

## **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 2

Protocol Version Date: 05 Oct 2011

**NPSP558**

**A 12-Month Open-label Study Investigating the Safety  
and Tolerability of NPSP558, a Recombinant Human  
Parathyroid Hormone (rhPTH [1-84]), for the  
Treatment of Adults with Hypoparathyroidism –  
A Clinical Extension Study (RACE)**

**Clinical Protocol PAR-C10-008**

US IND Number: 76,514

**NPS Pharmaceuticals, Inc.  
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**ISSUED:**

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CONFIDENTIAL

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## SUMMARY

**Title:** A 12-Month Open-label Study Investigating the Safety and Tolerability of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH [1-84]), for the Treatment of Adults with Hypoparathyroidism – A Clinical Extension Study (RACE)

**Protocol No:** PAR-C10-008 Amendment 2

**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 as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.

#### Secondary Objectives:

- To evaluate the impact of different preparations of calcium and calcitriol on the response to NPSP558 replacement therapy
- To demonstrate that dosing with NPSP558 across a dose range of 25 to 100 µg SC can be implemented in a safe and effective manner and can be maintained throughout 12 months (52 weeks) of treatment
- To evaluate the impact of calcium-sparing diuretics on serum and urinary calcium

### Study Rationale

This study is designed to evaluate 12-month treatment with NPSP558.

### Study Design

This study is a 12-month, open-label study using NPSP558 for the treatment of adults with hypoparathyroidism. Subjects can enroll if they either previously completed the NPSP558 RELAY study (8 weeks of active therapy) and/or completed the REPLACE study (Visit 18).

The goal of this study is to optimize NPSP558 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 NPSP558 and to the calcium/calcitriol supplements and safety monitoring of calcium levels are explained in [Appendix 2](#), NPSP558 and Supplement Titration Guideline.

- The starting dose of NPSP558 for this study will be 25 or 50 µg SC once daily

- Subjects may have their NPSP558 dose adjusted by the investigator at any time through Week 48 of 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 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 NPSP558, 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 will be conducted at Weeks 1 (baseline), 4, 8, and then every 8 weeks thereafter up to Week 48 (Visit 8). The End of Treatment Visit (Week 52, Visit 9) is scheduled 4 weeks later followed by a safety visit at Week 53 (Visit 10) and a follow-up telephone contact at Week 56 (Visit 11). See 6.2 for additional follow-up for subjects who develop antibodies specific to PTH.
- At the Week 16 (Visit 4), subjects who are on a stable dose of NPSP558 and have a 24-hour urine calcium > 300 mg may be treated for hypercalciuria with calcium-sparing diuretics.
- During Week 53, subjects will have their total serum calcium levels 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 Week 53 (Visit 10) in order to have serum calcium, phosphorus, and albumin checked.

**Number of Subjects Planned:** Approximately 40 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 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 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

### **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 total duration of treatment will be 12 months (52 weeks). Subjects will have a follow-up visit at Week 53 and will also be contacted by telephone at Week 56. See [6.2](#) 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 NPSP558 25 or 50  $\mu$ g SC QD in an open-label fashion as described in Section [3.1](#). Subjects may have their NPSP558 dose adjusted upwards in increments of 25  $\mu$ g to a maximum of 100  $\mu$ g SC QD. NPSP558 is to be administered into alternating thighs each morning via a multidose pen injector device.

**Supplements:**

Calcium citrate, calcium carbonate, and calcitriol will be supplied by the sponsor.

**Criteria for Evaluation:**

**Safety:**

Safety variables will be assessed by the following evaluations:

- Adverse events and serious adverse events
- Incidence of adverse events 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-hydroxyvitamin D levels
  - Creatinine clearance
  - Serum bone turnover markers
  - Urinalysis
  - 24-hour urine calcium, phosphate, sodium, and creatinine excretion
  - PTH 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 (calcium-phosphate ratio)

- 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, if available. 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 condition.

### **Efficacy Variables Summary**

#### **Primary Efficacy Endpoint:**

The proportion of subjects in whom the following three conditions are fulfilled at Week 52 (Visit 9) 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  $\leq 0.25$   $\mu$ g

**AND**

- An albumin-corrected total serum calcium concentration that is normalized or maintained compared to the baseline value ( $\geq 7.5$  mg/dL) and does not exceed the ULN for the central laboratory

#### **Secondary Efficacy Endpoints:**

- Mean percentage changes from baseline in supplemental oral calcium and supplemental calcitriol dosages at each visit



- Proportion of subjects achieving the primary endpoint 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>
- Distribution of subjects by NPSP558 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 adverse events 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.

## SIGNATURE PAGE

### Protocol PAR-C10-008 Amendment 2

#### Reviewed and Approved:

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## PRINCIPAL INVESTIGATOR PROTOCOL AGREEMENT PAGE

### Protocol PAR-C10-008 Amendment 2

I agree:

To assume responsibility for the proper conduct of this clinical study at this center and to conduct the study in compliance with this protocol, any future amendments, and with any other study conduct procedures provided by the sponsor,

That I am aware of, and will comply with, the internationally recognized code of Good Clinical Practice and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol and any amendments thereof, written informed consent or updates thereof, subject recruitment procedures (eg, advertisements), and any other written information to be provided to the subjects, before initiating this clinical study,

Not to implement any changes to, or deviations from the protocol without prior agreement from the sponsor and review and documented approval from the IRB/IEC, except to eliminate an immediate hazard to the study subjects, or when change(s) involves only logistical or administrative aspects of the clinical study,

To permit direct monitoring and auditing by the sponsor or sponsor's representatives and inspection by the appropriate regulatory authority(ies),

That I am thoroughly familiar with the appropriate use of the investigational product(s), as described in this protocol, and any other information provided by the sponsor or designee, including, but not limited to, the current Investigator's Brochure or equivalent document and approved product label (if applicable),

To provide sufficient time and an adequate number of qualified staff and facilities for the foreseen duration of the clinical study in order to conduct the study properly, ethically, and safely,

To ensure that all persons assisting in this study are adequately informed about the protocol, investigational product(s), and their clinical study-related duties and functions,

To 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.

