a condition in which there is deficient production of PTH from the parathyroid glands. Hypoparathyroidism results in decreased calcium reabsorption from renal tubules, malabsorption of calcium from the GI tract and reduced calcium mobilization from bone. Hypoparathyroidism may result from permanent injury to the parathyroid gland(s) during thyroid or parathyroid surgery or other surgical procedures in the neck, radiation to the neck region, autoimmune destruction of the parathyroid glands, or their congenital absence. Although rare, hypoparathyroidism can also result from genetic mutations, such as activating mutations in the calcium-sensing receptor (CaSR) gene that encodes CaSRs present on parathyroid and kidney tubule cells. Activating mutations of the CaSR gene result in an inappropriately low PTH secretion for the prevailing serum calcium level and increased fractional clearance of calcium by the kidney.

Since free ionized serum calcium stabilizes neural and muscle cell membranes, hypocalcemia can lead to neuromuscular irritability and contribute to the chief signs and symptoms of hypoparathyroidism, which are tetany, twitching, paresthesia, tremor, and spasm. Seizures and laryngospasm are severe symptomatic manifestations. Hypocalcemia may also influence cardiac function by inducing arrhythmias, hypotension, or heart failure. Psychiatric symptoms (anxiety,

irritability, depression, or delirium) may also be present in patients with hypocalcemia. Latent tetany may be demonstrated by eliciting a positive Chvostek sign (hyperirritability of the facial nerve when tapped) or Trousseau sign (carpal spasm induced by brachial nerve ischemia produced by inflating an arm blood pressure cuff above systolic for about 3 minutes). The manifestations of hypocalcemia, when present, vary greatly in severity among patients with hypoparathyroidism.

In hypoparathyroidism, concomitant hyperphosphatemia is a frequent occurrence. A resulting high calcium phosphate product may lead to the deposition of calcium phosphate salts in soft tissues. Such soft tissue calcification can result in important morbidities that include renal parenchymal damage and premature cataracts. Imaging studies in patients with hypoparathyroidism may reveal calcification of the basal ganglia and the grey-white matter interface in the brain.

Clinical effects of hypoparathyroidism can be ameliorated using oral calcium and calcitriol. Supplementation with an analog of vitamin D, 1-alpha-(OH) vitamin D<sub>3</sub> (alphacalcidol) is used in the place of calcitriol in some countries. The goal is to raise the serum calcium to a point where symptoms are no longer present. This generally means that the serum calcium should be maintained just below or at the low-normal range (8.0 to 8.5 mg/dL) ([Shoback 2008](#)). It is also desirable to avoid hypercalciuria ([Shoback 2008](#)). Acute or life-threatening tetany may be treated with an intravenous (IV) calcium infusion (eg, calcium gluconate) preferably under cardiac monitoring ([Bilezikian et al 2001](#)).

### **Hypercalciuria**

Parathyroid hormone promotes calcium reabsorption in the distal renal tubules, with decreasing nephrogenous cyclic adenosine monophosphate excretion and elevated tubular reabsorption of phosphate. Hypercalciuria is due to the lack of PTH effect on the renal tubules resulting in the inappropriate loss of calcium in the presence of normo- or hypocalcemia. Under normal conditions any decrease in serum calcium would result in increased PTH production. Parathyroid hormone then causes the kidney to limit calcium excretion, but without the presence of sufficient PTH the kidneys continue to excrete calcium into the urine, causing the hypercalciuria. Elevated vitamin D levels and oral supplementation of calcium to maintain the serum calcium level also contribute to hypercalciuria by increasing small bowel absorption of calcium and phosphate, enhancing renal filtration, further decreasing any residual PTH levels, and, therefore, additionally reducing renal tubular calcium absorption. Thiazide diuretics can be used to reduce (or prevent) hypercalciuria caused by calcium and vitamin D therapy. Once the 24-hour urinary calcium level approaches 250 mg, a thiazide diuretic combined with a low-salt diet can be added ([Shoback 2008](#)).

### **Hypercalcemia**

Hypercalcemia occurs when calcium entry into the circulation exceeds renal and other routes of calcium excretion. This may occur due to excessive dietary calcium absorption, hypervitaminosis D, increased bone resorption due to immobility, malignancy, and thiazide diuretics that decrease urinary calcium excretion, or increased PTH levels (hyperparathyroidism).

Symptoms of hypercalcemia are generally due to alterations in central and peripheral nervous system function (altered mental status, fatigue, weakness, muscle flaccidity) and other organ involvement such as the heart (ventricular arrhythmias). Bone resorption occurs over time. The kidneys are threatened by exposure to high serum calcium concentrations leading at times to renal calculi due to calcium phosphate precipitation in the renal pelvis and parenchyma. Frank renal dysfunction is not uncommon during an acute period of hypercalcemia with polyuria being a cardinal manifestation (due to antidiuretic hormone interference). When the albumin-corrected total serum calcium exceeds 14 mg/dL, the hypercalcemia needs attention on an urgent basis. Such emergencies can lead to many complications, particularly cardiac ones ([Bilezikian et al. 2001](#)).

## 1.2 Rationale for the Clinical Study

Treatment of hypoparathyroidism is complicated by the lack of national or international consensus management guidelines ([Shoback 2008](#)). Patients with hypoparathyroidism are unable to regulate normal albumin-corrected total serum calcium and phosphate handling physiologically. Current therapy is limited to calcium supplementation and parental or metabolic forms of vitamin D. These therapies, which are suboptimal, present specific challenges for adequate clinical care.

### Challenges Associated With Vitamin D Therapy

Patients with hypoparathyroidism are unable to efficiently convert precursor 25(OH) vitamin D to fully active 1,25(OH)<sub>2</sub> vitamin D in the kidney because they lack PTH and are hyperphosphatemic, both of which reduce the activity of 1 $\alpha$ -hydroxylase, the enzyme that drives production of calcitriol. Therefore, standard therapy for hypoparathyroidism usually relies on the administration of active vitamin D metabolites such as calcitriol (Rocaltrol<sup>®</sup>) or analogs such as alphacalcidol, which do not require PTH-dependent 1 $\alpha$ -hydroxylation. To demonstrate any appreciable clinical effect with less active forms of vitamin D (eg, cholecalciferol), these must be used at very high dosages. Such high doses of less active, precursor forms of vitamin D are more lipophilic than calcitriol and thus have a propensity to accumulate in fat, posing a real threat of vitamin D toxicity. Furthermore, active vitamin D forms can increase both calcium and phosphate absorption from the gut, which can, in turn, exacerbate the risk of hyperphosphatemia and an abnormal calcium phosphate product with subsequent soft tissue calcification.

### Challenges Associated With Oral Calcium Therapy

The US Institute of Medicine/National Academy of Sciences daily Dietary Reference Intake for calcium for individuals aged 18 to 70 years is 1000 to 1200 mg/day, while the daily Tolerable Upper Intake level (level at which there is no likely risk of adverse events [AEs]) is 2500 mg/day for adults. Patients with hypoparathyroidism typically require supplemental oral calcium therapy at or higher than this recommended limit, typically ranging between 2000 and 3500 mg/day. Impaired regulation of calcium and phosphate homeostasis due to a lack of PTH and pharmacological treatment with vitamin D metabolites/analogues combine with high oral calcium intake to increase the likelihood of soft tissue deposition of calcium salts. These can occur in the brain (ie, basal ganglia), kidneys, ocular lens, and other organs leading to structural damage and



a loss of function, as seen in premature cataracts, and even Parkinsonism. Without PTH to help conserve the filtered calcium in the kidney, substantial amounts of calcium can be lost leading to hypercalciuria with the attendant risks of nephrocalcinosis, hematuria and renal dysfunction. Thiazide diuretics such as hydrochlorothiazide may be used to stimulate the reabsorption of calcium in the distal nephron. In cases of profound hypocalcemia patients often require treatment with IV calcium along with cardiac monitoring. Some patients may require a permanent catheter placement for IV access.

In hypoparathyroidism, chronically low bone turnover results in significant abnormalities in bone structure, with bone mineral density (BMD) being very high because of increased mineralization. Several studies, mostly in animals and *in vitro*, have suggested that vitamin D and PTH act interdependently at the level of bone. In patients with hypoparathyroidism, the actions of vitamin D alone on bone remodeling are relatively minor. Langdahl et al studied bone biopsies in 12 hypoparathyroid patients treated with vitamin D or alfacalcidol and compared them with matched normal controls (Langdahl et al. 1996). With vitamin D alone, trabecular bone volume and thickness, marrow space volume, and trabecular volume were no different from controls, but bone turnover remained low. In the absence of PTH, therefore, vitamin D therapy alone is not able to normalize bone resorption and bone turnover. A recent study reported the abnormal structural/dynamic properties of bone in 33 patients with hypoparathyroidism treated with conventional oral calcium and vitamin D-based therapy as compared with matched controls (Rubin et al. 2008a). Histomorphometric assessment of iliac crest bone biopsies showed that hypoparathyroid patients had significantly greater cancellous bone volume and cortical bone width than healthy controls. In parallel, measures such as mineralizing surface and bone formation rate were profoundly decreased below normal in the hypoparathyroid group. The pathological effects of PTH deficiency on bone are largely asymptomatic, but can potentially include accumulation of microcracks in an environment of adynamic, dense bone tissue.

How this situation relates to rhPTH[1-84] and its potential therapeutic use in hypoparathyroidism differs fundamentally from its use in osteoporosis. In osteoporosis, PTH is used to increase BMD and improve bone structure, while in hypoparathyroidism, evidence from one recent study (Bilezikian 2008) indicates that PTH replacement appears to increase bone turnover from its low baseline level, potentially leading to improvements in bone structure.

### **Clinical Experience with PTH Peptides in the Treatment of Hypoparathyroidism**

Few studies of PTH use have been performed in the setting of hypoparathyroidism. Winer and colleagues have reported experience with twice-daily use of subcutaneously injected rhPTH(1-34) in the setting of adult and pediatric patients with hypoparathyroidism (Winer et al. 1998; Winer et al. 2003; Winer et al. 2008). In this setting, PTH(1-34) was shown to maintain eucalcemia and to reduce urinary calcium excretion. In these studies, PTH(1-34) was also compared to treatment with calcitriol, and showed that twice-daily PTH(1-34) or twice-daily calcitriol maintained similar albumin-corrected total serum calcium levels although urinary excretion of calcium was lower in the PTH(1-34) treated patients. PTH(1-34) is identical to the 34 N-terminal amino acids of the 84-amino acid hPTH, but unlike rhPTH[1-84] is not identical to the full 84 amino acid sequence.

One prospective, open-label clinical trial of PTH in the treatment of hypoparathyroidism is ongoing ([Bilezikian 2008](#)). In that study, patients with hypoparathyroidism are treated for 12 months with 100 µg of PTH(1-84) SC every other day (QOD). Despite the study having off-PTH days due to QOD dosing, there was, on average, a 30% reduction from baseline in supplemental calcium requirements over the course of the study. Total serum calcium concentrations remained stable. Improved renal calcium handling was also seen, with calcium excretion falling to 60% of baseline levels at the end of the study. Adverse event rates were low and PTH(1-84) was well tolerated.

Two-year data show that 100 µg of rhPTH[1-84] is a safe and effective replacement therapy in patients with hypoparathyroidism. Dosing with 100 µg of rhPTH[1-84] QOD resulted in an approximate decrease of 40% in requirements for supplemental calcium and calcitriol. These effects were seen as soon as 1 to 3 months after the onset of rhPTH[1-84] therapy. PTH(1-84) maintained serum calcium within the low normal range. Bone health was an outcome measure for this study and at baseline patients with hypoparathyroidism were reported to have increased cancellous bone volume, and increased trabecular and cortical bone width ([Rubin et al 2008b](#), [Rubin et al. 2008c](#), [Rubin et al. 2008d](#)). Bone turnover was suppressed and bone formation was low. PTH(1-84) therapy QOD led to a marked increase in bone turnover markers, which were accompanied by histopathological changes indicating increased osteoblast activity and alteration in BMD at the spine and radius. PTH(1-84) therapy was well tolerated throughout the 2 years of the study.

A randomized, double-blind, placebo-controlled, phase 3 study in adult subjects with hypoparathyroidism recently concluded (CL1-11-040, REPLACE). This study investigated the effects of daily SC injections of rhPTH[1-84] at doses of 50, 75, or 100 µg administered in the thigh. In addition, a randomized, dose-blinded study investigating fixed doses of rhPTH[1-84] 25 µg and 50 µg in adult subjects with hypoparathyroidism (PAR-C10-007, RELAY) also recently concluded as well as two phase 1 studies. One of the phase 1 studies (C09-002) was a pharmacokinetic/pharmacodynamic study to assess these aspects of rhPTH[1-84] administered at single SC doses of 50 and 100 µg in patients with hypoparathyroidism. The other study (PAR-C10-005) compared the bioequivalence of the Ypsomed and Haselmeier pen injection devices used to administer rhPTH[1-84] in the clinical studies.

## Summary

Parathyroid hormone replacement therapy may improve calcium homeostasis and thus reduce requirements for supplemental calcium and vitamin D metabolites or analogs in patients with hypoparathyroidism. rhPTH treatment can offset hypocalcemia by increasing bone turnover, renal tubular calcium reabsorption (while potentially inversely inhibiting renal phosphate reabsorption), and enhancing GI absorption of calcium via normalized endogenous formation of 1,25(OH)<sub>2</sub> vitamin D. This improved calcium handling may reduce risks of calcification and damage of soft tissues. Furthermore, because rhPTH[1-84] is identical in structure to endogenous human PTH(1-84), the potential for hypersensitivity reactions would be low as compared to nonbiologically identical peptides. Results from studies of rhPTH(1-34) twice daily SC and from an open-label study of rhPTH[1-84] 100 µg QOD SC in patients with

hypoparathyroidism provide a framework of information that supports the safety and potential clinical utility of PTH replacement therapy in hypoparathyroidism.

The purpose of the present study is to assess the long-term safety and efficacy of rhPTH[1-84] to treat hypoparathyroidism.

### **1.3 Rationale for Study Design**

#### **Dose**

In a phase 2 study of rhPTH[1-84] in osteoporosis, SC daily doses of 50, 75, and 100 µg were well tolerated. In these subjects with osteoporosis and intact parathyroid function, a dose-dependent increased incidence of hypercalcemia was observed. The recently completed REPLACE study evaluated these same doses in hypoparathyroid patients. An 8-week study of fixed doses of 25 and 50 µg (RELAY) was also undertaken to explore a broader range of treatment dose options. The clinical portion of RELAY has recently been completed. The RACE study will provide an opportunity for these subjects to continue NPSP558 (rhPTH[1-84]) treatment, at their discretion. The purpose of the RACE study is to assess the safety and tolerability of varying doses of rhPTH[1-84] during long-term treatment, while reducing requirements for supplemental oral calcium and calcitriol, maintaining stable total serum calcium levels, and controlling hypercalciuria in adult subjects with hypoparathyroidism.

#### **Route of Administration**

A single daily SC injection of PTH (versus infusion) increases PTH levels transiently. rhPTH[1-84] will be administered by daily SC injection into alternating thighs. The thigh was chosen due to the prolongation of the calcemic response when the drug is administered in the thigh compared to the abdomen.

## **2 OBJECTIVES**

### **2.1 Primary Objective**

The primary objective of this study is to demonstrate the long-term safety and tolerability of SC rhPTH[1-84] as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.

