STATISTICAL ANALYSIS PLAN

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)
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Study No. PAR-C10-008

Authorization Signature Page

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List of Figures and Tables

Modification History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
Amendment 1 v2.0	22MAR2018	PPD	Study design description and schedule tables were updated to be aligned with Protocol Amendment 6.

List of abbreviations and definition of terms

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
ATC	Anatomic Therapeutic Chemical classification
BMD	Bone mineral density
BMI	Body Mass Index
BSAP	Bone-specific alkaline phosphatase
BUN	Blood Urea Nitrogen
CBC	Complete blood count
CPK	Creatine phosphokinase
CTx	C-terminal telopeptide of type 1 collagen
DSMB	Data and Safety Monitoring Board
DXA	Dual-energy x-ray absorptiometry
ECG	Electrocardiogram
ECP	Escherichia coli protein
EOT	End of Treatment
eCRF	Electronic case report form
CLcr	Cockcroft-Gault Creatinine Clearance
FDA	Food and Drug Administration
FSH	Follicle-stimulating hormone
GFR	Glomerular filtration rate
GI	Gastrointestinal
HR	Heart Rate
ICF	Informed consent form
ICH	International Conference on Harmonization
ITT	Intent-to-Treat
IVR	Interactive Voice Response
IWR	Interactive Web Response
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
ms	milliseconds
NDA	New Drug Application
P1NP	Procollagen amino-terminal peptide
PR	In electrocardiography, the time from the beginning of the P wave (onset of atrial depolarization) to the beginning of the QRS complex
PT	Preferred Term
PTH	Parathyroid hormone
QD	Daily
QRS	In electrocardiography, the QRS complex represents the time it takes for depolarization of the ventricles
QT	In electrocardiography, the time from the beginning of the QRS complex to the end of the T wave
QTc	QT interval corrected for heart rate
QTcB	QT corrected for heart rate by the Bazett method
QTcF	QT corrected for heart rate by the Fridericia method
RBC	Red Blood Cell
RELAY	A Randomized, Dose-blinded Study to Investigate the Safety and Efficacy of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH[1-84]),, at Fixed Doses of 25 µg and 50 µg for the Treatment of Adults With Hypoparathyroidism. Study No. is PAR-C10-007
REPLACE	A Randomized, Double-blind, Placebo-Controlled, Phase 3 Study to Investigate the Use of NPSP558, a Recombinant Human Parathyroid Hormone (rhPTH[1-84]) for the Treatment of Adults with Hypoparathyroidism. Study No. is CL1-11-040
rhPTH	Recombinant human parathyroid hormone
RR	In electrocardiography, the time duration between two consecutive R waves

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SC	Subcutaneous
SI	International System of Units
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
TESAE	Treatment Emergent Serious Adverse Event
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. Introduction

This document describes the rules and conventions for data handling and methodologies for statistical analysis to be used in the presentation and analysis of efficacy and safety data for protocol PAR-C10-008 (RACE). It describes, in detail, the data and variables to be summarized and analyzed, including specifics of the statistical analyses to be performed. This statistical analysis plan is based on Protocol Amendment 6, dated October 24, 2016.

Hypoparathyroidism is a condition in which there is deficient production of parathyroid hormone (PTH) from the parathyroid glands. The deficiency of PTH results in decreased calcium reabsorption from renal tubules, malabsorption of calcium from the gastrointestinal (GI) tract and reduced calcium mobilization from bone. Hypoparathyroidism is the most common cause of chronic hypocalcemia.

NPSP558 (rhPTH[1-84]) is recombinant human parathyroid hormone that is identical in structure to endogenous human parathyroid hormone (hPTH), a single-chain polypeptide consisting of 84 amino acid residues (rhPTH[1-84]). This is a 12-month open-label study investigating the safety and tolerability of NPSP558 for the Treatment of Adults with Hypoparathyroidism.

A Phase 3 study is currently ongoing (CL1-11-040, REPLACE) to investigate the effects of daily subcutaneous (SC) injections of rhPTH[1-84] at doses of 50, 75, or 100 µg. An 8-week study of fixed doses of 25 and 50 µg (PAR-C10-007, RELAY) is currently being undertaken to explore a broader range of treatment dose options.

2. Study Objectives

2.1. Primary objective

To demonstrate the long-term safety and tolerability of SC rhPTH[1-84] as hormone replacement therapy for the treatment of adult subjects with hypoparathyroidism.