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Principal Investigator (Print Name)

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Principal Investigator (Signature)

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Date (DD MMM YYYY)

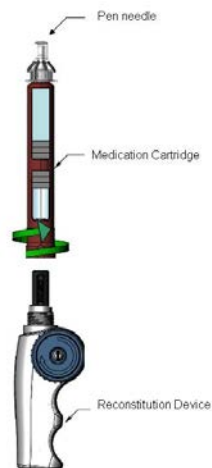
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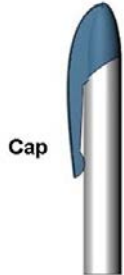
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## LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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
ECG	Electrocardiogram
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	Information for Use
IRB	Institutional Review Board
ITT	Intention to treat
IV	Intravenous
mm Hg	Millimeters of mercury
NPS	NPS Pharmaceuticals
NPSP558	Recombinant human parathyroid hormone (1-84)
PINP	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
RELAY	NPSP558 Study PAR-C10-007
REPLACE	NPSP558 Study C1-11-040
rhPTH	Recombinant human parathyroid hormone
SAE	Serious adverse event
SAP	Statistical analysis plan

## **LIST OF ABBREVIATIONS AND DEFINITION OF TERMS**

SC	Subcutaneous
s-CTx	Serum carboxy-terminal telopeptide of type I collagen
SMT	Safety Management Team
SOC	System organ class
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 as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.

### 1.1 Background

#### Compound

NPSP558 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). hPTH 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* 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  $35 \text{ mg}^2/\text{dL}^2$ . 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  $50 \text{ mg}^2/\text{dL}^2$  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  $1,25(\text{OH})_2$  vitamin D from its precursor 25-hydroxyvitamin D ( $25[\text{OH}]$  vitamin D). Although  $1,25(\text{OH})_2$  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  $1,25(\text{OH})_2$  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**

Hypoparathyroidism is one of the few hormonal deficiency syndromes in which replacement therapy using the native hormone is not clinically available. Treatment of hypoparathyroidism is also 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 alphacalcidol and compared them with matched normal controls (Langdahl et al, 1996). With vitamin D alone, trabecular bone volume and thickness, marrow space star volume, and trabecular star 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 et al, 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 NPSP558 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 et al, 2008). In that study, patients with hypoparathyroidism were



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.

An investigator-initiated open-label study evaluating the utility of PTH(1-84) 100 µg QOD for 24 months as hormone-replacement therapy in 30 patients with hypoparathyroidism is also ongoing ([Rubin et al, 2010](#)). 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, 2008c, 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 patients with hypoparathyroidism is currently ongoing (CL1-11-040, REPLACE). This study is investigating 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 phase 1 pharmacokinetic/pharmacodynamic study is also being conducted to assess these aspects of NPSP558 administered as single SC doses of 50 and 100 µg in patients with hypoparathyroidism.

## 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 NPSP558 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.

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

#### **Dose**

In a phase 2 study of NPSP558 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 ongoing REPLACE study is evaluating these same doses in hypoparathyroid patients. An 8-week study of fixed doses of 25 and 50 µg (RELAY) is currently being undertaken to explore a broader range of treatment dose options. The purpose of this study is to assess the 12-month safety and tolerability of varying doses of NPSP558 in reducing requirements for supplemental oral calcium and calcitriol, while 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. NPSP558 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 NPSP558 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 and calcitriol on the response to NPSP558 replacement therapy
- To demonstrate that dosing with NPSP558 across a dose range of 25 to 100 µg SC can be implemented in a safe and effective manner and can be maintained throughout 12 months (52 weeks) of 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 adverse events 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, phosphorus, and albumin)
  - Serum 25-hydroxyvitamin D levels
  - Creatinine clearance
  - Serum bone turnover markers
  - Urinalysis
  - 24-hour urine calcium, phosphate, sodium, and creatinine excretion
  - PTH 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

### **2.3.2 Efficacy Endpoints**

#### **2.3.2.1 Primary Efficacy Endpoint**

The proportion of subjects in whom the following three conditions are fulfilled at Week 52 (Visit 9) 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 ( $\geq 7.5$  mg/dL) and does not exceed the ULN for the central laboratory

**2.3.2.2 Secondary Efficacy Endpoints**

- Mean percentage changes from baseline in supplemental oral calcium and supplemental calcitriol dosages at each visit.
- Proportion of subjects achieving the primary endpoint 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  $\text{mg}^2/\text{dL}^2$
- Distribution of subjects by NPSP558 doses at the End of Treatment Visit
- Change from baseline in bone turnover markers (bone-specific alkaline phosphatase [BSAP], serum carboxy-terminal telopeptide of type I collagen [P1NP], serum procollagen type 1 amino-terminal propeptide [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 12-month, open-label study using NPSP558 for the treatment of adult male and female subjects with hypoparathyroidism. Either subjects must have previously completed the NPSP558 RELAY study (8 weeks of active therapy) and/or previously completed the NPSP558 REPLACE study (Visit 18).

The goal of this study is to optimize NPSP558 dosing while reducing calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible while maintaining total serum calcium levels (see [Appendix 2](#), NPSP558 and Supplement Titration Guideline).

- The starting dose of NPSP558 for this study will be 25 or 50  $\mu\text{g}$  SC once daily.
- Subjects with a total serum calcium value of  $\leq 9.5$  mg/dL will have a starting dose of 50  $\mu\text{g}$ .