### **2.2 Secondary Objectives**

The secondary objectives of this study are:

- To evaluate the impact of different preparations of calcium on the response to rhPTH[1-84] replacement therapy
- To demonstrate that dosing with rhPTH[1-84] 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

### **2.3 Endpoints**

#### **2.3.1 Safety Endpoints**

Safety variables will be assessed by the following evaluations:

- Adverse events and serious adverse events
- Incidence of AEs of hypocalcemia (eg, paresthesia, numbness, tetany) and hypercalcemia (eg, constipation, nausea, poor appetite or vomiting, frequent urination, thirst, and kidney stones)
- Incidence of hypercalciuria
- Laboratory test results
  - Hematology (hematocrit, hemoglobin, white blood cells, red blood cells, platelets, differential)
  - Serum chemistries (standard Chem-20 panel, including calcium, phosphate, and albumin)
  - Serum 25(OH) vitamin D levels
  - Serum 1,25-dihydroxyvitamin D levels
  - Creatinine clearance
  - Serum bone turnover markers
  - Urinalysis
  - 24-hour urine calcium, phosphate, sodium, and creatinine excretion
  - PTH and *E. coli* protein (ECP) antibodies
- Bone mineral density by dual-energy x-ray absorptiometry (DXA)

- Electrocardiogram (ECG) parameters
- Physical examinations (including vital signs)
- Reason for termination from the study
- Immunogenicity analysis (AEs and SAEs related to PTH antibodies)
- Injection pen-related events and/or complaints

### 2.3.2 Efficacy Endpoints

The proportion of subjects in whom the following three conditions are fulfilled at Week 52 (Visit 9) and at the End of Treatment will be summarized:

- $A \geq 50\%$  reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of  $\leq 500$  mg

**AND**

- $A \geq 50\%$  reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of  $\leq 0.25$   $\mu\text{g}$

**AND**

- An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value and does not exceed the ULN for the central laboratory

### 2.3.3 Other Efficacy Endpoints

- Mean percentage changes from baseline in supplemental oral calcium and supplemental calcitriol dosages at each visit
- Proportion of subjects achieving the first three conditions of the efficacy endpoints defined above, at each visit
- Mean change from baseline in 24-hour urine calcium excretion
- Impact of calcium source (carbonate vs. citrate) on response
- Impact of calcium-sparing diuretics on serum and urinary calcium
- Proportion of subjects that maintain a calcium phosphate product  $\leq 55 \text{ mg}^2/\text{dL}^2$  ( $4.4 \text{ mmol}^2/\text{L}^2$ )
- Distribution of subjects by rhPTH[1-84] doses at the End of Treatment Visit
- Change from baseline in bone turnover markers (bone-specific alkaline phosphatase [BSAP], serum procollagen type 1 amino-terminal propeptide [P1NP], serum carboxy-terminal telopeptide of type I collagen [s-CTX], and osteocalcin), PTH antibodies, and BMD by DXA
- Additional subgroup analyses that are specified in the Statistical Analysis Plan (SAP)

### 3 STUDY DESIGN

#### 3.1 Overall Design and Control Methods

This study is a long-term, open-label study using rhPTH[1-84] for the treatment of adult male and female subjects with hypoparathyroidism. The subjects must have previously completed the NPSP558 RELAY study (8 weeks of active therapy) and/or previously completed the NPSP558 REPLACE study (CL1-11-040) (Visit 18).

The goal of this study is to optimize rhPTH[1-84] dosing while reducing calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible while maintaining total serum calcium levels (see [Appendix 2](#), rhPTH[1-84] and Supplement Titration Guideline).

- The starting dose of rhPTH[1-84] for this study will be 25 or 50 µg SC once daily (QD).
- Subjects with a total serum calcium value of  $\leq 9.5$  mg/dL will have a starting dose of 50 µg.
- Subjects with a total serum calcium value of  $> 9.5$  mg/dL will have a starting dose as follows:
  - Subjects who are taking supplements ( $\geq 500$  mg calcium and/or any calcitriol) will have the supplements reduced or stopped and will start at a dose of 50 µg SC QD.
  - Subjects who are taking minimal or no supplemental calcium ( $< 500$  mg) and no calcitriol will have a starting dose of 25 µg SC QD.
- Study visits during the first 12 months of the study will be conducted at Weeks 1 (baseline), 4, 8, and then every 8 weeks thereafter up to Week 48 (Visit 8). The Week 52 visit (Visit 9) is scheduled 4 weeks later.
- At the end of Week 52, subjects will be invited to extend their study drug regimen until January 2018 or after the completion of the last patient's Month 72 visit, whichever comes last. During this time, subjects will return to the clinic for interim visits every 2 months (Months 14, 16, 18, etc).
- All subjects will have their total serum calcium checked by a local laboratory 3 to 5 days ( $\pm 2$  days) following the baseline visit.
- Subjects may have their rhPTH[1-84] dose increased in increments of 25 µg to a maximum of 100 µg SC QD by the investigator at any time during the study, with the goal of achieving or maintaining total serum calcium levels in the range of 8.0 to 9.0 mg/dL. The rhPTH[1-84] dose may be adjusted downward at any time as needed to maintain appropriate serum calcium levels (approximately 8.0 to 9.0 mg/dL) or due to any safety concerns.
- Adjustment of supplemental calcium and calcitriol regimens will be based on serum calcium levels, with the goal to be a reduction or removal of calcitriol treatment to the maximum degree clinically possible and to decrease the prescribed oral calcium supplementation to  $\leq 500$  mg daily.
- Subjects will have blood draws to assess total serum calcium levels (which may be performed locally) 3 to 5 days after ANY dose adjustment of rhPTH[1-84], after any significant change in doses of calcium and/or and calcitriol supplements, or at any other time

at the discretion of the investigator. Results of local total serum calcium levels will be recorded in the source document.

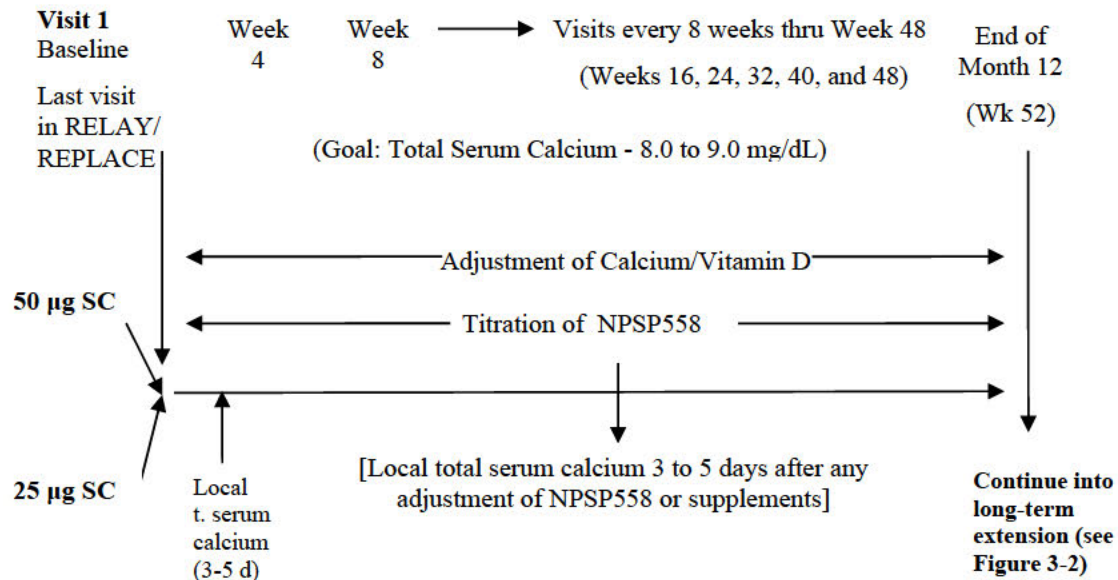
- Once a subject achieves a stable serum calcium (target: between 8.0 and 9.0 mg/dL) with the minimum doses of supplements possible, they will be maintained at that dose of rhPTH[1-84].
- If ANY predose (trough) total serum calcium is > 11.9 mg/dL study drug will be stopped. Once total serum calcium returns to the normal range, rhPTH[1-84] can be reintroduced. The rhPTH[1-84] dose may be maintained at the previous level if reductions in oral calcium supplements and/or calcitriol are possible. If oral calcium supplements have been previously reduced to ≤ 500 mg daily and calcitriol has been eliminated, then rhPTH[1-84] should be reintroduced at the next lowest dose level and supplemental oral calcium and calcitriol should then be adjusted accordingly to obtain a predose total serum calcium level of approximately 8.0 to 9.0 mg/dL.
- If the predose total serum calcium level remains above 10.0 mg/dL for two or more safety assessments or study visits on normal dietary intake and study drug alone, then the rhPTH[1-84] dose may be reduced to the next lowest dose level and supplemental oral calcium and calcitriol then adjusted accordingly to obtain a predose total serum calcium level of approximately 8.0 to 9.0 mg/dL. Study medication will be stopped if the predose total serum calcium remains above the upper limit of the laboratory normal range (ULN) for two or more safety assessments or study visits (no more than 5 days apart) at the lowest dose regimen, following withdrawal of all supplementary oral calcium and calcitriol therapy. Further choices on adaptation of treatment regimens, reinstitution of previous therapy, or discontinuation from study will be made in consultation with the Shire medical monitor.
- At and any time following the Week 16 (Visit 4), subjects who are on a stable dose of rhPTH[1-84] and have a 24-hour urine calcium > 300 mg (males) and > 250 mg (females) may be treated for hypercalciuria with calcium-sparing diuretics, if this therapy had not been introduced prior to the study. Newly started calcium-sparing diuretics will be given initially at a low dose.
- Monitoring for serum potassium, sodium, and calcium will be performed 1 week and again 1 month following the institution or change in dose of the calcium-sparing diuretic and then at each subsequent scheduled clinic visit.
- Monitoring of urine calcium will be performed at Weeks 16, 32, and 52 (Visits 4, 6, and 9) and every 4 months thereafter. For subjects on calcium-sparing diuretics, further dose adjustment of the diuretic will be done at the discretion of the investigator, based on urinary and serum calcium values.
- During the week following the last visit (End of Treatment or early termination visit), subjects who are discontinuing rhPTH[1-84] treatment (ie, those who are NOT continuing on commercial Natpara) will have oral calcium and/or active vitamin D adjusted to compensate for the cessation of NPSP558 (rhPTH[1-84]). Their total serum calcium levels will be checked locally at an interim visit scheduled 3 to 5 days after the last dose of study medication. Subjects will also be scheduled for a follow-up clinic visit at the end of this week in order to have serum calcium and phosphate checked.

- Subjects who terminate or complete the study and opt to continue treatment on commercial drug (Natpara), where available, will not require follow-up serum calcium and/or phosphate checks as a part of this study, but rather should continue follow-up serum calcium and/or phosphate monitoring by a physician according to approved labeling instructions. These subjects will be contacted one week after end of treatment for a wellness check.
- Approximately 4 weeks (30 days) following the End of Treatment visit, subjects will be contacted by telephone in order to assess AEs/serious AEs (SAEs).

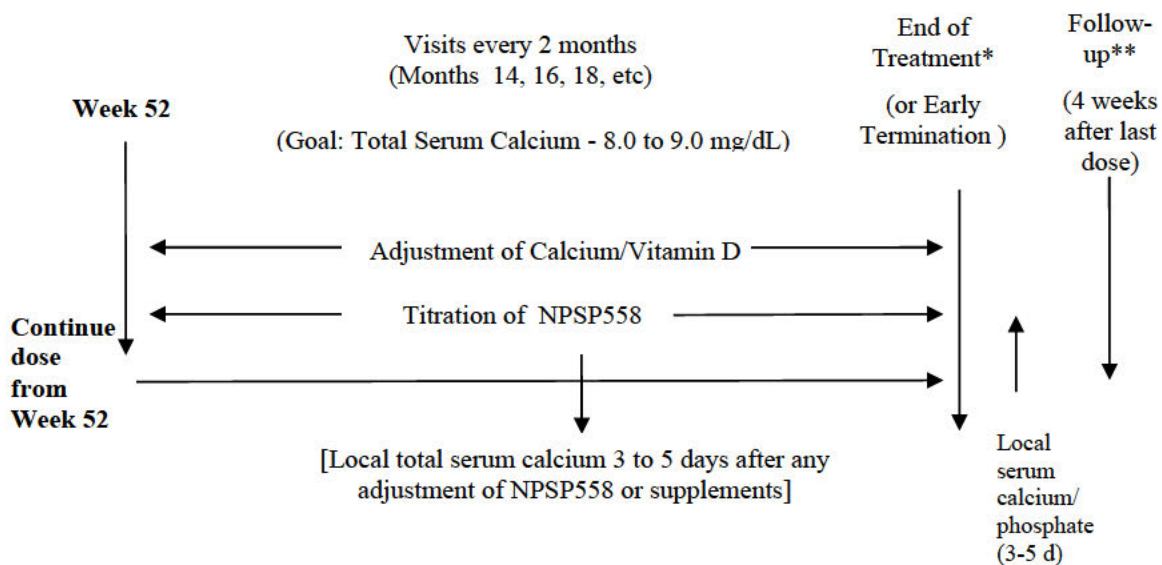
A schematic representation of the study design is displayed in [Figure 3-1](#) and [Figure 3-2](#).



**Figure 3-1 Study Design – First 12 Months of Study**



**Figure 3-2 Study Design – Long-term Extension**



\*Subjects who terminate or complete the study and opt to continue treatment on commercial drug (Natpara), will not require follow-up serum calcium and/or phosphate checks, but should continue treatment under the supervision of a physician under approved labeling instructions.  
\*\* Approximately 4 weeks (30 days) following the End of Treatment visit, all subjects will be contacted by telephone in order to assess AEs/SAEs.

### 3.2 Study Duration

The duration of the study was originally intended to be about 1 year. The study has been extended to up to 80 months of treatment with a 4-week follow up call/visit. Therefore, the overall duration of the study is expected to be approximately 81 months.

Study visits will be conducted every 2 months and will continue until the subject voluntarily withdraws or until termination of the study. See Section 6.2 for additional follow-up for subjects who develop antibodies specific to PTH. See Table 6-4 for additional follow-up for subjects who develop antibodies specific to PTH.

## 4 SUBJECT SELECTION AND PARTICIPATION

### 4.1 Number of Subjects

Approximately 50 subjects will be enrolled.

### 4.2 Inclusion Criteria

Subjects who meet all the following inclusion criteria can be enrolled into this study:

1. Signed and dated informed consent form (ICF) before any study-related procedures are performed
2. Previously completed the NPSP558 RELAY study 8 weeks of active therapy and/or previously completed the NPSP558 REPLACE study (Visit 18)
3. Able to perform daily SC self-injections of study medication (or have designee perform injection) via a multidose pen injector into the thigh
4. Willingness and ability to understand and comply with the protocol
5. Women who are: (1) postmenopausal defined as 12 months amenorrhea with appropriate serum follicle stimulating hormone (FSH) levels ( $> 40$  IU/L); (2) surgically sterilized; OR (3) of childbearing potential with a negative pregnancy test at screening and who consent to use two acceptable methods of contraception for the duration of the study, with pregnancy testing at every scheduled visit. Male subjects who have female partners of childbearing potential together also must use 2 acceptable forms of contraception during the subject's participation in the study.
6. Serum creatinine  $< 1.5$  mg/dL at enrollment
7. Total serum calcium  $\leq$  ULN based on local laboratory result prior to enrollment

8. Serum 25(OH) vitamin D  $\leq$  1.5 times the ULN within approximately 16 weeks prior to enrollment

#### **4.3 Exclusion Criteria**

Subjects who meet any of the following exclusion criteria at baseline (Visit 1) are not eligible for enrollment in this study:

1. Any condition that, in the investigator's opinion after consultation with the sponsor, would preclude the safe use of PTH
2. Any disease or condition, in the opinion of the investigator, which has a high probability of precluding the subject from completing the study or where the subject cannot or will not appropriately comply with study requirements
3. Pregnant or lactating woman

#### **4.4 Subject Withdrawal Criteria**

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified without prejudice to subsequent care. Withdrawn dosed subjects will not be replaced. A subject may be withdrawn from the study under any of the following circumstances:

- Withdrawal of informed consent
- If, in the opinion of the investigator, Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC/REB), Health Authority and/or Shire, it is no longer in the subject's best interest to continue in the study
- Subject no longer meets all inclusion criteria or meets any criterion for exclusion
- Lack of compliance with study procedures or study drug administration, as determined by the investigator
- Occurrence of an SAE determined by the investigator to be possibly related to study drug and not alleviated with treatment of symptoms
- Adverse event
- Hypersensitivity determined by the investigator to be possibly related to study drug
- Pregnancy or lactation
- Administrative reasons
- Treatment with commercial drug (Natpara)

In all cases, the reason for withdrawal must be recorded in the subject's medical records. If the reason is not known, the subject must be followed up to establish whether the reason was an AE and, if so, this must be reported in accordance with the procedures described in Section [6.2.1](#).