2.2. Secondary objective

- To evaluate the impact of different preparations of calcium on the response to rhPTH[1-84] replacement therapy
- To demonstrate that dosing with rhPTH[1-84] across a dose range of 25 to 100 µg SC can be implemented in a safe and effective manner and can be maintained throughout long-term treatment
- To evaluate the impact of calcium-sparing diuretics on serum and urinary calcium

3. Study Design

3.1. General Description

This study is a long-term, open-label study using rhPTH[1-84] for the treatment of adults with hypoparathyroidism. Subjects can enroll if they either previously completed the NPSP558 RELAY study (PAR-C10-007) (8 weeks of active therapy) and/or completed the REPLACE study (CL1-11-040) (Visit 18).

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

- The starting dose of rhPTH[1-84] for this study will be 25 or 50 μg SC once daily (QD)
- Subjects may have their rhPTH[1-84] dose adjusted by the investigator at any time during the study, with the goal of achieving or maintaining total serum calcium levels in the range of 8.0 to 9.0 mg/dL.
- If **ANY** predose (trough) total serum calcium is >11.9 mg/dL study drug will be stopped.
- Subjects will have blood draws to assess total serum calcium levels (which may be performed locally) 3 to 5 days after **ANY** dose adjustment of rhPTH[1-84], after any significant change in doses of calcium and/or calcitriol supplements, or at any other time at the discretion of the investigator.
- Study visits during the first 12 months of the study will be conducted at Weeks 1 (baseline), 4, 8, and then every 8 weeks thereafter up to Week 48 (Visit 8). The Week 52 visit (Visit 9) is scheduled 4 weeks later.
- At any time following the Week 16 (Visit 4), subjects who are on a stable dose of rhPTH[1-84] and have a 24-hour urine calcium >300 mg (males) and >250 mg (females) may be treated for hypercalciuria with calcium-sparing diuretics, if this therapy had not been introduced prior to the study.
- At the end of Week 52, subjects will be invited to extend their study drug regimen until January 2018 or after the completiong of the last patient's Month 72 visit, whichever comes laslt..
- During this time, subjects will return to the clinic for interim visits every 2 months (Months 14, 16, 18, etc).
- After the End of Treatment visit or early termination visit, subjects who will not continue rhPTH[1-84] treatment will have their total serum calcium and phosphate levels measured 3 to 5 days after the last dose of study medication. Doses of calcium and active vitamin D supplements will be adjusted by the Investigator as appropriate. Thereafter, the Investigator will repeat serum calcium/phosphate monitoring and supplement dose adjustments as appropriate to achieve target serum calcium/phosphate concentrations until the follow up phone call 4 weeks ± 7days after end of treatment visit. After the 4 weeks follow up phone call, further management of hypoparathyroidism will occur as part of the subject's long-term non-study medical care.

A schematic presentation of the study design is displayed in Figure 1.1 and Figure 1.2.