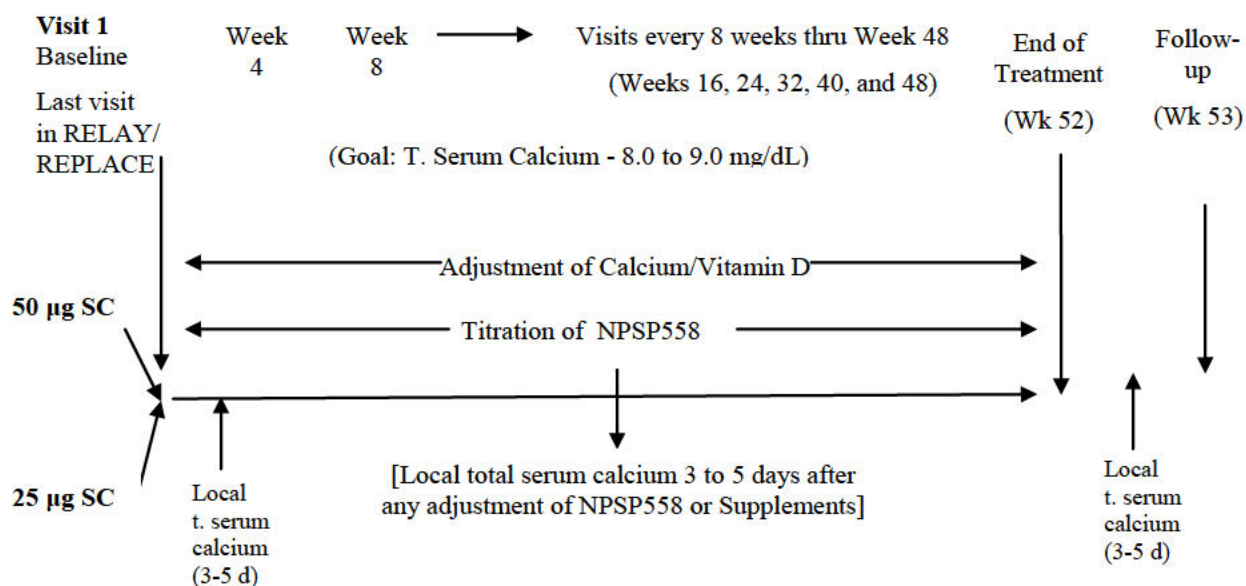
- Subjects with a total serum calcium value of  $> 9.5$  mg/dL will have a starting dose as follows:
  - Subjects who are taking supplements ( $\geq 500$  mg calcium and/or any calcitriol) will have the supplements reduced or stopped and will start at a dose of 50  $\mu$ g SC QD.
  - Subjects who are taking minimal or no supplemental calcium ( $< 500$  mg) and no calcitriol will have a starting dose of 25  $\mu$ g SC QD.
- Study visits will be conducted at Weeks 1 (baseline), 4, 8, and then every 8 weeks thereafter up to Week 48 (Visit 8). The End of Treatment Visit (Week 52, Visit 9) is scheduled 4 weeks later followed by a safety visit at Week 53 (Visit 10) and a follow-up telephone contact at Week 56 (Visit 11). See 6.2 for additional follow-up for subjects who develop antibodies specific to PTH.
- 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 NPSP558 dose increased by the investigator at any time through Week 48 of 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 NPSP558 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 NPSP558, after any significant change in doses of calcium and/or and calcitriol supplements, or at any other time at the discretion of the investigator.
- 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 NPSP558.
- If ANY predose total serum calcium is  $> 11.9$  mg/dL study drug will be stopped. Once total serum calcium returns to the normal range, NPSP558 can be reintroduced. The NPSP558 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  $\leq 500$  mg daily and calcitriol has been eliminated, then NPSP558 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 NPSP558 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 NPS medical monitor.
- At the Week 16 (Visit 4), subjects who are on a stable dose of NPSP558 and have a 24-hour urine calcium > 300 mg 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 visit.
- Monitoring of urine calcium will be performed at Weeks 16, 32, and 52 (Visits 4, 6, and 9) 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 Week 53, subjects will have their total serum calcium levels 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 Week 53 (Visit 10) in order to have serum calcium, phosphorus, and albumin checked.
- At Week 56 (Visit 11), approximately 4 weeks (30 days) following the End of Treatment visit (Week 52), subjects will be contacted by telephone in order to assess adverse events (AEs)/serious AEs (SAEs).

A schematic representation of the study design is displayed in Figure 3-1.

**Figure 3-1 Study Design**



### 3.2 Study Duration

The total duration of treatment will be 12 months (52 weeks). Subjects will have a follow-up visit at Week 53 and will be contacted by telephone at Week 56 approximately 30 days after the final dose of study drug, in order to follow up on any SAE or study drug-related AE. See 6.2 for additional follow-up for subjects who develop antibodies specific to PTH.

## 4 SUBJECT SELECTION AND PARTICIPATION

### 4.1 Number of Subjects

Approximately 40 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 that 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 (IRB/IEC), Health Authority and/or NPS, 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

In all cases, the reason for withdrawal must be recorded in the electronic case report form (eCRF) and 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 NPSP558 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)**

NPSP558 is manufactured using a strain of *E. coli* modified by DNA technology and is identical to native human PTH. NPSP558 is a single-chain polypeptide containing 84 amino acid residues. The drug substance is clear and colorless to light straw-colored.

NPSP558 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 currently is 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.

The preliminary results of a recent study (PAR-C10-005) comparing the Haselmeier pen to the Ypsomed pen, shows that the two pens are bioequivalent. The Haselmeier pen will now replace the Ypsomed pen in this study.

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 52 weeks. 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.

#### **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 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 have a maximum shelf-life of 36 months and 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. Additional data on the reconstituted solution demonstrates that it is stable for up to 7 days when stored at 25°C, which provides assurance of product quality during any unexpected excursions. 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 NPSP558. Subjects should be reminded to return all cartridges, even if empty, at the final 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, or destroyed, 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 or disposed of 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 NPSP558 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 NPSP558 SC injections will be self-administered into alternating thighs each morning using a multidose pen injection device (see [Appendix 1](#), Instructions for Use).

#### **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 NPSP558.

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](#)). The phase 3, randomized, double-blind placebo-controlled REPLACE study in subjects with hypoparathyroidism is ongoing. This registrational study is exploring the biologic activity of NPSP558 at doses of 50, 75, or 100 µg administered as SC injections to the thigh. An ongoing pharmacokinetic study (C09-002) utilizes two single doses of 50 and 100 µg each, also as SC injections to the thigh. The phase 3 fixed-dose study (RELAY) utilized dose of 25 and 50 µg SC daily. 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 NPSP558 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 NPSP558 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 the end of the study 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

In addition, concomitant active vitamin D supplements from outside sources are prohibited. 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 on the appropriate eCRF. Any medication which contains either calcium or vitamin D must be recorded on the eCRF 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 entered on the appropriate eCRF.