As far as possible, all examinations scheduled for the end-of-study evaluations must be performed on all subjects who participate but do not complete the study according to protocol.

## 5 TREATMENTS AND TREATMENT PLAN

### 5.1 Treatments Administered

Subjects will self-administer an SC injection of rhPTH[1-84] at a starting dose of either 25 or 50 µg daily into alternating thighs, based on their total serum calcium level at baseline as described in Section 3.1.

#### 5.1.1 Identification of Investigational Product(s)

RhPTH[1-84] is manufactured using a strain of *E. coli* modified by DNA technology and is identical to native human PTH. rhPTH[1-84] is a single-chain polypeptide containing 84 amino acid residues. The drug substance is clear and colorless to light straw-colored.

rhPTH[1-84] parathyroid hormone (rhPTH) product is provided in a dual-chamber cartridge. The front chamber (chamber 1) contains a sterile, white to off-white lyophilized powder containing rhPTH[1-84], sodium chloride, mannitol and citric acid. The rear chamber (chamber 2) contains a sterile diluent for reconstitution (m-cresol and sterile water for injection).

This study was initiated with study drug being administered using the Ypsomed pen injection device, in which the dual-chamber cartridge is installed by the user into a reusable pen injector device, in which reconstitution occurs in a total volume of 1.15 mL.

Based on the preliminary results of a recent study (PAR-C10-005) comparing the Haselmeier pen to the Ypsomed pen, showing that the two pens are bioequivalent; the Haselmeier pen has now replaced the Ypsomed pen in this study. The date the injection pen is switched will be recorded for each study subject.

In the case of the Haselmeier pen, the dual chamber cartridge comes pre-inserted in a cartridge holder. The cartridge in the cartridge holder is reconstituted using the Duoject mixing device and then loaded into the Haselmeier pen. The reconstituted volume is also 1.15 mL. Instructions for Use (IFU) for the Haselmeier pen and mixing device are provided in [Appendix 1](#).

Both pen injectors serve as holders for the cartridge and do not come in contact with rhPTH product. Using either pen injection device, each dual-chamber cartridge is designed to deliver 14 doses of 71.4 µL, each dose containing either 25, 50, 75, or 100 µg of rhPTH. The pen and reconstituted rhPTH product should be stored under refrigeration.

#### 5.1.2 Packaging and Labeling

##### Packaging

The study drug will be packaged, labeled, and delivered to the clinical centers by the sponsor or designee. Each subject will receive two pens for use during the study period and sufficient cartridges to provide daily doses for the duration of the study. Drug cartridges will be provided

in kits containing eight cartridges each and each kit will be sufficient for up to 16 weeks of treatment. Each cartridge will contain study drug for 14 doses. Drug cartridges will be provided at each clinic visit in sufficient quantity and at appropriate dose levels to ensure uninterrupted administration until the next study visit. Ancillary supplies including single use needles (31-gauge) and alcohol wipes will also be provided; once the inventory of ancillary kits is depleted, the clinical centers will receive the ancillary kit components separately and not as a kit (injection pen needles and alcohol prep pads).

### **Labeling**

Study drug will be supplied in individual kits labeled with the following information: investigational drug warning, company name, protocol number, lot number, storage conditions, contents, instructions regarding general dosing, and brief SC administration instructions. Label space will be provided for recording center and subject numbers. The label on the kit will be a tear-off label, which the study center can affix to the subject's source document or study document provided for this purpose. Boxes containing pens will be labeled with the following info: investigational warning, company name, protocol number, lot number, and subject number.

#### **5.1.3 Storage, Accountability, and Stability**

The clinical center's pharmacist or delegate is responsible for ensuring that all study drug received at the center is inventoried and accounted for throughout the study. All study drug must be kept in a locked area with access restricted to specific study personnel. The study drug and supplements are to be stored according to the manufacturers' specifications. The investigator or designee (ie, pharmacist) will conduct an inventory upon receipt of the clinical supplies from the sponsor, and will acknowledge receipt of the supplies to the sponsor or designee. A copy of the shipping documents must be maintained for the investigator's records.

Prior to reconstitution, cartridges should be stored at 2°C to 8°C (36°F to 46°F). After study drug reconstitution, the device can be used for up to 14 days when stored refrigerated at 2°C to 8°C and with infrequent exposure to room temperature for up to 30 minutes per day. Cartridges must be replaced 14 days after reconstitution. Cartridges should not be exposed to temperature extremes and should not be used if they have been or currently are frozen. Additional instructions for the storage of the Haselmeier pen and Duoject mixing device are included in the IFU.

In this study, subjects will be supplied with cartridges in sufficient quantity to maintain daily self-administration of varying dose of rhPTH[1-84]. Subjects should be reminded to return all cartridges, even if empty, at each study visit.

Pharmacy records will be maintained to capture the following information by lot number for each drug:

- quantity received
- current quantity on site
- quantity administered to each subject

- quantity removed from stock but not dispensed (eg, damaged, dropped, spilled)
- quantity remaining at the end of the study and retained, returned as per the sponsor's instructions

For each subject, dates that study medication was dispensed, administered, returned, or otherwise disposed of will be recorded.

All original containers, whether empty or containing study drug will be returned to the pharmacy. Contents of the study drug containers will not be combined. Unused study drug will be returned according to the sponsor's instructions.

## **5.2 Methods of Assigning Subjects to Treatment Groups**

Subjects will utilize the same 8-digit subject number that they had been assigned during the REPLACE or RELAY study. The first 4 digits consist of the center number and the last 4 digits are the sequential subject number. Subjects will receive study treatment in an open-label fashion at starting doses of rhPTH[1-84] 25 or 50 µg SC QD, as described in Section 3.1. On Day 1, the kit number from which cartridges are dispensed to a subject will be recorded on the appropriate eCRF. All subsequent kit numbers will be similarly recorded. All doses of study medication for each subject must be taken from the kit(s) designated for that subject and cartridges from an assigned kit will not be dispensed to any other subject.

## **5.3 Dose Regimens**

Daily rhPTH[1-84] SC injections will be self-administered into alternating thighs each morning using a multidose pen injection device (see [Appendix 1](#), Instructions for Use for the Haselmeier Pen Injector System).

### **5.3.1 Selection of Doses in Study**

rhPTH[1-84] given as a daily SC injection of 100 µg was approved in 2006 in the European Union for the treatment of postmenopausal osteoporosis (PMO). There is an extensive safety database with this product in subjects with PMO at doses ranging between 0.02 to 5.0 µg/kg. The phase 2 and 3 studies alone exposed 2891 subjects with PMO to doses ranging between 50 to 100 µg of rhPTH[1-84].

In subjects with hypoparathyroidism, several phase 1/2, single-center, open-label studies have demonstrated preliminary biologic activity of rhPTH[1-84] and PTH(1-34) given as daily or alternate day SC injections ([Bilezikian 2008](#); [Winer et al. 1998](#); [Winer et al. 2003](#); [Winer et al. 2008](#)). This current study will utilize varying doses starting at either 25 or 50 µg SC QD with the potential for upward adjustments in increments of 25 µg to a maximum dose of 100 µg SC QD, in order to assess its long-term effect in hypoparathyroid subjects.

### **5.3.2 Selection and Timing of Dose for Each Subject**

Subjects will self-administer rhPTH[1-84] in the morning, using the multidose pen injector devices. On the days of clinic visits, the injections of study drug will occur after the serum is taken for laboratory assessments and may be administered by the clinic study personnel.

Calcium and/or vitamin D should be taken in the morning as normal after the rhPTH[1-84] injection.

### 5.3.3 Compliance with Dosing Regimens

Paper diaries will be provided for the subjects to record study drug administration and supplement regimens. Subjects should be requested to bring the diaries to each clinic study visit for review. Subjects with  $\geq 80\%$  to  $\leq 120\%$  compliance level will be considered to be compliant with regard to study drug administration. Diaries will be collected at monitoring visits and submitted to the sponsor.

## 5.4 Prior and Concomitant Medications

### 5.4.1 Exclusionary Prior/Concomitant Medications

Subjects may remain on baseline concomitant medications during the trial (eg, hormone replacement therapy, antihypertensives, calcium-sparing diuretics, etc.). Prohibited prior and concomitant medications are generally those that may affect bone metabolism, confound efficacy or safety measurements, potentially pose a safety concern, or adversely potentiate or antagonize study drug therapy. Incidental or transient use of most of these medications (see list below) will not preclude a subject's entry into this study.

Exclusionary concomitant medications are shown in [Table 5-1](#).

**Table 5-1 Prohibited Medications or Therapies**

Medication/Therapy
Raloxifene hydrochloride
Bisphosphonates, intravenous
Bisphosphonates, oral
Calcitonin, cinacalcet or other drugs that influence calcium or bone metabolism
Fluoride tablets

Over the counter medications such as TUMS<sup>®</sup> are not to be taken as calcium supplementation. Please refer to Section [5.4.2](#) for information on calcium and vitamin D supplementation.

Permissible medications are:

- Nonprescription topical medications (that are not systemically absorbed)
- Acetaminophen
- Oral, implantable, vaginal rings, transdermal patch and injectable contraceptives and/or hormone replacement therapy
- All prescription and over the counter medication (including vitamins, herbs, or dietary supplements) being taken at baseline and all medications started during the study (from

signing the ICF through study exit), including administration dates and dosage, are to be recorded in the source document. Any medication which contains either calcium or vitamin D must be recorded in the source document with the amount of calcium and/or vitamin D content. To the extent possible, no changes should be made to the concomitant treatment during the study. Any additions, deletions or changes in the dose of these medications during the study also will be recorded in the source document.

#### **5.4.2 Active Vitamin D, Calcium, Native Vitamin D, and Magnesium Supplementation**

##### **Active Vitamin D**

Subjects enrolled in this study will be taking active vitamin D to control serum calcium levels. Oral calcitriol supplements will be provided during the first 52 weeks of this study by the sponsor or designee; no other sources of calcitriol should be used during the first year of study. Prescribed doses of calcitriol will be recorded in the source document. Calcitriol will not be supplied for the long-term extension portion of this study.

##### **Calcium**

Oral calcium supplements (either calcium carbonate or calcium citrate) will be provided throughout this study through approximately May 2014. Calcium citrate will continue to be supplied through the long-term extension; calcium carbonate will not be supplied through the remaining long-term extension portion of this study. No other sources of calcium supplementation should be used during the study. Calcium supplements should be taken regularly with meals, ideally morning and evening. Prescribed doses of calcium will be recorded in the source document.

In the case that extra calcium supplementation is taken by the subject due to symptoms of hypocalcemia, the dose/time and associated symptoms should be recorded by the subject in the diary.

##### **Native Vitamin D [25(OH) vitamin D]**

The serum 25(OH) vitamin D levels will be measured at the beginning of the study and at all scheduled study visits through the End of Treatment visit. During the study, sufficient supplemental native vitamin D should be administered in order to maintain the subject's serum 25(OH) vitamin D level in the normal range. Any dose taken by the subject must be recorded in the source document.

##### **Magnesium**

Magnesium is required for normal parathyroid function and disordered magnesium levels can exacerbate hypoparathyroidism. Subjects with low serum magnesium should undergo supplementation at a clinically appropriate level until the serum magnesium is within the normal range and normal serum magnesium should be maintained throughout the remainder of the study. Any dose taken by the subject must be recorded in the source document.



## **6 STUDY EVALUATIONS AND PROCEDURES**

### **6.1 Efficacy Evaluations**

Efficacy variables will be assessed by one or more of the following evaluations:

- Laboratory test results
  - Total serum calcium
  - 24-hour urinary calcium excretion
  - Serum phosphate
- Supplement usage
  - Concomitant supplemental oral calcium dosage
  - Concomitant supplemental oral calcitriol dosage

### **6.2 Safety Evaluations**

Safety variables will be assessed by the following evaluations:

- Adverse events and serious adverse events
- Incidence of AEs of hypocalcemia (eg, paresthesia, numbness, tetany) and hypercalcemia (eg, constipation, nausea, poor appetite or vomiting, frequent urination, thirst, and kidney stones)
- Incidence of hypercalciuria
- Immunogenicity analysis (AEs and SAEs related to PTH antibodies)
- Laboratory test results
  - Hematology (hematocrit, hemoglobin, white blood cells, red blood cells, platelets, differential)
  - Serum chemistries (standard Chem-20 panel, including calcium, phosphate, and albumin)
  - Serum 25-hydroxyvitamin D levels
  - Serum 1,25-dihydroxyvitamin D levels
  - Creatinine clearance
  - Serum bone turnover markers
  - Urinalysis
  - 24-hour urine calcium, phosphate, sodium, and creatinine excretion
  - PTH and ECP antibodies (Any subject who tests positive for PTH-specific antibodies at the last 2 consecutive visits at which antibodies are measured and does NOT continue treatment on commercial Natpara, will have follow-up blood draws for PTH antibodies at Months 3 and 6 poststudy. If a subject's results are negative at Month 3, follow-up may be terminated. Subjects may remain on study if they develop

PTH-specific antibodies during the study, providing that there are no concurrent AEs related to immunogenicity.)

- Bone mineral density by DXA
- Electrocardiogram parameters
- Physical examinations (including vital signs)
- Reason for termination from the study
- Pen-related events and/or complaints

### **6.2.1 Adverse Events**

The investigator is responsible for the detection and documentation of any AE or SAE, as defined in this protocol, during the study. Adverse events that were ongoing at the end of the REPLACE or RELAY study will be recorded and updated for this study. Any newly occurring AEs in this study will be recorded separately.

#### **6.2.1.1 Adverse Event Definition**

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical/medicinal product. An AE does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including a clinically significant abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product (investigational or marketed), whether or not considered related to treatment with the medicinal product.

An AE includes:

- An exacerbation of a pre-existing illness, sign, symptom, or clinically significant (as determined by the investigator) laboratory test abnormality and clinically significant ECG abnormality
- An illness, sign, symptom, or clinically significant laboratory abnormality that is detected or diagnosed after study drug administration
- Pretreatment or post-treatment events that occur as a result of protocol-mandated procedures

An AE does not include:

- The disease or disorder being studied or signs and symptoms associated with the disease or disorder, unless there is worsening of the condition of the disease or disorder
- A pre-existing disease or condition, present at the start of the study, that does not worsen

#### **6.2.1.2 Abuse, Misuse, Overdose, and Medication Error**

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described

in Section 6.2.2.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

The categories below are not mutually exclusive; the event can meet more than 1 category.

- Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society
- Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)
- Overdose – Intentional or unintentional intake of a dose of an investigational product exceeding the prescribed daily dose of the product
- Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

Medication errors should be collected/reported for NPSP558 (rhPTH[1-84]) only. Cases of missed doses are not considered reportable as medication errors. The administration and/or use of an expired investigational product should be considered as a reportable medication error.

#### **6.2.1.3 Procedures for Reporting Adverse Events**

Adverse events may be spontaneously reported by the subject, obtained through nonleading questioning, or noted during examination of a subject. All AEs and SAEs will be recorded from the signing of the ICF through the last study visit or the last study required procedure (including the follow-up telephone call 4 weeks after end of treatment). SAEs will be monitored with a telephone call by the investigator, as necessary, for approximately 4 weeks after the last dose of study drug, or until resolution or the SAE is judged by the investigator to have stabilized.