Figure 1. 1 Study Design – First 12 Months of Study

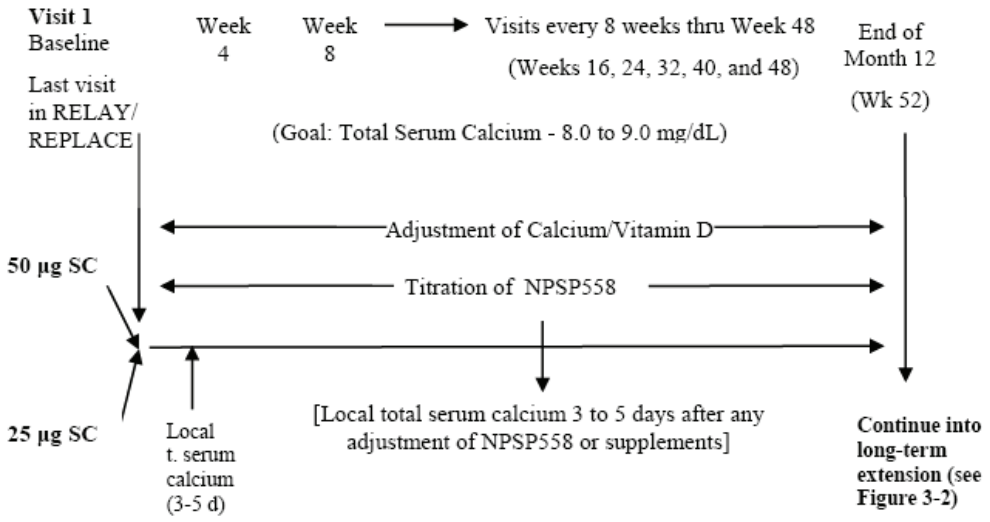
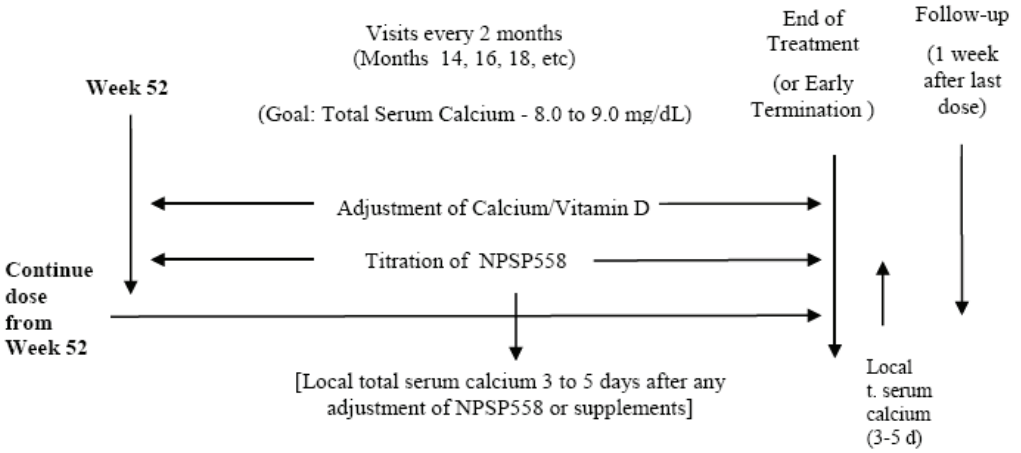


Figure 1. 2 Study Design – Long-term Extension



3.2. Treatments

3.2.1. Treatments Administered

At the beginning of the study, subjects will receive rhPTH[1-84] 25 or 50 µg SC QD in an open-label fashion. Subjects may have their rhPTH[1-84] dose adjusted upwards in increments of 25 µg to a maximum of 100 µg SC QD, with the goal of achieving or maintaining total serum calcium levels in the range of 8.0 to 9.0 mg/dL. The rhPTH[1-84] dose may be adjusted downward at any time as needed to maintain appropriate total serum calcium levels

(approximately 8.0 to 9.0 mg/dL) or due to any safety concerns. rhPTH[1-84] is to be administered into alternating thighs each morning via a multi-dose injection pen device.

3.2.2. Method of Assigning Subjects

Subjects previously enrolled in or who completed the REPLACE or RELAY studies will utilize the same 8-digit subject number that they had been assigned during that study. This number will be utilized to identify the subject throughout the study period. New subjects who were never entered into the REPLACE study will be assigned a new 8-digit subject number.

Subjects will receive study treatment in an open-label fashion at starting doses of rhPTH[1-84] 25 or 50 µg SC QD:

- Subjects with a total serum calcium value of ≤ 9.5 mg/dL will have a starting dose of 50 µg.
- Subjects with a total serum calcium value of > 9.5 mg/dL will have a starting dose as follows:
    - Subjects who are taking supplements (≥ 500 mg oral calcium and/or any calcitriol) will have the supplements reduced or stopped and will start at a dose of 50 µg SC QD.
    - Subjects who are taking minimal or no supplemental calcium (< 500 mg oral calcium) and no calcitriol will have a starting dose of 25 µg SC QD.

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.

3.3. Determination of Sample Size

Approximately 50 subjects are anticipated to be enrolled. This sample size is based on an estimate of the number of subjects who potentially could roll over from RELAY and/or REPLACE study and is not calculated based on the statistical assumptions.

3.4. Changes in the Conduct of the Study or Planned Analyses

3.4.1. Changes in the Conduct of the Study

The SAP is based on Protocol Amendment 6, dated October 24, 2016. Any change of the conduct of the study will be documented in the clinical study report. Any significant changes in the planned analysis will prompt another version of the SAP and therefore a revised SAP.

3.4.2. Changes from Analyses Planned in the Protocol

No changes from protocol specified analyses are planned.