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

##### **Calcitriol**

Subjects enrolled in this study will be taking calcitriol to control serum calcium levels. Oral calcitriol supplements will be provided for this study by the sponsor or designee; no other sources of calcitriol should be used during the study. Prescribed doses of calcitriol will be entered on the appropriate eCRF.

##### **Calcium**

Oral calcium supplements (either calcium carbonate or calcium citrate) will be provided for 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 entered on the appropriate eCRF.

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 Week 52 (End of Treatment). 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 on the concomitant medication eCRF.

### **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 on the concomitant medication eCRF.

## **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 (calcium-phosphate ratio)
- 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 adverse events 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, phosphorus, and albumin)
  - Serum 25-hydroxyvitamin D levels
  - Creatinine clearance
  - Serum bone turnover markers
  - Urinalysis
  - 24-hour urine calcium, phosphate, sodium, and creatinine excretion
  - PTH antibodies (If any subject tests positive for PTH-specific antibodies at the final visit, they will have follow-up blood draws for PTH antibodies at Months 2, 3, and 6 poststudy. If a subject's results are negative at 2 successive visits within this timeframe, follow-up may be terminated. If at the end of 6 months the subject is still determined to have PTH-specific antibodies, the PI and the sponsor will determine if additional follow-up may be required. During this time, subjects also will be evaluated for AEs or SAEs related to immunogenicity, which will be collected in the Pharmacovigilance database.)
- Bone mineral density by DXA
  - Electrocardiogram parameters
  - Physical examinations (including vital signs)
  - Reason for termination from the study

### **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

### **Overdose**

Defined as an accidental or intentional administration of an excessive dose of a product, an overdose should be reported to the sponsor using the SAE form. This information will be shared with the Safety Management Team (SMT) and medical monitor.

#### **6.2.1.2 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 completion of the study. AE/SAEs will be monitored by the site with a telephone call at Week 56, approximately 30 days following the last dose of study drug.

At each visit, new AEs will be recorded sequentially on the AE page of the eCRF. 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**

A serious event must be reported as described in [Section 6.2.2.2](#). An SAE requires expeditious handling to comply with regulatory requirements.

### **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 enter the SAE information into InForm and fax supplemental data (e.g., medical records or lab values, if applicable) to 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 sponsor or designee will provide a FAX cover sheet for the investigators in the Study Reference Manual.

Autopsy reports, if applicable, will be forwarded as they become available. All pertinent laboratory results should be entered on the sponsor's SAE form.

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 6.2.1.2](#)). 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 NPS 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).

NPS Pharmaceuticals (sponsor) 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 the sponsor 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 with subjects in a fasted state (6 to 8 hours) at baseline and Week 52 (End of Treatment), unless otherwise noted. 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 will be analyzed by a central laboratory, with the exception of all urine pregnancy tests and total serum calcium levels obtained at baseline, Week 53, 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 outlined in [Table 6-1](#):

- Hematology: hemoglobin concentration, hematocrit, erythrocyte count, platelet count, and leukocyte counts with differential
- Serum Chem-20 panel: alanine transaminase, aspartate transaminase, alkaline phosphatase, lactate dehydrogenase, inorganic phosphorus, 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
- Urinalysis: specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, and microscopic analysis of sediment
- Creatinine clearance
- Total serum calcium (local)
- Total serum calcium, albumin, and phosphorus
- Serum 25-hydroxyvitamin D levels
- 24-hour urine calcium, phosphate, sodium, and creatinine
- Serum bone turnover markers (BSAP, s-CTx, P1NP, and osteocalcin)
- Serum beta human chorionic gonadotropin ( $\beta$ -HCG) pregnancy test (women of child-bearing potential [WOCBP] only)
- An FSH test to confirm postmenopausal status, if necessary.
- Urine pregnancy test (WOCBP only)
- PTH antibodies

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 at baseline and each clinic study visit through Week 52 and will include systolic and diastolic blood pressure (mm Hg), pulse (beats per minute or bpm), and body temperature (°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 and Week 52, at the study center on the same model unit. 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 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 and the eCRF. Two copies of the ECG tracings should be retained in the subject source record.

#### **6.2.6 Physical Examinations**

Physical examinations will be performed at baseline and Week 52 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.

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 and Week 52 and 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, and 52. Pregnancy occurring during the trial will necessitate immediately 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 an SAE supplemental form will be completed to capture potential drug exposure during pregnancy and will be 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, an additional SAE form will be completed and submitted to the sponsor or designee within 24 hours as discussed above.

An SAE supplemental 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](#). Details of the exact date and time of medical assessments (day/month/year) will be documented in the eCRF. Any deviations from protocol requirements will be documented in the eCRF.

**Table 6-1 Schedule of Evaluations and Procedures**

Visit Number	1*	Int.	2	3	4	5	6	7	8	9	Int.	10	11
Study Procedures / Proposed Study Week <sup>a</sup>	BL <sup>b</sup>	1 <sup>c</sup>	4	8	16	24	32	40	48	52 (EoT)	53 <sup>c, d</sup>	53 <sup>d</sup> (F/up)	56 (F/up) Phone
Visit Windows	± 3 days	± 2 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 2 days	± 3 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		X	X
Adverse event monitoring (new)	X		X	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>e</sup> and weight	X		X	X	X	X	X	X	X	X			
Electrocardiogram (12-lead)	X									X			
Bone mineral density by DXA <sup>f</sup>	X									X			
Hematology	X									X			
Serum chemistry (20-panel) <sup>g</sup>	X									X			
Serum calcium (local)**	X	X									X	X	
Serum calcium, phosphorus, and albumin	X		X	X	X	X	X	X	X	X		X	
Serum 25-hydroxyvitamin D	X		X	X	X	X	X	X	X	X			
Serum bone turnover markers	X			X	X	X		X		X			
Serum thyroid function test <sup>g,h</sup>	X												
Creatinine clearance (estimated GFR)	X				X		X			X			
PTH antibodies <sup>i</sup>	X					X		X		X <sup>j</sup>			
FSH (newly menopausal women only)	X												
Serum pregnancy test	X				X	X	X	X	X	X			
Urine pregnancy test	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	X		X	X	X	X	X	X	X	X			