The AE term should note the diagnosis whenever possible, not the individual signs or symptoms (eg, myocardial infarction should be recorded rather than chest pain, elevated cardiac enzymes, and abnormal ECG). Also recorded are:

- Start and stop date and time
- Whether the event is continuing
- Frequency (intermittent, continuous)
- Intensity (mild, moderate, severe)
  - Mild: usually transient, requiring no special treatment and generally not interfering with usual daily activities
  - Moderate: usually ameliorated by simple therapeutic maneuvers and impairs usual activities
  - Severe: requires vigorous therapeutic intervention and interrupts usual activities. Hospitalization may or may not be required.

- Relationship to study drug (not related, related): identify relationship as “related” if a causal relationship between the investigational product and an AE is at least a reasonable possibility (ie, the relationship cannot be ruled out)
- Whether the AE is serious (ie, an SAE). If identified as an SAE, the AE should be reported on the SAE form according to Section 6.2.2.2 below.
- Actions taken (none; study drug dose changed, interrupted, or discontinued; other medication change; nondrug therapy)
- Outcome (resolved, resolved with sequelae, ongoing, fatal). An individual AE receives only one outcome.

Adverse events that are related to study drug and that have not resolved at the end of treatment will be followed by the site until resolution or until the AE is judged by the investigator to have stabilized.

Laboratory values, blood pressure, ECG evaluations, and clinical findings at the scheduled physical examinations must be reported as AEs if they:

- Are considered clinically significant by the investigator
- Fulfill SAE criteria, and/or
- Cause subject discontinuation from the study.

## **6.2.2 Serious Adverse Events**

All serious events must be reported as described in Section 6.2.2.2 and recorded in the appropriate electronic Case Report Form (CRF) in the EDC system InForm, and electronically signed by the investigator within 24 hours of event awareness. In case of EDC system unavailability the sponsor’s SAE Form must be used. An SAE requires expeditious handling to comply with regulatory requirements. Any SAEs occurring from the signing of the ICF through 30 days after the last dose of study drug will be captured and must be reported to the Shire Pharmacovigilance Department and the Shire Medical Monitor within 24 hours after the investigator is made aware of the event.

### **6.2.2.1 Serious Adverse Event Definition**

An SAE is an AE that results in any of the following outcomes:

- Death
- Is life-threatening. A life-threatening AE is any AE that places the subject—in the investigator’s opinion—at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more serious form, might have caused death.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions
- Hospitalization or prolongation of existing hospitalization
- Congenital anomaly/birth defect

- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.

Scheduled and/or elective hospitalizations occurring under the following circumstances will not be defined as SAEs for this clinical study:

- planned before entry into the clinical study
- are for elective treatment of a condition unrelated to the studied indication or its treatment
- occur on an emergency, outpatient basis and do not result in admission (unless fulfilling the previous criteria)
- are part of the normal treatment or monitoring of the studied indication and not associated with any deterioration in condition

#### **6.2.2.2 Procedures for Reporting Serious Adverse Events**

Within 24 hours of becoming aware of ANY SAE (regardless of its relationship to investigational product) that occurs during the course of the clinical study from the time the subject signs the ICF through 30 days after the study drug is completed, the investigator must notify the sponsor. The SAE information will include the description of the event and the date that the investigator became aware of the event. Supplemental data (eg, medical records or lab values, if applicable) will be faxed/emailed to Shire Pharmacovigilance and Risk Management Department, if requested by the sponsor. This ensures timely reporting of applicable reports to Health Authorities.

Note: Minimum criteria for reporting an SAE are the SAE term, an identifiable subject, a suspect investigational medical product (study drug), and a reporter. Hospitalization is not an AE, but a serious event criterion. The SAE term is the medical event that led to the hospitalization. Surgery is not an adverse event, but the event that required the subject to have surgery is the SAE term. Death is not an SAE, but an outcome.

The investigator is responsible for notifying the local, regional, or country-specific authorities of all SAEs and device failures that occur at his or her site, as required by local regulations.

All SAEs must be reported, whether or not they are considered causally related to the study drug. Appropriate clinical, diagnostic, and laboratory measures should be performed to delineate the cause of the SAE in question and the results reported. Follow-up for the SAE should occur at appropriate intervals until the event/laboratory abnormality:

- Returns to baseline or
- Becomes stable to a clinically acceptable level that is safe for the subject.

The investigator is required to assess the causal relationship of each reported SAE, to the study drug (see Section 6.2.1.3). A causality assessment should always be included on the sponsor's

SAE form. The investigator should make the causality assessment based on the information available at the time of the event. The causality can be updated at a future date if additional information is received.

The causality categories are:

Not related

- May or may not follow a reasonable temporal sequence from administration of the study product
- Is biologically implausible and does not follow a known response pattern to the suspect study product (if response pattern is previously known)
- Can be explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject

Related (Possibly Related/Probably Related/Related)

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (eg, angioedema, hepatic injury, Stevens-Johnson Syndrome)
- Follows a reasonable temporal sequence from administration of the study product
- May follow a known response pattern to the study product (if response pattern is previously known)
- Could not be reasonably explained by the known characteristics of the subject's clinical state or other modes of therapy administered to the subject, if applicable
- Recurs upon rechallenge after withholding and then reintroducing study product

Contact information for SAE reporting and emergency contact details can be found at the beginning of the protocol and in the Study Reference Manual.

As required by International Conference of Harmonisation (ICH) guidelines and global health authorities, the sponsor or designee will notify investigators of all adverse drug reactions that are serious, unexpected, and deemed by the reporting investigator or sponsor to be related to study drug (suspected, unexpected, serious, adverse reaction [SUSAR]). Causality, while assessed, does not negate reporting requirements to the sponsor. An AE, whether serious or not serious, is designated unexpected (unlabeled) if it is not reported in the clinical safety section of the Investigator Brochure (IB) or if the event is of greater frequency, specificity, or severity than is mentioned in the IB. The investigator will receive a copy of the current valid version of the IB prior to the start of the study; however, the investigator will not be required to assess expectedness, nor should expectedness impact the investigator reporting SAEs within the timeframe herein defined.

Upon receiving such notices, the investigator must review and retain the notice. As per the Food and Drug Administration (FDA) *Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs-Improving Human Subject Protection, January 2009* if it is

determined that there is an unanticipated signal, the Shire SMT will analyze the data and prepare a summary supporting the determination and interpretation of the findings. The sponsor or designee will send this summary to the investigators with instructions to provide it to their IRB.

The investigator should also comply with the IRB procedures for reporting any other safety information (ie, autopsy reports).

Shire will be responsible for submitting SUSAR reports to the appropriate health authorities. These reports will be submitted within the expedited timeframe. All fatal and life-threatening SUSAR reports will be submitted by Shire or designee within 7 days of receipt (Day 0) of the initial report. All other SUSAR reports will be submitted by Day 15 following the event.

### 6.2.3 Laboratory Evaluations

The following laboratory tests will be performed. Final RELAY study parameters may be used as baseline parameters for this study. Subjects from the REPLACE study who did not participate in the RELAY study will have to complete Visit 1 procedures. All laboratory tests collected during the study will be analyzed by a central laboratory, with the exception of all urine pregnancy tests and total serum calcium levels obtained at baseline and interim time points for safety checks, which will be done at the investigators' or subjects' local laboratories. The following laboratory parameters will be collected according to the schedule of procedures as noted below and outlined in [Table 6-1](#) and [Table 6-2](#):

- Hematology (fasted): hemoglobin concentration, hematocrit, erythrocyte count, platelet count, and leukocyte counts with differential (baseline, Week 52, every 12 months during the long-term extension, and at the End of Treatment visit).
- Serum Chem-20 panel (fasted): alanine transaminase, aspartate transaminase, alkaline phosphatase, lactate dehydrogenase, inorganic phosphate, total and direct bilirubin, creatine kinase, blood urea nitrogen, glucose, electrolytes (sodium, potassium, chloride, and bicarbonate), creatinine, calcium (standard and albumin-corrected), magnesium, total protein, albumin, and uric acid (baseline, Week 52, every 12 months during the long-term extension, and at the End of Treatment visit).
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, and microscopic analysis of sediment (baseline, Week 52, and at the End of Treatment visit).
- Creatinine clearance (baseline, Weeks 16, 32, and 52, every 4 months during the long-term extension, and at the End of Treatment visit).
- Total serum calcium (local) (baseline, interim Week 1, as needed at any other time during the study, and at the poststudy interim visit)
- Total serum calcium, albumin, and phosphate (every visit through Week 52; calcium and phosphate only at every long-term extension visit and at the 1-week follow-up visit)
- Serum potassium, sodium, and calcium (1 week and again 1 month following the institution or change in dose of the calcium-sparing diuretic and then at each subsequent scheduled clinic visit)
- Serum 25 (OH) vitamin D levels (every visit through the End of Treatment visit)

- Serum 1,25-dihydroxyvitamin D levels (Weeks 24 and 52, every 6 months during the long-term extension, and at the End of Treatment visit).
- 24-hour urine calcium, phosphate, sodium, and creatinine (baseline, Weeks 16, 32, and 52, every 4 months during the long-term extension, and at the End of Treatment visit).
- Serum bone turnover markers (BSAP, s-CTx, P1NP, and osteocalcin) (baseline, Weeks 8, 16, 24, 40, and 52, every 4 months during the long-term extension, and at the End of Treatment visit).
- Serum beta human chorionic gonadotropin ( $\beta$ -HCG) pregnancy test (women of child-bearing potential [WOCBP] only) (baseline, Weeks 16, 24, 32, 40, 48, 52 and End of Treatment visit)
- An FSH test to confirm postmenopausal status, if necessary (baseline only)
- Urine pregnancy test (WOCBP only) (baseline, Weeks 4 and 8, and every 2 months during the long-term extension)
- PTH and ECP antibodies (predose at baseline, Weeks 24, 40, 52, every 6 months during the long-term extension, and at the End of Treatment visit)
- Serum PTH[1-84] for PK analysis (Week 48 only)

Clinically significant (as determined by the investigator) abnormal laboratory test results will be considered AEs. A result outside of the normal range may be repeated for confirmation. Any laboratory test result that meets the criteria for an SAE (see Section 6.2.2.1) must also be recorded in an SAE report so that the sponsor or designee can collect additional information about that abnormality, including information regarding relationship to investigational product or other causes, any action taken, and outcome.

#### **6.2.4 Vital Signs and Body Weight**

Vital signs will be measured prior to blood draws at baseline and each clinic study visit through the End of Treatment visit and will include systolic and diastolic blood pressure (mm Hg), pulse (beats per minute or bpm), and body temperature ( $^{\circ}$ C) after the subject has been sitting for 5 minutes. Body weight will also be recorded.

If any of the subject's measurements are outside of the normal range at screening (prior to receiving the first dose) the investigator will determine, based on medical history, whether the subject can safely continue in the study. A measurement outside the normal range may be repeated during the course of the visit for confirmation.

#### **6.2.5 Electrocardiograms**

A 12-lead ECG will be done at baseline, Week 52, and at the End of Treatment visit. Baseline and Week 52 ECGs (and early termination visits occurring in the first year) will be done at the study center on the same model unit. The end of treatment ECG may be done locally. Recorded data will include general findings, ventricular rate (bpm) and P-R, QRS, and QTc intervals (seconds). Any ECG abnormalities, as determined by the investigator, at screening will be recorded as medical history. Any clinically significant adverse change from the status at the screening visit and noted to be clinically significant by the investigator should be captured as an



AE. All ECGs conducted during the first year of the study will be assessed by a central reader and this assessment will be used as the primary data readout for the study. However, investigators are also responsible for providing their own interpretation of the ECG, and this will be captured on the ECG print out. Two copies of the ECG tracings should be retained in the subject source record. The local, end of treatment ECG will not be sent to the central reader, unless necessary in order to confirm an ambiguous result or serious abnormality.

#### **6.2.6 Physical Examinations**

Full physical examinations will be performed at baseline, Week 52, and at the End of Treatment visit and will consist of general assessments of the head, eyes, ears, nose, throat, lymph nodes, skin, extremities, and respiratory, gastrointestinal, musculoskeletal, cardiovascular, nervous, and dermatologic systems. The physical examination should be performed by the same person each time, whenever possible. Brief physical exams will be conducted every 6 months during the long-term extension portion of the study.

Physical examination abnormalities determined by the investigator to be clinically significant at screening should be recorded as medical history if they developed since the RELAY or REPLACE study.

Any clinically significant adverse change from the status at the baseline visit and noted to be clinically significant by the investigator should be captured as an AE.

#### **6.2.7 Dual-energy X-ray Absorptiometry**

DXA scans will be performed at baseline, Week 52, yearly during the long-term extension portion of the study, and at the End of Treatment visit, if it is greater than 3 months since the previous DXA scan. These scans will evaluate BMD of the lumbar vertebra (L1-L4), hip (total, trochanter, intertrochanter, Ward's triangle, and femoral neck), and  $\frac{1}{3}$  distal radius (arm). Calcium supplements should be withheld for 24 hours prior to the scan, if possible. If a subject cannot withhold the calcium supplements due to safety concern, the DXA should be performed 2 hours after the last calcium tablet has been ingested. Please note: DXA will NOT be completed at baseline if subject had a scan performed within the past 6 months within one of the previous studies.

#### **6.2.8 Women of Childbearing Potential**

Any subject that has become postmenopausal since entering the RELAY or REPLACE study should be re-evaluated at baseline for this study. For a woman to be considered postmenopausal there must have been an absence of menses for 12 consecutive months with appropriate serum FSH levels (ie, > 40 IU/L).

If the result is not in the postmenopausal range and the subject is not surgically sterile, then the subject should be considered a woman of childbearing potential (WOCBP).

A WOCBP may be included in the study, but must have a negative serum pregnancy test at baseline. Lack of pregnancy will be confirmed by urine pregnancy tests at baseline and Weeks 4 and 8 (Visits 2 and 3). A serum pregnancy test will be repeated at Weeks 16, 24, 32, 40, 48, 52,

and at the End of Treatment visit. A urine pregnancy test will be done at all interim visits during the long-term extension portion of the study. Pregnancy occurring during the trial will necessitate immediate withdrawal from study. A WOCBP must be willing to use 2 medically acceptable methods of contraception for the duration of the study (see [Appendix 3](#)). Male subjects with female partners of childbearing potential together also must use 2 medically acceptable means to avoid pregnancy during the subject's participation in the study.

### **6.2.9 Pregnancy Reporting**

Pregnant and lactating women are excluded from participation in this study. In the event a subject becomes pregnant during the study, study drug will be discontinued and the Shire Investigational and Marketed Product Pregnancy Report form will be completed to capture potential drug exposure during pregnancy and reported to the sponsor or designee within 24 hours of becoming aware of the pregnancy. The pregnant subject will be followed until an outcome is known (ie, normal delivery, abnormal delivery, spontaneous/voluntary/therapeutic abortion). If a pregnant subject also experiences an SAE, the Shire Clinical Study Serious Adverse Event and Non-Serious AEs as Required by the Protocol Form will be completed and submitted to the sponsor or designee within 24 hours as discussed above.

The Shire Investigational and Marketed Products Pregnancy Report Form should be completed in the event that a female partner of a male subject becomes pregnant within 30 days after his last dose of study drug or study completion, if agreed upon and consented to by the pregnant partner. The pregnancy (mother and fetus) will be followed up through delivery with regard to outcome.

## **6.3 Schedule of Evaluations and Procedures**

All clinical study evaluations will be performed according to [Table 6-1](#), [Table 6-2](#), and [Table 6-3](#). Details of the exact date and time of medical assessments (day/month/year) will be documented in the source document. Any deviations from protocol requirements will be documented in the source document. A schedule of follow-up visits and procedures for subjects who test positive for PTH-specific antibodies at the last visit is provided in [Table 6-4](#).