4. Efficacy and Safety Variables

4.1. Schedule of Evaluations and Procedures

All clinical study evaluations will be performed according to Table 6.1, Table 6.2, and Table 6.3. Details of the exact date and time of medical assessments (day/month/year) will be documented in the eCRF. Any deviations from protocol requirements will be documented in the eCRF. A schedule of follow-up visits and procedures for subjects who test positive for PTH-specific antibodies at the last visit is provided in Table 6.4.

Table 4. 1 Schedule of Evaluations and Procedures – First 12 Months of Study

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

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

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

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

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

[a] Study visits will be conducted at Weeks 1 (baseline), 4, 8, every 8 weeks thereafter through Week 48, and at Weeks 52.
[b] Week 8 from the RELAY study; subjects will return all used/unused drug, supplements, and pens from RELAY/REPLACE.
[c] After the End of Treatment visit or early termination visit, subjects who will not continue rhPTH[1-84] treatment will have their total serum calcium and phosphate levels measured 3 to 5 days after the last dose of study medication. Doses of calcium and active vitamin D supplements will be adjusted by the Investigator as appropriate. Thereafter, the Investigator will repeat serum calcium/phosphate monitoring and supplement dose adjustments as appropriate to achieve target serum calcium/phosphate concentrations until the follow up phone call 4 weeks ± 7days after end of treatment visit. After the 4 week follow up phone call, further management of hypoparathyroidism will occur as part of the subject's long-term non-study medical care.
[d] Vital signs should be done prior to blood draws.
[e] Calcium supplements should be withheld for 24 hours prior to the DXA scan. If a subject cannot withhold the calcium supplements due to safety concern, the DXA should be performed 2 hours after the last calcium tablet has been ingested. Please note: DXA will NOT be completed at baseline if subject had a scan performed within the past 6 months in one of the previous studies (all subjects will have a DXA performed at Week 52 (Visit 9)
[f] Fasting for at least 6 to 8 hours prior to test
[g] Serum potassium, sodium, and calcium is to be collected 1 week and again 1 month following the institution or change in dose of a calcium-sparing diuretic and then at each subsequent scheduled clinic visit.
[h] Thyroid function tests done for final visit of the RELAY/REPLACE studies only.
[i] Blood draw for PTH and ECP antibodies will be done predose.
[j] A paper diary will be dispensed at baseline for the investigator's use to assess subject's compliance and adherence to the protocol procedures.
[k] Subject is to return unused and used cartridges and supplements at each visit.
[l] See Protocol Section 6.2 for instructions on follow-up for subjects with PTH-specific antibodies and Table 6-3 for a schedule of follow-up procedures for these subjects.
[m] Blood samples for pharmacokinetic analysis will be drawn predose (0 hour) and postdose between 1 and 2 hours and between 6 and 10 hours following study drug administration.

Table 4. 2 Schedule of Evaluations and Procedures – Long-term Extension to Month 36

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

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

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

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

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

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

[c] Brief physical exams will be conducted at 6-month intervals.

[d] Vital signs should be done prior to blood draws.

[e] 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.

[f] DXA will be performed at End of Treatment visit ONLY if the previous DXA was ≥3 months prior.

[g] Fasting for at least 6 to 8 hours prior to test

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

[i] Blood draw for PTH and ECP antibodies will be done predose.

[j] See Protocol Section 6.4.9 for instructions on follow-up for subjects with PTH-specific antibodies and Table 6-4 for a schedule of follow-up procedures for these subjects.

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

[l] Subjects are to return unused and used cartridges at each visit. Pens will be collected at the final visit.

Table 4. 3 Schedule of Evaluations and Procedures – Long-term Extension after Month 36