*Continued on next page*

**Table 6-1 Schedule of Evaluations and Procedures (continued)**

Visit Number	1	Int.	2	3	4	5	6	7	8	9	Int.	10	11
Study Procedures / Proposed Study Week <sup>a</sup>	BL <sup>b</sup>	1 <sup>c</sup>	4	8	16	24	32	40	48	52 (EoT)	53 <sup>c, d</sup>	53 <sup>d</sup> (F/up)	56 (F/up) Phone
Visit Windows	± 3 days	± 2 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 7 days	± 2 days	± 3 days	± 7 days
Dispense/accountability of calcium/calcitriol supplements (see guideline)	X		X	X	X	X	X	X	X	X			
Collect used/unused study drug, supplements, and pen injectors <sup>k</sup>			X	X	X	X	X	X	X	X			

BL = baseline; DXA = dual-energy x-ray absorptiometry; EoT = end of treatment; FSH = follicle stimulating hormone; F/up = follow up; GFR = glomerular filtration rate; Int.= interim visit; PTH = parathyroid hormone

\*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 and 53. Week 56 is telephone contact only.

<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> Interim total serum calcium for all subjects 3 to 5 days (±2 days) after baseline and after last dose of study drug

<sup>d</sup> Week 53 will be comprised of 2 visits: one interim safety check and one end of week study visit.

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

<sup>f</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 1 of the previous studies (all subjects will have a DXA performed at the end of the study Visit 9)

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

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

<sup>i</sup> Blood draw for PTH 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. Pens will be collected at the final visit.

<sup>l</sup> See Section 6.2 for instructions on follow-up for subjects with PTH-specific antibodies.

## **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, phosphorus, 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 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](#), NPSP558 and Supplement Titration Guideline) based on this value. If further adjustments are made to the NPSP558 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 calcium, phosphorus, and albumin (all visits)
- Serum bone turnover markers (Weeks 8, 16, 24, and 40)
- Serum  $\beta$ -HCG pregnancy test (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 antibodies (predose on Weeks 24 and 40)
- 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 (Weeks 16 and 32)

#### **6.4.4 Week 52 (Visit 9) End of Study Visit**

Subjects will be instructed to come into the study center after having fasted for approximately 6 to 8 hours and prior to taking their last dose of 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, phosphorus, and albumin), hematology, serum 25(OH) vitamin D, creatinine clearance, and bone turnover markers
- Blood sample for PTH antibodies (predose) (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
- A BMD test by DXA
- Serum  $\beta$ -HCG pregnancy test (females only)
- Review the subject's diary to assess compliance to protocol procedures and dosing/supplement regimens.

- Collect used and unused drug cartridges, supplements (calcium and calcitriol), and pen injectors for assessment of accountability and subject diaries.

#### **6.4.5 Week 53 Interim Safety Check**

Subjects will have a total serum calcium level drawn locally between 3 to 5 days ( $\pm 2$  days) following the last dose of study drug. Poststudy adjustments of supplemental calcium and calcitriol will be made (see [Appendix 2](#), NPSP558 and Supplement Titration Guideline) based on this value.

#### **6.4.6 End of Week 53 (Visit 10) Follow-up Safety Visit**

Subjects will have blood drawn for total serum calcium, phosphorus, and albumin levels. This sample will be split in order to provide blood for a local total serum calcium to be done at the investigator's local laboratory. Further adjustment of subjects' supplemental calcium and calcitriol doses will be made based on these values (see [Appendix 2](#), NPSP558 and Supplement Titration Guideline). Subjects will also be monitored for 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.

#### **6.4.7 Week 56 (Visit 11) Follow-up Telephone Contact**

Subjects will be contacted approximately 30 days 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.\

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

If any subject tests positive for PTH-specific antibodies at the final visit, they will have follow-up blood draws for PTH antibodies at Months 2, 3, and 6 poststudy. If a subject's results are negative at 2 successive visits within this timeframe, follow-up may be terminated. If at the end of 6 months the subject is still determined to have PTH-specific antibodies, the PI and the sponsor will determine if additional follow-up may be required. During this time, subjects also will be evaluated for AEs or SAEs related to immunogenicity, which will be collected in the Pharmacovigilance database. (see [Section 6.2](#))

## **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 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. 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**

Statistical analyses 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, if available. 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 and surgical 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, 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.

### 8.2.1 Efficacy Variables

#### Primary Efficacy Endpoint:

The proportion of subjects in whom the following three conditions are fulfilled at Week 52 (Visit 9) 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 ( $\geq 7.5$  mg/dL) 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 primary endpoint 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  $\text{mg}^2/\text{dL}^2$
- Distribution of subjects by NPSP558 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.

### **8.3 Other Variables**

Other variables to be analyzed will include the following:

- Subject accounting
- 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.

### **8.4 Analysis Populations, Data Sets, and Time Points**

#### **8.4.1 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.

### **8.5 Statistical/Analytical Issues**

#### **8.5.1 Adjustments for Covariates**

No preselected covariates are selected for adjustments.

#### **8.5.2 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.

### **8.5.3 Interim Analyses and Data Monitoring**

An interim study report will be completed to look at safety and efficacy at a date to be determined.

### **8.5.4 Multiple Comparisons/Multiplicity**

No adjustment for multiplicity in treatment is planned.

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

No pharmacokinetic subset of subjects was selected for analysis.

### **8.5.6 Examination of Subgroups**

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

## **8.6 Determination of Sample Size**

Approximately 40 subjects are anticipated to be enrolled. Sample sizes were not estimated for this extension study.

## **8.7 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 NPS 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 partner of male subjects who is a WOCBP) 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 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 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 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 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 “Principal Investigator Protocol Agreement 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.