**Table 6-1 Schedule of Evaluations and Procedures – First 12 Months of Study**

Visit Number	1*	Int.	2	3	4	5	6	7	8	9
Study Procedures / Proposed Study Week <sup>a</sup>	BL <sup>b</sup>	1 <sup>c</sup>	4	8	16	24	32	40	48	52
Visit Windows	± 3 days	± 2 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Informed Consent	X									
Review Inclusion/Exclusion Criteria	X									
Medical History (updated from RELAY/REPLACE)	X									
Concomitant medications (ongoing)	X		X	X	X	X	X	X	X	X
Concomitant medications (new)	X		X	X	X	X	X	X	X	X
Adverse event monitoring (ongoing)	X		X	X	X	X	X	X	X	X
Adverse event monitoring (new)	X		X	X	X	X	X	X	X	X
Assessment of clinical episodes of hypocalcemia and hypercalcemia	X		X	X	X	X	X	X	X	X
Physical examination	X									X
Vital signs <sup>d</sup> and weight	X		X	X	X	X	X	X	X	X
Electrocardiogram (12-lead) (centrally read)	X									X
Bone mineral density by DXA <sup>e</sup>	X									X
Hematology <sup>f</sup>	X									X
Serum chemistry (20-panel) <sup>f</sup>	X									X
Serum calcium (local)**	X	X								
Serum calcium, phosphate, and albumin	X		X	X	X	X	X	X	X	X
Serum calcium, potassium, sodium <sup>g</sup>					X	X	X	X	X	X
Serum 25-hydroxyvitamin D	X		X	X	X	X	X	X	X	X
Serum 1,25-dihydroxyvitamin D						X				X
Serum bone turnover markers	X			X	X	X		X		X
Serum thyroid function test <sup>h</sup>	X									
Creatinine clearance (estimated GFR)	X				X		X			X
PTH and ECP antibodies <sup>i</sup>	X					X		X		X <sup>l</sup>
Serum PTH [1-84] for pharmacokinetic analysis									X <sup>m</sup>	
FSH (newly menopausal women only)	X									
Serum pregnancy test (WOCBP only)	X				X	X	X	X	X	X
Urine pregnancy test (WOCBP only)	X		X	X						
Urinalysis	X									X
24-hour urine calcium, phosphate, sodium, creatinine	X				X		X			X
Diary review <sup>j</sup>			X	X	X	X	X	X	X	X
Dispense/administration/accountability of study drug and pen injectors/ancillary supplies	X		X	X	X	X	X	X	X	X

**Table 6-1 Schedule of Evaluations and Procedures – First 12 Months of Study**

Visit Number	1*	Int.	2	3	4	5	6	7	8	9
Study Procedures / Proposed Study Week <sup>a</sup>	BL <sup>b</sup>	1 <sup>c</sup>	4	8	16	24	32	40	48	52
Visit Windows	± 3 days	± 2 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days
Dispense/accountability of calcium/calcitriol supplements (see guideline)	X		X	X	X	X	X	X	X	X
Dispense subject diaries	X									X
Collect used/unused study drug and supplements <sup>k</sup>			X	X	X	X	X	X	X	X

BL = baseline; DXA = dual-energy x-ray absorptiometry; ECP = *E.coli* protein; FSH = follicle stimulating hormone; GFR = glomerular filtration rate; Int.= interim visit; PTH = parathyroid hormone; WOCBP = women of child-bearing potential

\*Note: Final RELAY study parameters may be used as baseline parameters for this study.

\*\*Any adjustment of study drug or supplemental calcium and calcitriol doses requires testing of total serum calcium concentrations at interim time points.

<sup>a</sup> Study visits will be conducted at Weeks 1 (baseline), 4, 8, every 8 weeks thereafter through Week 48, and at Weeks 52.

<sup>b</sup> Week 8 from the RELAY study; subjects will return all used/unused drug, supplements, and pens from RELAY/REPLACE.

<sup>c</sup> After the End of Treatment visit or early termination visit, subjects who will not continue rhPTH[1-84] treatment will have their total serum calcium and phosphate levels measured 3 to 5 days after the last dose of study medication. Doses of calcium and active vitamin D supplements will be adjusted by the Investigator as appropriate. Thereafter, the Investigator will repeat serum calcium/phosphate monitoring and supplement dose adjustments as appropriate to achieve target serum calcium/phosphate concentrations until the follow up phone call 4 weeks ± 7 days after end of treatment visit. After the 4 week follow up phone call, further management of hypoparathyroidism will occur as part of the subject's long-term non-study medical care.

<sup>d</sup> Vital signs should be done prior to blood draws.

<sup>e</sup> Calcium supplements should be withheld for 24 hours prior to the DXA scan. If a subject cannot withhold the calcium supplements due to safety concern, the DXA should be performed 2 hours after the last calcium tablet has been ingested. Please note: DXA will NOT be completed at baseline if subject had a scan performed within the past 6 months in one of the previous studies (all subjects will have a DXA performed at Week 52 (Visit 9))

<sup>f</sup> Fasting for at least 6 to 8 hours prior to test

<sup>g</sup> Serum potassium, sodium, and calcium is to be collected 1 week and again 1 month following the institution or change in dose of a calcium-sparing diuretic and then at each subsequent scheduled clinic visit.

<sup>h</sup> Thyroid function tests done for final visit of the RELAY/REPLACE studies only.

<sup>i</sup> Blood draw for PTH and ECP antibodies will be done predose.

<sup>j</sup> A paper diary will be dispensed at baseline for the investigator's use to assess subject's compliance and adherence to the protocol procedures.

<sup>k</sup> Subject is to return unused and used cartridges and supplements at each visit.

<sup>l</sup> See Section 6.2 for instructions on follow-up for subjects with PTH-specific antibodies and Table 6-3 for a schedule of follow-up procedures for these subjects.

<sup>m</sup> Blood samples for pharmacokinetic analysis will be drawn predose (0 hour) and postdose between 1 and 2 hours and between 6 and 10 hours following study drug administration.

**Table 6-2 Schedule of Evaluations and Procedures – Long-term Extension to Month 36**

Study Procedures / Proposed Study Month <sup>a, b</sup>	Months 14/26	Months 16/28	Months 18/30	Months 20/32	Months 22/34	Months 24/36**
Visit Windows	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks
Concomitant medications	X	X	X	X	X	X
Adverse event monitoring, including pen-related events/complaints	X	X	X	X	X	X
Assessment of clinical episodes of hypocalcemia and hypercalcemia	X	X	X	X	X	X
Physical examination			X <sup>c</sup>			X <sup>c</sup>
Vital signs <sup>d</sup> and weight	X	X	X	X	X	X
Bone mineral density by DXA <sup>e</sup>						X <sup>f</sup>
Hematology <sup>g</sup>						X
Serum chemistry (20-panel) <sup>g</sup>						X
Serum calcium (local)*						
Serum calcium, phosphate	X	X	X	X	X	X
Serum calcium, potassium, sodium <sup>h</sup>	X	X	X	X	X	X
Serum 25-hydroxyvitamin D	X	X	X	X	X	X
Serum 1,25-dihydroxyvitamin D			X			X
Serum bone turnover markers		X		X		X
Creatinine clearance (estimated GFR)		X		X		X
PTH and ECP antibodies <sup>i, j</sup>			X			X
Serum pregnancy test (WOCBP only)						
Urine pregnancy test (WOCBP)	X	X	X	X	X	X
Urinalysis						
24-hour urine calcium, phosphate, sodium, creatinine		X		X		X
Diary review <sup>k</sup>	X	X	X	X	X	X
Dispense/administration/accountability of study drug, calcium, and pen injectors/ancillary supplies	X	X	X	X	X	X
Collect used/unused study drug and pen injectors <sup>l</sup>	X	X	X	X	X	X

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**Table 6-2      Schedule of Evaluations and Procedures – Long-term Extension to Month 36**

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DXA = dual-energy x-ray absorptiometry; ECP = *E. coli* protein; EoT = end of treatment; F/up = follow up; GFR = glomerular filtration rate; Int.= interim visit;  
PTH = parathyroid hormone; WOCBP = women of child-bearing potential)

\*Any adjustment of study drug or oral calcium and active vitamin D doses requires testing of total serum calcium concentrations at interim time points.

**\*\*Following Month 24, the every 2-month visit schedule will repeat (ie, visits procedures for Month 26 are the same as those shown at Month 14.)**

<sup>a</sup> Study visits will be conducted every 2 months during the extension portion and will continue until the subject voluntarily withdraws or until termination of the study.

<sup>b</sup> After the End of Treatment visit or early termination visit, subjects who will not continue rhPTH[1-84] treatment will have their total serum calcium and phosphate levels measured 3 to 5 days after the last dose of study medication. Doses of calcium and active vitamin D supplements will be adjusted by the Investigator as appropriate. Thereafter, the Investigator will repeat serum calcium/phosphate monitoring and supplement dose adjustments as appropriate to achieve target serum calcium/phosphate concentrations until the follow up phone call 4 weeks  $\pm$  7days after end of treatment visit. After the 4 week follow up phone call, further management of hypoparathyroidism will occur as part of the subject's long-term non-study medical care.

<sup>c</sup> Brief physical exams will be conducted at 6-month intervals.

<sup>d</sup> Vital signs should be done prior to blood draws.

<sup>e</sup> Calcium supplements should be withheld for 24 hours prior to the DXA scan. If a subject cannot withhold the calcium supplements due to safety concern, the DXA should be performed 2 hours after the last calcium tablet has been ingested.

<sup>f</sup> DXA will be performed at End of Treatment visit ONLY if the previous DXA was  $\geq 3$  months prior.

<sup>g</sup> Fasting for at least 6 to 8 hours prior to test

<sup>h</sup> Serum potassium, sodium, and calcium is to be collected 1 week and again 1 month following the institution or change in dose of a calcium-sparing diuretic and then at each subsequent scheduled clinic visit.

<sup>i</sup> Blood draw for PTH and ECP antibodies will be done predose.

<sup>j</sup> See Section 6.4.9 for instructions on follow-up for subjects with PTH-specific antibodies and Table 6-4 for a schedule of follow-up procedures for these subjects.

<sup>k</sup> Subjects will record diary information during the 2-week period prior to the next scheduled visit during the long-term extension portion of the study. If the subject does not record the diary information as indicated during this time period, he/she may record it during the 2 weeks following the visit, for review at the next visit or via phone.

<sup>l</sup> Subjects are to return unused and used cartridges at each visit. Pens will be collected at the final visit.

**Table 6-3 Schedule of Evaluations and Procedures – Long-term Extension after Month 36**

Study Procedures	Proposed Study Month <sup>a</sup>	Months 38/50/62	Months 40/52/64	Months 42/54/66/74	Months 44/56/68/76	Months 46/58/70/78	Months 48/60/72/80	End of Treatment <sup>b</sup>	4 weeks F/up Phone <sup>c</sup>
Visit Windows		± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 1 week	± 7 days
Re-consent subject <sup>d</sup>		X							
Concomitant medications		X	X	X	X	X	X	X	
Adverse event monitoring, including pen-related events/complaints		X	X	X	X	X	X	X	X
Assessment of clinical episodes of hypocalcemia and hypercalcemia		X	X	X	X	X	X	X	
Physical examination <sup>e</sup>				X <sup>e</sup>			X <sup>d</sup>	X	
Vital signs <sup>f</sup> and weight		X	X	X	X	X	X	X	
Electrocardiogram (12-lead)								X <sup>g</sup>	
Bone mineral density by DXA <sup>h</sup>							X	X <sup>i</sup>	
Hematology <sup>j</sup>							X	X	
Serum chemistry (20-panel) <sup>j</sup>							X	X	
Serum calcium (local)*									
Serum calcium, phosphate		X	X	X	X	X	X	X	
Serum calcium, potassium, sodium <sup>k</sup>		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	
Serum bone turnover markers			X		X		X	X	
Creatinine clearance (estimated GFR)			X		X		X	X	
PTH and ECP antibodies <sup>l</sup>				X			X	X <sup>m</sup>	
Serum pregnancy test (WOCBP only)								X	
Urine pregnancy test (WOCBP)		X	X	X	X	X	X		
Urinalysis								X	
24-hour urine calcium, phosphate, sodium, creatinine			X		X		X	X	
Diary review <sup>n</sup>		X	X	X	X	X	X	X	
Dispense/administration/accountability of study drug, and pen injectors/ancillary supplies <sup>o</sup>		X	X	X	X	X	X	X	
Collect used/unused study drug / pen injectors <sup>p</sup>		X	X	X	X	X	X	X	

DXA = dual-energy x-ray absorptiometry; ECP = *E. coli* protein; EoT = end of treatment; F/up = follow up; GFR = glomerular filtration rate; Int.= interim visit; PTH = parathyroid hormone; WOCBP = women of child-bearing potential

NOTE: Following Month 72, the every 2-month visit schedule will repeat (ie, visits procedures for Month 74 will repeat starting with those shown at Months 26/38/50.)

\*Any adjustment of study drug or oral calcium and active vitamin D doses requires testing of total serum calcium concentrations at interim time points.

**Table 6-3 Schedule of Evaluations and Procedures – Long-term Extension after Month 36**

Study Procedures	Proposed Study Month <sup>a</sup>	Months 38/50/62	Months 40/52/64	Months 42/54/66/74	Months 44/56/68/76	Months 46/58/70/78	Months 48/60/72/80	End of Treatment <sup>b</sup>	4 weeks F/up Phone <sup>c</sup>
	Visit Windows	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 2 weeks	± 1 week	± 7 days

<sup>a</sup> Study visits will be conducted every 2 months and will continue until the subject voluntarily withdraws or until termination of the study. At that time, and periodically following that milestone, the study will be reviewed in regard to continuation/termination status.

<sup>b</sup> After the End of Treatment visit or early termination visit, subjects who will not continue rhPTH[1-84] treatment will have their total serum calcium and phosphate levels measured 3 to 5 days after the last dose of study medication. Doses of calcium and active vitamin D supplements will be adjusted by the Investigator as appropriate. Thereafter, the Investigator will repeat serum calcium/phosphate monitoring and supplement dose adjustments as appropriate to achieve target serum calcium/phosphate concentrations until the follow up phone call 4 weeks ± 7 days after end of treatment visit. After the 4 week follow up phone call, further management of hypoparathyroidism will occur as part of the subject's long-term non-study medical care.

<sup>c</sup> Follow-up phone contact 4 weeks after the last dose of study medication to check on any ongoing or new drug-related AEs or SAEs

<sup>d</sup> Study subjects must be re-consented at their next study visit prior to implementation of Amendment 6.

<sup>e</sup> Brief physical exams will be conducted at 6-month intervals.

<sup>f</sup> Vital signs should be done prior to blood draws.

<sup>g</sup> The End of Treatment ECG will be read locally.

<sup>h</sup> Calcium supplements should be withheld for 24 hours prior to the DXA scan. If a subject cannot withhold the calcium supplements due to safety concern, the DXA should be performed 2 hours after the last calcium tablet has been ingested.

<sup>i</sup> DXA will be performed at End of Treatment visit ONLY if the previous DXA was ≥3 months prior.

<sup>j</sup> Fasting for at least 6 to 8 hours prior to test

<sup>k</sup> Serum potassium, sodium, and calcium is to be collected 1 week and again 1 month following the institution or change in dose of a calcium-sparing diuretic and then at each subsequent scheduled clinic visit.

<sup>l</sup> Blood draw for PTH and ECP antibodies will be done predose.

<sup>m</sup> See Section 6.4.9 for instructions on follow-up for subjects with PTH-specific antibodies and Table 6-4 for a schedule of follow-up procedures for these subjects.

<sup>n</sup> Subjects will record diary information during the 2-week period prior to the next scheduled visit during the long-term extension portion of the study. If the subject does not record the diary information as indicated during this time period, he/she may record it during the 2 weeks following the visit, for review at the next visit or via phone.

<sup>o</sup> Ancillary supplies (ie, needles and alcohol wipes) may be supplied, as allowed by local regulations.