## 10 REFERENCES

- Bilezikian J. PTH(1-84): A therapy for hypoparathyroidism. Independent Investigator Study Report, 2008.
- Bilezikian JP, Marcus R, Levine MA (eds). The Parathyroids. Basic and Clinical Concepts 2<sup>nd</sup> ed. San Diego: Academic Press;2001.
- Horwitz MJ, Stewart AF. Hypoparathyroidism: is it time for replacement therapy? J Clin Endocrinol Metab. 2008 Sep;93(9):3307-9.
- Langdahl BL, Mortensen L, Vesterby A, Eriksen EF, Charles P. Bone histomorphometry in hypoparathyroid patients treated with vitamin D. Bone. 1996;18(2):103-8.
- Rubin MR, Dempster DW, Zhou H, Shane E, Nickolas T, Sliney J, et al. Dynamic and structural properties of the skeleton in hypoparathyroidism. J Bone Miner Res. 2008a Aug 4;23(12):2018-24.
- Rubin MR, Cremers S, Dempster DW, Sliney J, McMahon DJ, Zhou H, et al. PTH increases bone turnover in hypoparathyroidism [abstract]. J Bone Miner Res. 2008b;23:S128.
- Rubin MR, Dempster DW, Cremers S, Zhou H, McMahon DJ, Sliney J, et al. Circulating osteoblast lineage cells increase with PTH treatment of hypoparathyroidism [abstract]. J Bone Miner Res. 2008c;23:S42.
- Rubin MR, Dempster DW, Sliney J, McMahon DJ, Zhou H, Nickolas T, et al. PTH reverses abnormal bone remodeling and structure in hypoparathyroidism [abstract]. J Bone Miner Res. 2008d;23:S12.
- Rubin MR, Sliney J Jr, McMahon DJ, Silverberg SJ, Bilezikian JP. Therapy of hypoparathyroid with intact parathyroid hormone. Osteoporos Int. 2010;21(11):1927-34.
- Shoback D. Clinical practice. Hypoparathyroidism. N Engl J Med. 2008 Jul 24; 359(4):391-403. Review.
- Winer KK, Yanovski JA, Sarani B, Cutler GB Jr. A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1-34 in treatment of hypoparathyroidism. J Clin Endocrinol Metab. 1998 Oct;83(10):3480-6.
- Winer KK, Ko CW, Reynolds JC, Dowdy K, Keil M, Peterson D, et al. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. J Clin Endocrinol Metab. 2003 Sep;88(9):4214-20.

Winer KK, Sinaii N, Peterson D, Sainz B Jr, Cutler GB Jr. Effects of once versus twice-daily parathyroid hormone1-34 therapy in children with hypoparathyroidism. J Clin Endocrinol Metab. 2008 Sep;93(9):3389-95. Epub 2008 May 20.

## **APPENDIX 1      INSTRUCTIONS FOR USE FOR THE PTH HASSELMEIER PEN INJECTOR SYSTEM**

INSTRUCTIONS FOR USE

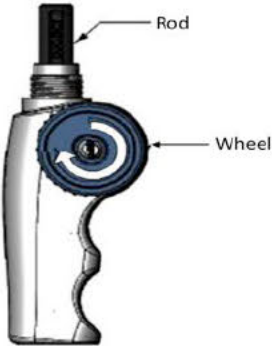
- You will need to give yourself an injection of NPSP558 into alternating thighs every day as instructed by your doctor.
- Each Medication Cartridge provides 14 days of therapy and will come separately from the pen as refills that should be stored in the refrigerator.
- After the Pen Injector contains 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 instruction on how to prepare and inject NPSP558. 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.

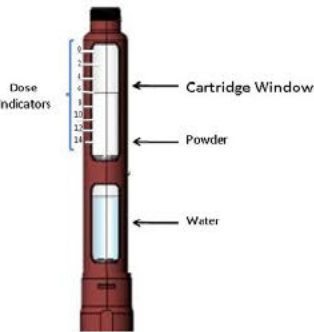
1. MIXING DEVICE

This device will help to mix NPSP558 with water to form a solution.



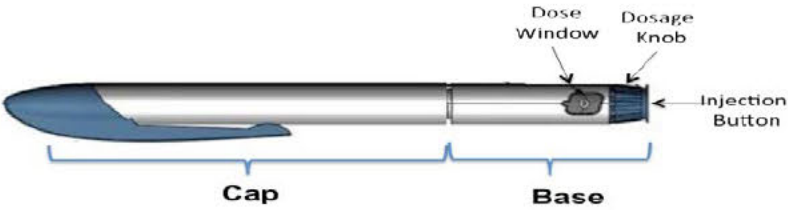
2. MEDICATION CARTRIDGE

Each Medication Cartridge has 14 doses of NPSP558 and contains both a powder and water.



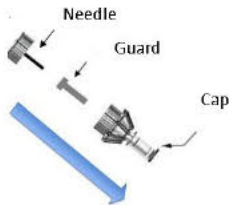
3. PEN INJECTOR

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.



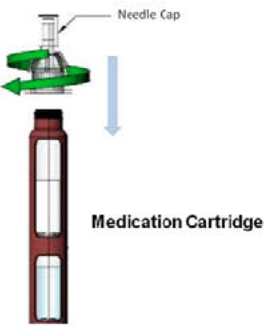
STEP 1A: PREPARE NEW OR REPLACE MEDICATION CARTRIDGE  
WASH HANDS AND GET READY  
COMPLETE CARTRIDGE USE CARD



- 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

Cartridge Use Card		
Cartridge	Date the cartridge was first mixed	Date to change the cartridge (Date of same day of the week as today 14 days later)
1		
2		

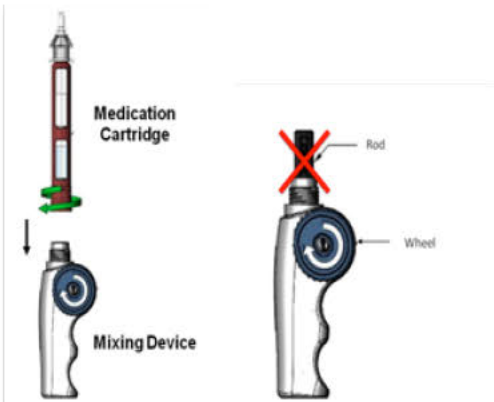
STEP 1B: ATTACH NEEDLE



- 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.