<sup>p</sup> Subjects are to return unused and used pen injectors at each visit.



**Table 6-4 Schedule of Follow-up Visits and Procedures for Subjects with PTH-specific Antibodies at the Final 2 Visits**

Follow-up Procedures <sup>a</sup>	Follow-up (Month 3) <sup>b</sup>	Follow-up (Month 6)
<b>Visit Number:</b>	<b>F3</b>	<b>F4</b>
<b>Visit Window (± Days)</b>	<b>±7</b>	<b>±7</b>
Antibodies to PTH	X	X
Adverse events	X	X

AE = adverse event; F = follow-up; PTH = parathyroid hormone

<sup>a</sup> Follow-up visits will be conducted for only those subjects who are determined to have PTH-specific antibodies at the final two consecutive visits (at End of Study or at the time of discontinuation) and are NOT continuing treatment on commercial Natpara. See Section 6.4.9.

<sup>b</sup> Subjects who have negative antibody results at Month 3 do not need the Month 6 follow-up visit.

## 6.4 Description of Study Procedures

### 6.4.1 Visit 1 Baseline Procedures

RELAY study Week 8 procedures must be performed prior to any baseline procedures. Subjects must sign an ICF for this study prior to having any study-related procedures performed. Additionally, REPLACE completers, who did not participate in the RELAY study, will have to undergo ALL Visit 1 procedures.

Subjects will be instructed to come into the study center after having fasted for approximately 6 to 8 hours. Appointments should be scheduled accordingly to accommodate this fasting status (ie, in the morning). The following procedures will be performed prior to enrollment:

- Update the subject's medical history, demographic information, ongoing concomitant medications, and ongoing AEs from the RELAY/REPLACE study
- Review inclusion/exclusion criteria
- Record all new prescription and nonprescription medications, dietary and nutritional supplements, and vitamins and their doses, frequencies, and durations.
- The occurrence of any new or continuing AE, including episodes of hypocalcemia or hypercalcemia, will be recorded following the signing of the ICF, regardless of whether or not study drug had been administered
- Vital signs measurements (prior to blood draws) and weight
- Physical examination
- 12-lead electrocardiogram
- Blood samples for serum chemistries (including calcium, phosphate, and albumin), hematology, serum 25(OH) vitamin D, creatinine clearance, and bone turnover markers. The

blood sample for serum chemistries will be split and a local total serum calcium will also be performed

- Blood sample for PTH and ECP antibodies
- Urinalysis and 24-hour urine calcium, phosphate, sodium, and creatinine
- Serum  $\beta$ -HCG pregnancy test (WOCBP only)
- Urine pregnancy test for immediate confirmation of non-pregnant status (WOCBP only)
- A BMD test by DXA (omit if subject had a scan performed within the past 6 months in either RELAY or REPLACE studies)
- An FSH test to confirm postmenopausal status, EXCEPT if subjects have met the definition of postmenopausal after the beginning the RELAY/REPLACE study (for newly postmenopausal females only)
- The first dose of study medication will be administered after appropriate fasting laboratory evaluations have been taken
- Subjects will be provided with the following study supplies:
  - Study medication cartridges in sufficient number to supply daily doses until the next scheduled clinic visit
  - Two pen injectors
  - Ancillary injection supplies (ie, alcohol swabs, needles, etc.)
  - Paper diaries
  - Calcium (carbonate or citrate) and calcitriol supplements in sufficient quantity to supply daily doses until the next scheduled clinic visit

#### **6.4.2 Week 1 Interim Safety Check**

Subjects will have blood drawn locally to assess total serum calcium levels between 3 to 5 days ( $\pm 2$  days) following baseline. Adjustments of supplemental calcium and calcitriol will be made (see [Appendix 2](#), rhPTH[1-84] and Supplement Titration Guideline) based on this value. If further adjustments are made to the rhPTH[1-84] dose or there are significant changes in calcium or calcitriol supplements, serum calcium will be retested at approximately 3 to 5 days following that change.

#### **6.4.3 Weeks 4, 8, 16, 24, 32, 40, and 48 (Visits 2 through 8) Study Clinic Visits**

The following procedures will be performed as indicated:

- Record any change in concomitant medications on the appropriate concomitant medication eCRF, including dose and frequency (all visits)
- Adverse event evaluation/update, including any incidences of hypocalcemia or hypercalcemia (all visits)
- Review the subject's diary for compliance with protocol procedures and dosing/supplement regimens (all visits)

- Collect used and unused drug cartridges and supplements (calcium and calcitriol) for assessment of accountability (all visits).
- Vital signs measurements (prior to blood draws) and weight (all visits)
- Serum 25(OH) vitamin D (all visits)
- Serum 1,25-dihydroxyvitamin D (Week 24)
- Serum calcium, phosphate, and albumin (all visits)
- Serum bone turnover markers (Weeks 8, 16, 24, and 40)
- Serum  $\beta$ -HCG pregnancy test (WOCBP only) (Weeks 16, 24, 32, 40, and 48)
- Urine pregnancy test (WOCBP only) (Weeks 4 and 8)
- Creatinine clearance (Weeks 16 and 32)
- 24-hour urine calcium, phosphate, sodium, and creatinine (Weeks 16 and 32)
- Blood sample for PTH and ECP antibodies (predose on Weeks 24 and 40)
- Blood samples for pharmacokinetic analysis will be drawn predose (0 hour) and postdose between 1 and 2 hours and between 6 and 10 hours following study drug administration (Week 48 only)
- Administration of study medication following the predose PTH blood samples for PK analysis (Week 48)
- If calcium-sparing diuretics are instituted (allowed at Week 16) and/or the dose subsequently changed, monitoring for serum potassium, sodium, and calcium will be done 1 week and again 1 month later and then at each subsequent scheduled clinic visit.
- Subjects will be provided with the following study supplies:
  - Study medication cartridges in sufficient number to supply daily doses until the next scheduled clinic visit
  - Ancillary injection supplies (ie, alcohol swabs, needles, etc.)
  - Calcium (carbonate or citrate) and calcitriol supplements in sufficient quantity to supply daily doses until the next scheduled clinic visit
  - Collection container for 24-hour urine (Dispense on Weeks 8, 24, and 48 for collections prior to Weeks 16, 32, and 52)

#### **6.4.4 Week 52 (Visit 9)**

Subjects will be instructed to come into the study center after having fasted for approximately 6 to 8 hours and prior to taking their study medication. Appointments should be scheduled accordingly to accommodate this fasting status (ie, in the morning). The following procedures will be performed:

- Record any change in concomitant medications on the appropriate concomitant medication eCRF, including dose and frequency.
- Adverse event evaluation/update, including any incidences of hypocalcemia or hypercalcemia
- Vital signs measurements (prior to blood draws) and weight

- Physical examination
- 12-lead electrocardiogram
- Blood samples for serum chemistries (including calcium, phosphate, albumin, and magnesium), hematology, serum 25(OH) vitamin D, serum 1,25-dihydroxyvitamin D, creatinine clearance, and bone turnover markers
- Blood sample for PTH and ECP antibodies (predose) (See Section 6.2 for additional follow-up for subjects who develop antibodies specific to PTH.)
- Urinalysis
- 24-hour urine calcium, phosphate, sodium, and creatinine
- A BMD test by DXA
- Serum  $\beta$ -HCG pregnancy test (WOCBP only)
- Review the subject's diary to assess compliance to protocol procedures and dosing/supplement regimens.
- Collect used and unused drug cartridges and supplements (calcium and calcitriol) for assessment of accountability.
- Subjects will be provided with the following study supplies:
  - Study medication cartridges in sufficient number to supply daily doses until the next scheduled clinic visit
  - Calcium (carbonate or citrate) supplements in sufficient quantity to supply daily doses until the next scheduled clinic visit
  - Ancillary injection supplies (ie, alcohol swabs, needles, etc.)
  - Paper diaries
  - Collection container for 24-hour urine

#### **6.4.5 Long-term Extension Visits**

Subjects who continue into the long-term extension will have the following evaluations performed every 2 months unless otherwise indicated:

- Record any change in concomitant medications on the appropriate concomitant medication eCRF, including dose and frequency.
- Adverse event evaluation/update, including any incidences of hypocalcemia or hypercalcemia
- Urine pregnancy test (WOCBP only)
- Brief physical examination (every 6 months)
- Vital signs measurements (prior to blood draws) and weight
- Blood samples for serum chemistries and hematology (every 12 months)
- Blood samples for creatinine clearance and bone turnover markers (every 4 months)
- Local total serum calcium (as needed)
- Blood sample for PTH and ECP antibodies (predose) (every 6 months)
- Serum calcium and phosphate

- Serum 25(OH) vitamin D
- Serum 1,25-dihydroxyvitamin D (every 6 months)
- 24-hour urine calcium, phosphate, sodium, and creatinine (every 4 months)
- A BMD test by DXA (every 12 months)
- If calcium-sparing diuretics are instituted and/or the dose subsequently changed, monitoring for serum potassium, sodium, and calcium will be done 1 week and again 1 month later and then at each subsequent scheduled clinic visit.
- Review the subject's diary to assess compliance to protocol procedures and dosing/supplement regimens. Subjects will complete the diary for the 2-week period prior to the scheduled study visit. If the subject does not record the diary information as indicated during this time period, he/she may record it during the 2 weeks following the visit. This information will then be reviewed with the subject by phone or at the next scheduled visit.
- Collect used and unused drug cartridges and pen injectors for assessment of accountability.
- Subjects will be provided with the following study supplies:
  - Study medication cartridges in sufficient number to supply daily doses until the next scheduled clinic visit
  - Ancillary injection supplies (ie, alcohol swabs, needles, etc.)
  - Calcium (carbonate or citrate) supplements in sufficient quantity to supply daily doses until the next scheduled clinic visit through approximately May 2014. Following this date, only calcium citrate will be provided.
  - Collection container for 24-hour urine

#### **6.4.6 End of Treatment Visit or Early Termination**

- Record any change in concomitant medications on the appropriate concomitant medication eCRF, including dose and frequency.
- Adverse event evaluation/update, including any incidences of hypocalcemia or hypercalcemia
- Full physical examination
- Vital signs measurements (prior to blood draws) and weight
- 12-lead ECG (may be local)
- A BMD test by DXA (if previous DXA was  $\geq 3$  months prior)
- Blood samples for serum chemistries (including calcium and phosphate), hematology, serum 25(OH) vitamin D, serum 1,25-dihydroxyvitamin D, creatinine clearance, and bone turnover markers
- Blood sample for PTH and ECP antibodies (See Section 6.2 for additional follow-up for subjects who develop antibodies specific to PTH.)
- Administration of the last dose of study medication following the predose PTH samples
- Urinalysis
- 24-hour urine calcium, phosphate, sodium, and creatinine
- Serum  $\beta$ -HCG pregnancy test (WOCBP only)

- Review the subject's diary
- Collect used and unused drug cartridges and pen injectors, for assessment of accountability, and subject diaries.
- Subjects will either be prescribed appropriate oral calcium and/or active vitamin D to compensate for the cessation of NPSP558 (rhPTH[1-84]) or may opt to continue treatment on commercial drug (Natpara). Subjects who continue treatment with Natpara will continue to be monitored under the care of a physician according to approved labeling instructions.

#### **6.4.7 Posttreatment Serum Calcium/Phosphate Follow Up**

After the End of Treatment visit or early termination visit, subjects who will not continue rhPTH[1-84] treatment will have their total serum calcium and phosphate levels measured 3 to 5 days after the last dose of study medication. Doses of calcium and active vitamin D supplements will be adjusted by the Investigator as appropriate. Thereafter, the Investigator will repeat serum calcium/phosphate monitoring and supplement dose adjustments as appropriate to achieve target serum calcium/phosphate concentrations until the follow up phone call 4 weeks  $\pm$  7 days after end of treatment visit. After the 4-weeks follow-up telephone call, further management of hypoparathyroidism will occur as part of the subject's long-term non-study medical care.

#### **6.4.8 Follow-up Telephone Contact**

Subjects will be contacted approximately 4 weeks following the last dose of study medication to monitor for and/or follow-up on any study drug-related AE or any SAE that may have occurred during the study period or any SAE that may have occurred since the last study drug injection.

#### **6.4.9 Follow-up assessment for PTH antibodies**

Any subject who tests positive for PTH-specific antibodies at the last 2 consecutive visits at which antibodies are measured and does NOT continue treatment on commercial Natpara, will have follow-up blood draws for PTH antibodies at Months 3 and 6 poststudy. If a subject's results are negative at Month 3, follow-up may be terminated.

### **7 DATA MANAGEMENT**

#### **7.1 Data Collection**

Data collected during the study will be recorded in the subject's eCRF by the study center's research team. The research team will keep records of the subject's visit in the files considered as source documents for that center, eg, hospital chart, research chart, etc. To ensure that data have been entered correctly on the eCRF, eCRFs will be 100% source-data verified by a monitor from the sponsor/designee, who will notify the investigator regarding questions or missing data. The investigator or designee will be responsible for the timely recording of subject data.

The investigator will review all eCRFs (including the termination page after the subject's final visit) for completeness and accuracy, and will electronically sign the eCRFs attesting to this prior to submitting them to the sponsor. The investigator will be responsible for submitting the data to

the sponsor (or designee) in a timely manner, on the eCRFs provided by the sponsor (or designee) for this purpose. Non-CRF data including, but not limited to central laboratory tests, ECG, and radiographic (DXA) results will be sent to the sponsor or designee via a data transfer from the appropriate vendor for assimilation into the database. SAE reporting must be done within the times described in Section 6.2.2.2.

All data collected in this study will be integrated into an appropriate preformatted database by the sponsor or designee for subsequent statistical evaluation. Data validation and edit checks will be conducted on the data. Any discrepancies will be noted and queries will be generated by the sponsor or designee to be resolved by the center. Queries should be completed by the investigational center and signed by the investigator or approved designee in a timely manner.

When all subjects' data have been entered into the database, verified, and all outstanding issues have been resolved with the center, the data will be evaluated for quality purposes. A clean file is defined as when the data in the database and the reference values are complete and logical according to the clinical study protocol, general guidelines, data management plan, and data entry instructions. Once the sponsor acknowledges that all data are acceptable, the data will be declared to represent a "clean file" and the database will be frozen.

A quality assurance audit will be performed on the data by the Data Management group. When all issues from the audit are resolved, and all data management processes are completed for finalizing the database, the database will be locked and ready for analysis.

The investigator and clinical center must permit study-related monitoring, audits, IRB/IEC/REB review, and regulatory inspections by providing direct access to source data/documents.

Subjects will retain the subject number utilized in the RELAY/REPLACE study. The first four digits consist of the center number and the last four digits are the sequential subject number. This number is the main identifier for subjects.

## **7.2 Record Retention**

The clinical investigators will maintain drug records, copies of eCRFs, laboratory records, data sheets, correspondence records, and signed subject consent documents for at least 5 years or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor. In accordance with US Federal Regulations, these records will be available for inspection and copying if requested by a properly authorized employee of the FDA.

## **8 STATISTICAL METHODOLOGY AND SAMPLE SIZE**

Detailed statistical analysis methods will be conducted as described in the SAP for this study. Deviations from the SAP (if any) will be described and justified in the clinical study report (CSR).

## 8.1 Demographic and Baseline Variables

Demographic variables (such as sex, age, race, birthdate, etc.) will be obtained from the REPLACE or RELAY study. Medical history from the RELAY study will be reviewed and updated as necessary. Visit 1 (baseline) for this study (PAR-C10-008, RACE) may be the same day as Visit 4 of the RELAY study. Demographic and/or other variables at baseline will be summarized for medical history, demography, physical examination, vital signs, prior medications, ECG, and laboratory test results.

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary with regard to drug class and drug name. The number and percentage of subjects with specific prior medications will be summarized. Medical history will be coded using the Medical Dictionary for Regulatory Activities. The number and percentage of subjects with specific histories will be summarized by system organ class and by high-level term and preferred term for each condition.

## 8.2 Safety Variables

Safety data including vital signs assessments, physical examinations, AEs, SAEs, pen-related events or complaints, concomitant medications, clinical laboratory tests, ECG monitoring, and termination from study will be summarized by treatment group and point of time of collection. Descriptive statistics (arithmetic mean, standard deviation, median, minimum and maximum) will be calculated for quantitative safety data as well as for the difference from baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data.

## 8.3 Efficacy Variables

### Efficacy Endpoints:

The proportion of subjects in whom the following three conditions are fulfilled at Week 52 (Visit 9) and at End of Treatment will be summarized:

- A  $\geq 50\%$  reduction from baseline in dose of oral calcium supplementation or an oral calcium dose of  $\leq 500$  mg

**AND**

- A  $\geq 50\%$  reduction from baseline in dose of oral calcitriol supplementation or an oral calcitriol dose of  $\leq 0.25$   $\mu\text{g}$

**AND**

- An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value and does not exceed the ULN of the central laboratory

In addition, the following efficacy variables will be summarized:



- Mean percentage changes from baseline in supplemental oral calcium and supplemental calcitriol dosages at each visit
- Proportion of subjects achieving the first three conditions of the efficacy endpoints defined above, at each visit
- Mean change from baseline in 24-hour urine calcium excretion
- Impact of calcium source (carbonate vs. citrate) on response
- Impact of calcium-sparing diuretics on serum and urinary calcium
- Proportion of subjects that maintain a calcium phosphate product  $\leq 55 \text{ mg}^2/\text{dL}^2$  ( $4.4 \text{ mmol}^2/\text{L}^2$ )
- Distribution of subjects by rhPTH[1-84] doses at the End of Treatment Visit
- Change from baseline in bone turnover markers (BSAP, s-CTx, P1NP, and osteocalcin), PTH antibodies, and BMD by DXA
- Additional subgroup analyses that are specified in the SAP

Note that the baseline parameters for the efficacy variables for the RACE study will be the end of study and baseline parameters from the RELAY or REPLACE studies. The visits will be defined in the SAP. No between-group comparisons with p-values are planned. No statistical testing will be conducted to compare between group differences.

#### 8.4 Other Variables

Other variables to be analyzed will include the following:

- Calcium and active Vitamin D intake (based on diary entries)
- Duration of study medication exposure
- Subject compliance
- The number and percentage of subjects who complete the study, are lost to follow-up, and who are discontinued from the study (including reason for study withdrawal) will be summarized.

Subjects will be considered compliant if study drug was taken according to protocol for  $\geq 80\%$  to  $\leq 120\%$  of doses. The number and percentage of subjects who were compliant will be summarized.

#### 8.5 Analysis Populations, Data Sets, and Time Points

##### 8.5.1 Analysis Populations

The primary and secondary efficacy analyses will be based on the intention-to-treat (ITT) population. This population includes all subjects who received at least one dose of study drug and had at least one efficacy measurement.

The safety analyses will be based on the Safety population. This population includes all subjects who received at least one dose of study drug with any follow-up information.

## **8.6 Statistical/Analytical Issues**

### **8.6.1 Adjustments for Covariates**

No preselected covariates are selected for adjustments.

### **8.6.2 Handling of Dropouts or Missing Data**

No safety data will be imputed. The missing patterns of the efficacy variables will be assessed and an unbiased imputations method will be documented in the SAP.

### **8.6.3 Interim Analyses and Data Monitoring**

An interim analysis was performed in 2013. Interim analyses may be performed as necessary to support regulatory interactions and/or publications.

### **8.6.4 Multiple Comparisons/Multiplicity**

No adjustment for multiplicity in treatment is planned.

### **8.6.5 Use of a Pharmacokinetic Subset of Subjects**

No pharmacokinetic subset of subjects was selected for analysis.

### **8.6.6 Examination of Subgroups**

Subgroup analyses (if any), in addition to the possible ones by gender, will be discussed in the SAP.

## **8.7 Determination of Sample Size**

Approximately 50 subjects are anticipated to be enrolled. Sample sizes were not estimated for this extension study.

## **8.8 Changes to Planned Statistical Analyses**

Changes made to planned statistical analyses (if any) described within this protocol will be incorporated into the SAP and any deviations from the SAP will be documented and justified in the final CSR.

# **9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS**

## **9.1 Declaration of Helsinki and Ethical Review**

This protocol will be conducted in accordance with the applicable ICH Guidelines, Good Clinical Practice, and the World Medical Association (WMA) Declaration of Helsinki and its amendments concerning medical research in humans (Declaration of Helsinki, 'Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects', Helsinki 1964, amended in Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West, Republic of South Africa 1996, and Edinburgh 2000 (5th revision), and Notes of Clarification added by the WMA General Assembly in Washington 2002 and in Tokyo 2004).

In accordance with guidelines, the protocol, any advertisements and ICFs will be reviewed and approved by the IRB/IEC. The sponsor will supply relevant material for the investigator to submit to the IRB/IEC for the protocol's review and approval. Verification of the IRB/IEC approval of the protocol and the written ICF will be forwarded to the sponsor (or designee).

The investigator will inform the IRB/IEC of subsequent protocol amendments and any SUSARs if the Shire SMT has assessed it as an unanticipated problem. Approval for protocol amendments will be transmitted in writing to the investigator.

The investigator will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed 1 year) and a study summary report following the completion, termination, or discontinuation of the investigator's participation in the study.

## **9.2 Subject Information and Consent**

In accordance with applicable guidelines, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject before any screening and protocol-specific procedures are performed. A consent form model will be provided by the sponsor or designee and adapted by the investigator to meet center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the subject the nature of the study, the action of the test product, and any risks and benefits. The subject will be informed that participation is voluntary and that he or she can withdraw from the study at any time without prejudice to their subsequent care. Information for a WOCBP (and a female of child-bearing potential who is the partner of a male subject) and lactating females should be provided in the ICF regarding unintended pregnancy and methods of contraception.

The subject will be given a copy of the fully executed consent form and the original will be maintained with the subject's records.

## **9.3 Subject Data Protection**

All data provided to the sponsor or designee will be identified only by subject number, date of birth, and initials, thereby ensuring that the subject's identity remains unknown. Subjects should be informed in writing, that their data will be stored and analyzed in a computer, with confidentiality maintained in accordance with national and local legislation. Center-specific information must be added to the ICF as appropriate.

Subjects also should be informed in writing that authorized representatives of the sponsor/designee and/or regulatory authorities may require access to those parts of the hospital/clinic records which are relevant to the study, including medical history, for data verification purposes.

The principal investigator is responsible for keeping a subject identification list of all subjects screened and enrolled which includes the following information: subject number, full name, and

a secondary unique identifier (ie, hospital/clinic number). A list of subjects who failed screening must also be maintained and be available for inspection.

#### **9.4 Financial Disclosure**

In 2001, the FDA issued a guidance document entitled “Financial Disclosure by Clinical Investigators” which provides guidance to industry on its final rule on financial disclosure that became effective 02 February 1999 and was published as Title 21 Code of Federal Regulations Part 54. This rule applies to all investigators participating in clinical studies to be submitted to the FDA in support of an application for market approval. The financial disclosure statement must be updated annually during the course of the study and for 1 year after the completion of the study.

According to the guidance, disclosable financial arrangements are defined as the following:

- Compensation made to the investigator in which the value of compensation could be affected by study outcome
- A proprietary interest in the tested product, including, but not limited to, a patent, trademark, copyright, or licensing agreement
- Any equity interest in the sponsor of a covered study (ie, any ownership interest, stock options, or other financial interest whose value cannot be readily determined through reference to public prices)
- An equity interest in a publicly held company that exceeds \$50,000 in value
- Significant payments of other sorts, which are payments that have a cumulative monetary value of \$25,000 or more made by the sponsor of a covered study to the investigator or the investigator’s institution to support activities of the investigator exclusive of the costs of conducting the clinical study or other clinical studies, (eg, a grant to fund ongoing research, compensation in the form of equipment or retainers for ongoing consultation, or honoraria) during the time the clinical investigator is carrying out the study and for 1 year after completion of the study

Clinical investigator means only a listed or identified investigator or subinvestigator who is directly involved in the treatment or evaluation of research subjects. The term also includes the spouse and each dependent child of the investigator. Participating investigators must provide this information and complete necessary documentation as requested by the sponsor.

The intent of this regulation is to ensure the proper identification and disclosure of financial interests of clinical investigators that could affect the reliability of data submitted to the FDA in support of a market application. Companies must meet these financial disclosure requirements, and failure to do so may result in the refusal by the FDA to accept an application for market approval of the study drug.

#### **9.5 Changes to the Protocol**

No change in the study procedures shall be effected without the mutual agreement of the sponsor and the investigator. All changes must be documented as signed protocol amendments, or as a

revised protocol. Changes to the protocol may require notification to or approval by the IRB/IEC/REB and the regulatory authorities before implementation. Local regulatory requirements must be followed. Instructions for reporting deviations from the protocol can be found in the Study Reference Manual.

The sponsor or designee is responsible for the distribution of protocol amendment(s) to the principal investigator(s) and those concerned within the conduct of the study. The principal investigator is responsible for the distribution of all amendments to the IRB/IEC/REB and all staff concerned at his/her center.

## **9.6 Investigator Obligations**

The principal investigator at each center must provide the following to the sponsor/designee prior to the start of the study:

- A completed and signed FDA Form 1572. If during the course of the study any changes are made that are not reflected on the original FDA Form 1572, a revised FDA Form 1572 form must be completed and returned to the sponsor for submission to the FDA.
- A current (within 2 years) signed and dated curriculum vitae for the principal investigator and all subinvestigators listed on FDA Form 1572, including a current office address
- Financial disclosure statement for the principal investigator, and subinvestigators (listed on the FDA Form 1572). An updated financial disclosure statement must be provided to the sponsor 1 year after completion of the study.
- A copy of the original approval for conducting the study from the IRB/IEC. Renewals must be submitted at yearly intervals if the study is ongoing or as required by the institution.
- A copy of the IRB/IEC-approved ICF
- IRB/IEC/REB membership list or Department of Health and Human Services General Assurance Number, which must be maintained current during the trial
- Laboratory certification and normal ranges, unless a central laboratory is being used exclusively

The "Protocol Signature Page" of this protocol must be signed and dated by the principal investigator for the center.

## **9.7 Confidentiality/Publication of the Study**

Any information shared by the sponsor regarding this study, including this protocol, is considered proprietary information and should be kept confidential.

The data generated by this clinical study are the property of the sponsor. These data may be used by the sponsor, now and in the future, for presentation or publication at the sponsor's discretion and/or for submission to regulatory agencies. In addition, the sponsor reserves the right to review data from this study relative to the potential release of proprietary information 30 days prior to submission to any publication or for any presentation.

## **9.8 Selection of a Primary Principal Investigator**

The sponsor will select one primary principal investigator as a representative of all investigators for this study. The selection will be based on a variety of factors, including rate of enrollment, overall enrollment totals, and subject retention. The principal investigator selected will be identified in the synopsis of the CSR as the principal investigator for the study. Roles, affiliations, and qualifications for the principal investigators will be included in the CSR appendices. Where the signature of the principal investigator is required by regulatory authorities, this will also be included in the CSR appendices.

## **9.9 Study Termination**

The sponsor reserves the right to discontinue the study for medical and/or administrative reasons at any time.

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**Appendix 1**

**INSTRUCTIONS FOR USE FOR THE PTH HASELMEIER PEN  
INJECTOR SYSTEM**



24 Oct 2016

HASELMEIER PEN INJECTOR SYSTEM: PATIENT INSTRUCTIONS FOR USE (IFU) V5.0

THE FOLLOWING 4 COMPONENTS WILL BE NEEDED TO PREPARE AND INJECT NPSF655

INSTRUCTIONS FOR USE

- You will need to give yourself an injection of **ch27H[1-84]** into alternating thighs every day as instructed by your doctor.
- Each Medication Cartridge provides 14 days of therapy and will come separately from the pen as a refill that should be stored in the refrigerator.
- After the Pen Injector contains the Medication Cartridge, it must be stored in the refrigerator between injections and the Medication Cartridge replaced every 14 days. It may be left a maximum of 30 minutes at room temperature per day. The Pen Injector should be kept for repeated usage. Do not store the Medication Cartridge in the freezer. If the cartridge is frozen, do not use.
- You must use a new Needle for each injection, safely disposing of the used Needle after use.
- The following guide contains important information and will provide step-by-step instructions on how to prepare and inject **ch27H[1-84]**. Please read this guide carefully and follow the steps in order. It is important that you always wash your hands with soap and water or sanitizer before and after you handle the Pen Injector and Medication Cartridge.



- It is normal for a few drops to remain on the tip of your needle after your injection is complete. If you see more than a few drops, you may not have received your full dose. Do not inject another dose. Talk with your healthcare provider about what to do about a partial dose.

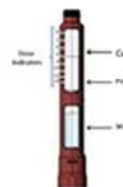
1. MIXING DEVICE

This device will help to mix **ch27H[1-84]** with water to form a solution.



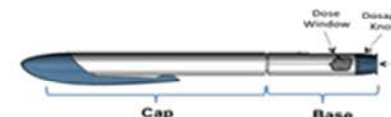
2. MEDICATION CARTRIDGE

Each Medication Cartridge has 14 doses of **ch27H[1-84]** and contains both a powder and water.



3. PEN INJECTOR

You will use this to inject the medicine.



4. NEEDLE

Use 31G 8mm Pen Needles. The Needle is covered with a Guard and is contained within the Needle Cap.



STEP 1A: PREPARE NEW OR REPLACE MEDICATION CARTRIDGE  
WASH HANDS AND GET READY  
COMPLETE CARTRIDGE USE CARD

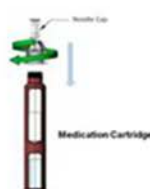


- Wash your hands with soap and water or sanitizer and dry.
- Take a Medication Cartridge from the refrigerator.
- Check that the strength (25, 50, 75, or 100 mcg) is correct.
- Mark today's date and the date 14 days later on the Cartridge Use Card.

Figure 1 Cartridge Use Card

Cartridge	Date the cartridge was first used	Date to change the cartridge (14 days after first use)
1		
2		

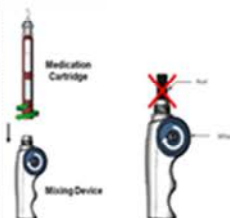
STEP 1B: ATTACH NEEDLE



- Remove the Paper Tab from the Needle and hold the Needle Cap by the side.
- Screw the needle tightly onto the Medication Cartridge, while keeping the needle cap straight.

Do not remove the Needle Cap or Guard until ready to inject.

STEP 2A: ATTACH TO MIXING DEVICE



- Turn the Wheel on the Mixing Device in the opposite direction of the arrow on the Wheel until you can no longer see the Rod.
- Screw the Medication Cartridge onto the Mixing Device.

STEP 2B: MIX PRODUCT TOGETHER



- Turn the blue Wheel in the direction of the arrow.
- As you turn the Wheel the first time, look at the Cartridge Window and continue turning the Wheel until two stoppers meet together.



- STOP turning the wheel at this point.
- There will be a little bit of space at the top of the Medication Cartridge.