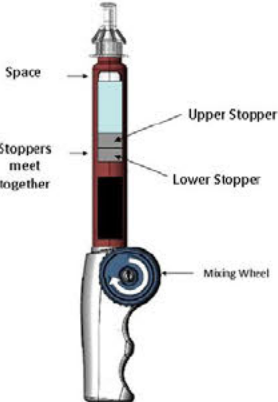
**Do not remove the Needle Cap or Guard until ready to inject.**

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

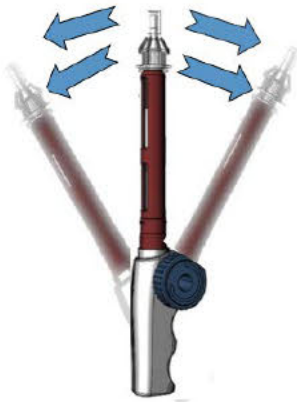


- Turn the blue Wheel in the direction of the arrow.
- As you turn the Wheel the **first time**, look at the Cartridge Window and continue turning the Wheel until two stoppers meet together.



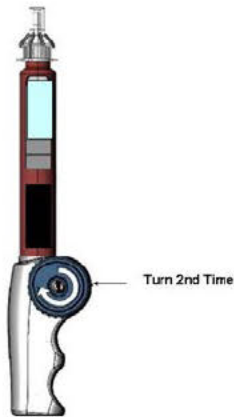
- STOP** turning the wheel at this point.
- There will be a little bit of space at the top of the Medication Cartridge.

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.

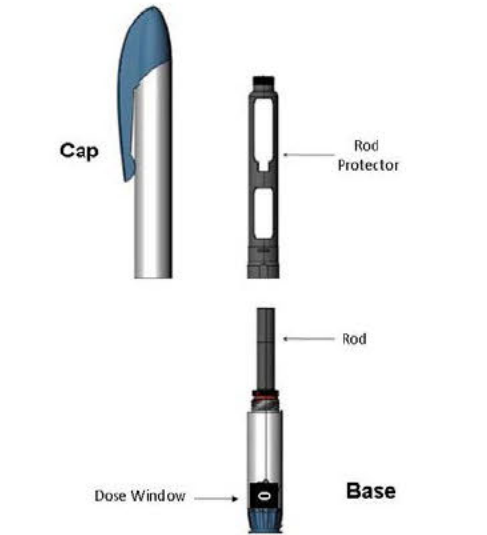
STEP 2D: FINAL MIXING STEP  
TURN THE BLUE WHEEL THE SECOND TIME TO REMOVE REMAINING AIR



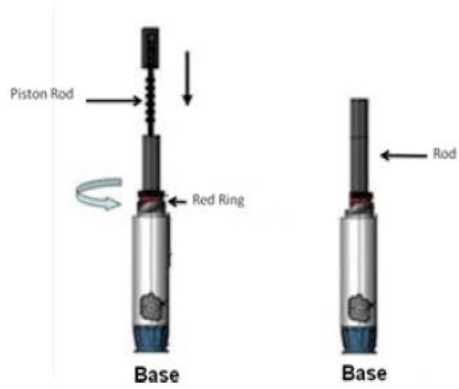
- Keeping the device upright, **turn the blue wheel the second time** in the same direction as the arrow until the stoppers no longer move to remove any remaining air in the cartridge. The wheel will continue to turn freely.
- Put the Medication Cartridge aside while you prepare the Pen Injector.
- It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



STEP 3: PREPARE THE PEN INJECTOR

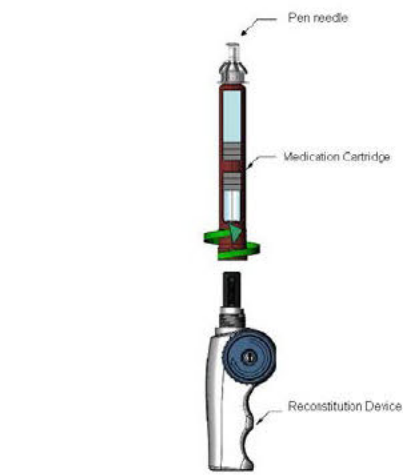


- Remove the Cap from the Pen Injector by pulling. Save the Cap for later use.
- Unscrew the Rod Protector. Do not discard the Rod Protector because you may use it to protect the Rod when a Medication Cartridge is not installed.
- Ensure that the Dose Window reads “0” and the Rod is all the way down.



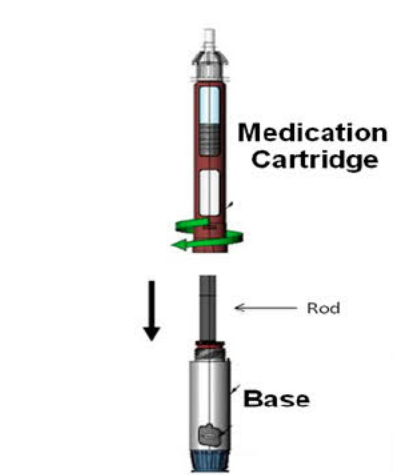
- If the Rod is extended, turn the red ring on the Base to the left to retract the piston rod until it is fully down and the Red Ring stops.

STEP 4A: REMOVE THE MEDICATION CARTRIDGE FROM THE MIXING DEVICE



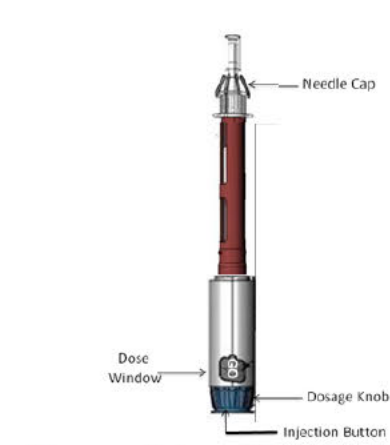
- Place the Pen Injector aside and pick up the Mixing Device with the Medication Cartridge attached and hold the unit pointing upwards. Gently unscrew the Medication Cartridge from the Mixing Device.

STEP 4B: ATTACH THE MEDICATION CARTRIDGE TO THE PEN INJECTOR



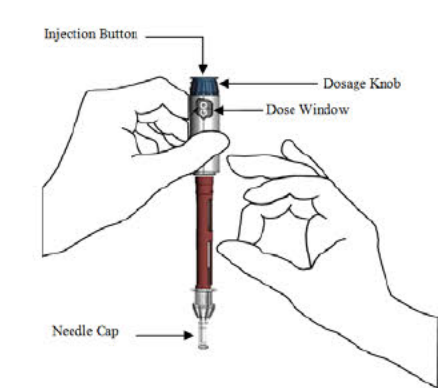
- Screw the Medication Cartridge onto the Base.
- A small amount of liquid may leak out during this process, which is normal.

STEP 5: PRIME THE PEN INJECTOR WITH NEW MEDICATION CARTRIDGE



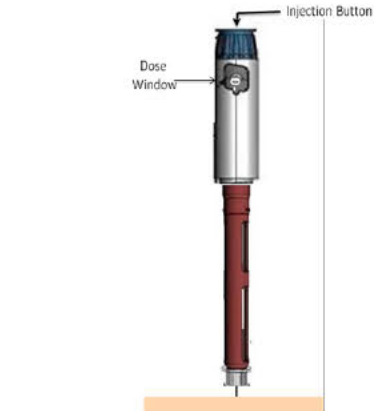
- When you attach a **new** Medication Cartridge to the Pen Injector, you must prime the Pen Injector **prior to the first injection**.
- Turn the blue dosage knob to “GO”.
- Hold the Pen Injector with the **NEEDLE CAP POINTING UP**.
- Press the **blue Injection Button** until it stops and the “0” mark becomes visible. During this process some liquid may leak out from the Needle. This is normal.
- You only need to do this step once for each new Medication Cartridge every 14 days.

STEP 6A: PREPARE INJECTION SITE AND SET THE DOSE



- If you have not done so already, **Wash your hands** with soap and water or sanitizer and dry.
- **Clean the injection area of your thigh** with an alcohol swab or soap and water. Allow to completely dry.
- Hold the Pen Injector with the **NEEDLE CAP POINTING DOWN**. Tap gently to move any existing air bubbles away from the Needle.
- Hold the Pen Injector so that you can see the pen display “0”.
- **NOTE:** 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 **Do NOT Force** it.
- Pull off the Needle Cap and Guard and discard.

STEP 6B: INJECT THE MEDICATION

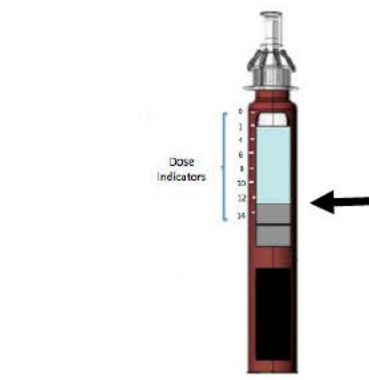


- Hold the Pen Injector with the **NEEDLE POINTING DOWN** so you can see the pen displays “GO”.
- Insert the Needle fully into the thigh skin.
- Press the **blue Injection Button** until it stops and the pen displays “0”.
- **Slowly count to 10 seconds**. During this process, you may either hold the Injection Button down or release it, while keeping the needle in the skin.



- 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.
- **Do not inject a second dose**

STEP 6C: CONFIRM THE INJECTION WAS DELIVERED



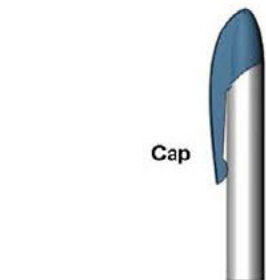
- **Confirm that you have given an injection** by checking to see that the **Dose Indicator scale shows one less dose** (this illustration indicates that there are 13 doses remaining).
- The pen injector dosage knob will NOT turn to “GO” when the cartridge is empty.
- The dose scale marks are evenly 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.

STEP 7A: DISCARD THE NEEDLE



- Safely dispose of the needle in a sharps container designed for pen needles following the Instruction For User on the sharps container.
- While holding the medication cartridge (still attached to the pen injector), insert pen tip and needle into the opening designed for pen needles.
- 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.

STEP 7B: STORE THE PEN INJECTOR



- 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.
- **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.
- 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.



- **Wash your hands** with soap and water or sanitizer to remove any spilled medication.

STEP 8: GIVING A DAILY INJECTION



- **Wash your hands** with soap and water or sanitizer and dry.
- **Check that the cartridge contains at least one dose (Pictured in step 6C).**
- Repeat steps 1B, 6A, 6B, 6C, 7A, and 7B.

STEP 9: REPLACING THE MEDICATION CARTRIDGE

- 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. Do NOT force the blue dosage knob to “GO”. A small visible amount of liquid may still remain in the cartridge.
- Unscrew the empty Medication Cartridge and discard it.
- Repeat Steps 1 to 5

STEP 10: STORING THE PEN INJECTOR FOR LATER USE

- 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.

## APPENDIX 2 NPSP558 AND SUPPLEMENT TITRATION GUIDELINE

In this study the goal is to continue NPSP558 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 NPSP558. 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, NPSP558 (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 NPSP558 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 NPSP558 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, NPSP558 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 NPSP558 reviewed with the subject to ensure proper administration. At planned study visits (Week 4, 8 etc until Week 48) the NPSP558 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)	NPSP558 dose	Supplement dose adjustment
<b>Visit 1 (Baseline)</b>	> 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 adjustment</b> <b>in NPSP558 dose</b> <b>*or if clinically 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	Stop 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 NPSP558 is advised if needed after an observation of the initial response to 25 or 50 µg/d.



Visit number	Serum calcium (mg/dL)	NPSP558 dose	Supplement dose adjustment
Visits 2 to 8 (Weeks 4 to 48)	< 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 NPSP558 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

\* Any changes in the NPSP558 dose or calcitriol and/or oral calcium supplement dose must be followed by a safety laboratory check for of 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.