STEP 2C: MIX THE MEDICATION TO FORM A SOLUTION

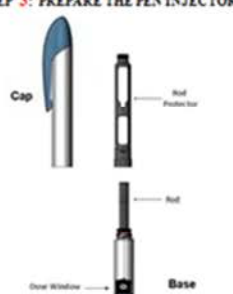

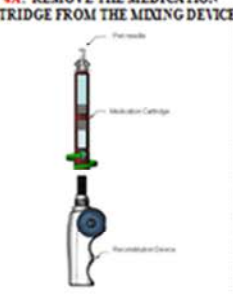
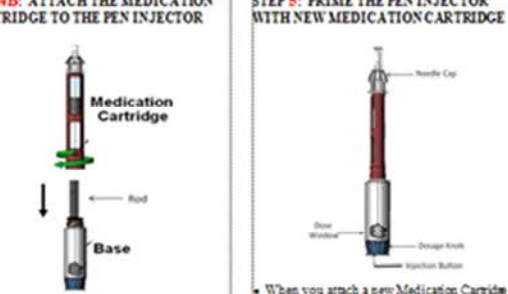
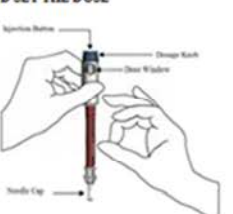
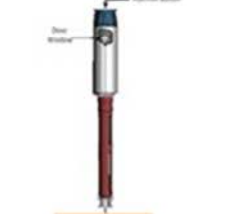
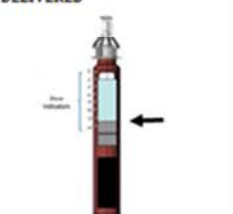







- Gently rock the device back and forth a few times. Do not shake.
- Let it sit for 1 full minute.
- After the full minute, check the window to ensure it is a clear solution and is not cloudy or colored and that it does not contain any particles. It is okay to see small bubbles.
- If it is cloudy, colored, or has particles in it, gently rock the device back and forth a few more times and allow it to sit for 4 additional minutes. Again, do not shake.
- If the medication is still not a clear solution without particles, discard the Medication Cartridge and begin at Step 1B with a new cartridge.

STEP 2D: FINAL MIXING STEP  
TURN THE BLUE WHEEL THE SECOND TIME TO REMOVE REMAINING AIR



- Keeping the device upright, turn the blue wheel the second time in the same direction as the arrow until the stoppers no longer move to remove any remaining air in the cartridge. The wheel will continue to turn freely.
- Put the Medication Cartridge aside while you prepare the Pen Injector.
- It is OK to lay the device on its side.

<p><b>STEP 3: PREPARE THE PEN INJECTOR</b></p>  <ul style="list-style-type: none"> <li>Remove the Cap from the Pen Injector by pulling. Save the Cap for later use.</li> <li>Unscrew the Rod Protector. Do not discard the Rod Protector because you may use it to protect the Rod when a Medication Cartridge is not installed.</li> <li>Ensure that the Dose Window reads "0" and the Rod is all the way down.</li> </ul>	<p><b>STEP 4A: REMOVE THE MEDICATION CARTRIDGE FROM THE MIXING DEVICE</b></p>  <ul style="list-style-type: none"> <li>If the Rod is extended, turn the red ring on the Base to the left to retract the piston rod until it is fully down and the Red Ring stops.</li> </ul>	<p><b>STEP 4B: ATTACH THE MEDICATION CARTRIDGE TO THE PEN INJECTOR</b></p>  <ul style="list-style-type: none"> <li>Screw the Medication Cartridge onto the Base.</li> <li>A small amount of liquid may leak out during this process, which is normal.</li> </ul>	<p><b>STEP 5: PRIME THE PEN INJECTOR WITH NEW MEDICATION CARTRIDGE</b></p>  <ul style="list-style-type: none"> <li>When you attach a <u>new</u> Medication Cartridge to the Pen Injector, you must prime the Pen Injector <u>prior to the first injection</u>.</li> <li>Turn the blue dosage knob to "GO".</li> <li>Hold the Pen Injector with the <b>NEEDLE CAP POINTING UP</b>.</li> <li>Press the <b>blue Injection Button</b> until it stops and the "0" mark becomes visible. During this process some liquid may leak out from the Needle. This is normal.</li> <li>You only need to do this step once for each new Medication Cartridge every 14 days.</li> </ul>	
<p><b>STEP 6A: PREPARE INJECTION SITE AND SET THE DOSE</b></p>  <ul style="list-style-type: none"> <li>If you have not done so already, <b>Wash your hands</b> with soap and water or sanitizer and dry.</li> <li><b>Clean the injection area of your thigh</b> with an alcohol swab or soap and water. Allow to completely dry.</li> <li>Hold the Pen Injector with the <b>NEEDLE CAP POINTING DOWN</b>. Tap gently to move any existing air bubbles away from the Needle.</li> <li>Hold the Pen Injector so that you can see the pen display "0".</li> <li><b>NOTE:</b> If the blue dosage knob is difficult to turn to "GO", check that the cartridge contains at least one dose. If so, Turn the blue dosage knob until the pen displays "GO", but <b>Do NOT Force</b> it.</li> <li>Pull off the Needle Cap and Guard and discard.</li> </ul>	<p><b>STEP 6B: INJECT THE MEDICATION</b></p>  <ul style="list-style-type: none"> <li>Hold the Pen Injector with the <b>NEEDLE POINTING DOWN</b> so you can see the pen displays "GO".</li> <li>Insert the Needle fully into the thigh skin.</li> <li>Press the <b>blue Injection Button</b> until it stops and the pen displays "0".</li> <li>Slowly count to 10 seconds. During this process, you may either hold the Injection Button down or release it, while keeping the needle in the skin.</li> <li>Remove the Needle from skin by pulling straight up. A few drops may remain on the tip of the needle after your injection is complete.</li> <li><b>Do not inject a second dose</b></li> </ul>	<p><b>STEP 6C: CONFIRM THE INJECTION WAS DELIVERED</b></p>  <ul style="list-style-type: none"> <li>Confirm that you have given an injection by checking to see that the Dose Indicator scale shows <b>one less dose</b> (this illustration indicates that there are 13 doses remaining).</li> <li>The pen injector dosage knob will <b>NOT</b> turn to "GO" when the cartridge is empty.</li> <li>The dose scale marks are evenly numbered 0, 2, 4, 6, 8, 10, 12, and 14. The odd doses, 1, 3, 5, 7, 9, 11, and 13 will be between the lines.</li> </ul>	<p><b>STEP 7A: DISCARD THE NEEDLE</b></p>  <ul style="list-style-type: none"> <li>Safely dispose of the needle in a sharps container designed for pen needles following the Instruction For User on the sharps container.</li> <li>While holding the medication cartridge (still attached to the pen injector), insert pen tip and needle into the opening designed for pen needles.</li> <li>Rotate the pen counterclockwise to twist off the needle. The needle will fall into the container. It may be helpful to push the side of the pen against the cap of the sharps container to increase the friction between the needle collar and the opening designed for pen needles.</li> </ul>	<p><b>STEP 7B: STORE THE PEN INJECTOR</b></p>  <ul style="list-style-type: none"> <li>If there are doses left, put the Cap back on the Pen Injector. This may require a slight turn until a click can be heard when the Cap is snapped into place. Place the Pen Injector in a refrigerator until the next injection.</li> <li><b>The mixed medication must be stored in the refrigerator. Do not freeze it. After 14 days, a new Medication Cartridge must be prepared and the old Medication Cartridge discarded.</b></li> <li>If you are storing the pen injector without a medication cartridge, screw the rod protector (See step 3) into the pen injector base prior to putting the pen cap back onto the pen injector.</li> <li><b>Wash your hands</b> with soap and water or sanitizer to remove any spilled medication.</li> </ul>
<p><b>STEP 8: GIVING A DAILY INJECTION</b></p>  <ul style="list-style-type: none"> <li>Wash your hands with soap and water or sanitizer and dry.</li> <li>Check that the cartridge contains at least one dose (Pictured in step 6C).</li> <li>Repeat steps 1B, 6A, 6B, 6C, 7A, and 7B.</li> </ul>		<p><b>STEP 9: REPLACING THE MEDICATION CARTRIDGE</b></p>  <ul style="list-style-type: none"> <li>Once 14 doses have been delivered, the upper edge of stopper in the chamber will have reached the "0" mark and you will not be able to move the blue dosage knob to "GO" with ease. <b>Do NOT</b> force the blue dosage knob to "GO". A small visible amount of liquid may still remain in the cartridge.</li> <li>Unscrew the empty Medication Cartridge and discard it.</li> <li>Repeat Steps 1 to 5</li> </ul>		<p><b>STEP 10: STORING THE PEN INJECTOR FOR LATER USE</b></p>  <ul style="list-style-type: none"> <li>If you are not replacing a new Medication Cartridge right away, screw the Rod Protector (Pictured in Step 3) into the Base to protect the Rod while storing the Pen Injector.</li> </ul>

## Appendix 2                      RHPATH[1-84] AND SUPPLEMENT TITRATION GUIDELINE

In this study the goal is to continue rhPTH[1-84] dosing and to reduce calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible, while maintaining total serum calcium levels. In patients with hypoparathyroidism treated with oral calcium and calcitriol, it is suggested to maintain total serum calcium levels in the lower half of the normal range (eg, between 8.0 and 9.0 mg/dL; [Shoback 2008](#)). This is to reduce symptoms and to avoid the hypercalciuria which can occur in the hypoparathyroid patient on calcitriol and oral calcium supplementation ([Horwitz and Stewart 2008](#)). In the current trial, all subjects will receive rhPTH[1-84]. Hence, down-titration of calcitriol and oral calcium must be undertaken, where appropriate, to avoid hypercalcemia. At all times, changes in calcitriol and oral calcium dosing should be undertaken at the discretion of the investigator, based on total serum calcium concentrations and the subject's clinical condition.

To help facilitate a more standardized approach to dose adjustment across study centers, the following guideline has been prepared. The guideline is non-mandatory but the approach suggested should be assessed when adjustments in calcitriol and oral calcium are being considered. In the guideline, all references to total serum calcium levels indicate "predose" (trough) values drawn prior to administration of study drug, rhPTH[1-84] (ie, approximately 23 to 24 hours after the previous injection).

The order and magnitude of subsequent reductions in either calcitriol or oral calcium supplementation is left to the investigator's discretion, based on individual subject response. After any change in the rhPTH[1-84] dose, or a significant change in calcitriol or oral calcium supplement dose, a total serum calcium level **MUST** be measured 3 to 5 days later for safety purposes (unless earlier or more frequent testing is clinically required) and to guide further changes in supplement doses.

At the end of the study (this includes any subject that terminates early) subjects must be assessed clinically at their study center to ensure that they return safely to an appropriate calcium and calcitriol supplementation level. This includes the performance of necessary testing for total serum calcium 3 to 5 days later for safety purposes (unless earlier or more frequent testing is clinically required) to ensure a stable total serum calcium level has been achieved. The completion of these procedures should be documented by the site.

### Significant Hypercalcemia

Any instances of significant hypercalcemia, which is defined as any total serum calcium level of > 11.9 mg/dL (even on a non-trough measurement), require **MANDATORY** immediate stopping of rhPTH[1-84] treatment. Suspension of dosing with calcitriol and oral calcium as clinically appropriate and testing of serum total calcium levels at least daily should be undertaken until the subject's serum total calcium returns to the normal range. Other clinically appropriate actions for the treatment of significant hypercalcemia should be undertaken as usual by the investigator to ensure subject safety. Thereafter, rhPTH[1-84] can be reintroduced with clinically appropriate doses of calcitriol and oral calcium, with the aim to avoid further episodes of abnormal serum calcium.

## Hypocalcemia

If the total serum calcium level falls below 8.0 mg/dL (or below the baseline values, if the subject entered the study with a total serum calcium < 8.0 mg/dL), then the subject's calcitriol and oral calcium doses should be checked and the injection technique of rhPTH[1-84] reviewed with the subject to ensure proper administration. At planned study visits (Week 4, 8 etc) the rhPTH[1-84] dose can be uptitrated if indicated in the opinion of the investigator following discussion with the sponsor. During interim safety checks, hypocalcemia should be addressed by clinically indicated increases in calcitriol or supplemental oral calcium doses according to the guideline below, with the goal of attaining a total serum calcium level of 8.0 to 9.0 mg/dL. Laboratory testing should be repeated as indicated in order to ensure that changes in dosing are accompanied by improved serum calcium levels.



Visit number	Serum calcium (mg/dL)	rhPTH[1-84] dose	Supplement dose adjustment
Visit 1 (Baseline)	> 9.5 mg/dL and < 500 mg supplemental oral calcium and no calcitriol	Start at 25 µg	Receive no supplemental calcitriol and oral calcium
	> 9.5 mg/dL on any dose of supplemental calcitriol or ≥ 500 mg oral calcium	Start at 50 µg	Stop supplemental calcitriol and oral calcium
	≤ 9.5 mg/dL on any dose of supplemental calcitriol or oral calcium	Start at 50 µg	Maintain supplemental calcitriol and oral calcium
<b>Interim Safety Check:</b> <b>* 3-5 days post Visit 1</b>  <b>AND</b>  <b>* after significant</b> <b>change in supplements</b>  <b>*or after any</b> <b>adjustment in</b> <b>rhPTH[1-84] dose</b> <b>*or if clinically</b> <b>indicated</b>	< 8.0 mg/dL	Maintain	Increase calcitriol dose or oral calcium dose as required*
	8.0 - 9.0 mg/dL	Maintain	No change in calcitriol dose; no change in oral calcium dose
	9.1 - 10.5 mg/dL	Maintain	Reduce calcitriol dose by up to 50%; if no longer receiving calcitriol then reduce oral calcium dose by up to 50% *
	10.6 - 11.9 mg/dL	Maintain	Reduce by up to 50% or eliminate calcitriol dose and/or oral calcium dose *
	> 11.9 mg/dL	<b>Stop</b> Study Drug until serum calcium is in the normal range on at least daily retesting	<b>STOP</b> calcitriol <b>AND</b> oral calcium dosing until serum calcium is in the normal range on at least daily retesting

At baseline, the starting dose should be 25 or 50 µg/d, as no experience is available with a higher starting dose. A stepwise dose increase of rhPTH[1-84] is advised if needed after an observation of the initial response to 25 or 50 µg/d.

Visit number	Serum calcium (mg/dL)	rhPTH[1-84] dose	Supplement dose adjustment
Weeks 4 to End of Study	< 8.0 mg/dL	Uptitrate	Reduce calcitriol dose by up to 50% (if not receiving calcitriol, reduce oral calcium dose by up to 50% as required) *
	8.0 - 9.0 mg/dL	Maintain	No change in calcitriol dose; no change in oral calcium dose
	9.1 - 10.5 mg/dL	Maintain	Once both calcitriol and calcium doses have been reduced by $\geq 50\%$ from Baseline, further reduction or elimination of calcitriol and reduction of oral calcium to 500mg/day can be made at the investigator's discretion based on serum calcium levels*
	10.6 - 11.9 mg/dL	Maintain	
	> 11.9 mg/dL	Stop rhPTH[1-84] until serum calcium is in the normal range on at least daily retesting	STOP calcitriol AND oral calcium dosing until serum calcium is in the normal range on at least daily retesting

\* Any changes in the rhPTH[1-84] dose or calcitriol and/or oral calcium supplement dose must be followed by a safety laboratory check for total serum calcium 3 to 5 days afterwards (or earlier if deemed clinically necessary). The safety laboratory checks can be performed using a local laboratory.

### **Appendix 3                    METHOD OF BIRTH CONTROL**

Women of childbearing potential must consent to use 2 acceptable methods of birth control from the list below:

- Hormonal methods of contraception such as oral, injected, vaginal rings, transdermal patch, implanted.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: Condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
- Male partner sterilization (vasectomy).

Male subjects with female partners of childbearing potential together also must use 2 acceptable forms of contraception during the subject's participation.

## Appendix 4                      PROTOCOL HISTORY

NPS Pharmaceuticals, the original sponsor of this study, was acquired by Shire Pharmaceuticals on 21 February 2015.

Document	Date	Global/Country/Site Specific
Original Protocol Version 1.0	30 December 2010	Global
Amendment 1 Version 2.0	29 June 2011	
Amendment 2 Version 3.0	05 October 2011	
Amendment 3 Version 4.0:	15 March 2012	
Site Amendment 4 Version 5.0	30 May 2013	Site-Specific
Amendment 5	3 May 2016	Global
Amendment 6	24 October 2016	Global