Proposed Study Month[a] Study Procedures	Months 38/50/62	Months 40/52/64	Months 42/54/66	Months 44/56/68	Months 46/58/70	Months 48/60/72	End of Treatment[b]	4 weeks F/up Phone[c]
Visit Windows	**± 2 weeks**	**± 2 weeks**	**± 2 weeks**	**± 2 weeks**	**± 2 weeks**	**± 2 weeks**	**± 1 week**	**± 7 days**
Re-consent subject[d]	X							
Concomitant medications	X	X	X	X	X	X	X	
Adverse event monitoring, including pen-related events/complaints	X	X	X	X	X	X	X	X
Assessment of clinical episodes of hypocalcemia and hypercalcemia	X	X	X	X	X	X	X	
Physical examination[e]			X[e]			X[d]	X	
Vital signs[f] and weight	X	X	X	X	X	X	X	
Electrocardiogram (12-lead)							X[g]	
Bone mineral density by DXA[h]						X	X[i]	
Hematology[j]						X	X	
Serum chemistry (20-panel)[j]						X	X	
Serum calcium (local)*								
Serum calcium, phosphate	X	X	X	X	X	X	X	
Serum calcium, potassium, sodium[k]	X	X	X	X	X	X	X	
Serum 25-hydroxyvitamin D	X	X	X	X	X	X	X	
Serum 1,25-dihydroxyvitamin D			X			X	X	
Serum bone turnover markers		X		X		X	X	
Creatinine clearance (estimated GFR)		X		X		X	X	
PTH and ECP antibodies[l]			X			X	X[m]	
Serum pregnancy test (WOCBP only)							X	
Urine pregnancy test (WOCBP)	X	X	X	X	X	X		
Urinalysis							X	
24-hour urine calcium, phosphate, sodium, creatinine		X		X		X	X	
Diary review[n]	X	X	X	X	X	X	X	
Dispense/administration/accountability of study drug, and pen injectors/ancillary supplies[o]	X	X	X	X	X	X	X	
Collect used/unused study drug / pen injectors[p]	X	X	X	X	X	X	X	

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

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

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

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

[a] Study visits will be conducted every 2 months and will continue until the subject voluntarily withdraws or until termination of the study (**currently extended at least until December 2016**). At that time, and periodically following the December 2016 milestone, the study will be reviewed in regard to continuation/termination status.

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

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

[d] Study subjects must be re-consented at their next study visit prior to implementation of Amendment 5.

[e] Brief physical exams will be conducted at 6-month intervals.

[f] Vital signs should be done prior to blood draws.

[g] The End of Treatment ECG will be read locally.

[h] 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.

[i] DXA will be performed at End of Treatment visit ONLY if the previous DXA was ≥3 months prior.

[j] Fasting for at least 6 to 8 hours prior to test

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

[l] Blood draw for PTH and ECP antibodies will be done predose.

[m] See Protocol Section 6.4.9 for instructions on follow-up for subjects with PTH-specific antibodies and Table 6-4 for a schedule of follow-up procedures for these subjects.

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

[o] Ancillary supplies (ie, needles and alcohol wipes) may be supplied, as allowed by local regulations.

[p] Subjects are to return unused and used pen injectors at each visit.

Table 4. 4 Schedule of Follow-up Visits and Procedures for Subjects with PTH-specific Antibodies at Final Visit

Follow-up Procedures[a]	Follow-up (Month 3)b	Follow-up (Month 6)
Visit Number:	**F3**	**F4**
Visit Window (± Days)	±7	±7
Antibodies to PTH	X	X
Adverse events	X	X

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

[a] Follow-up visits will be conducted for only those subjects who are determined to have PTH-specific antibodies at the end of the End of Study visit (or at the time of discontinuation) and are NOT continuing treatment on commercial Natpara.

[b] Subjects who have negative antibody results at Month 3 do not need the Month 6 follow-up visit.

4.2. Efficacy Endpoint

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

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

4.3. Other Efficacy Endpoints

- Mean percentage changes from baseline in supplemental oral calcium and supplemental calcitriol dosages at each visit
- Proportion of subjects achieving the three conditions of the efficacy endpoint defined above at each visit
- Mean change from baseline in 24-hour urine calcium excretion
- Impact of calcium source (carbonate vs. citrate) on response
- Impact of calcium-sparing diuretics on serum and urinary calcium
- Proportion of subjects that maintain a calcium phosphate product in the range of 35 to 55 mg^2/dL^2
- Distribution of subjects by rhPTH[1-84] doses at the End of Treatment Visit
- Change from baseline in bone turnover markers, bone-specific alkaline phosphatase, 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

4.4. Exploratory Endpoints

There is no exploratory endpoint specified for this study.

4.5. Safety Endpoints

The safety endpoints include:

- 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
  - Serum 1,25-dihydroxyvitamin D levels
  - Creatinine clearance
  - Serum bone turnover markers
  - Urinalysis
  - 24-hour urine calcium, phosphate, sodium, and creatinine excretion
  - PTH and *E. coli* protein (ECP) antibodies
- Bone mineral density (BMD) by dual-energy x-ray absorptiometry (DXA)
- Electrocardiogram (ECG) parameters
- Physical examinations (including vital signs)
- Reason for termination from the study

5. Statistical Methods

5.1. General Methodology

All statistical procedures will be completed using SAS version 9.4[1]. No formal statistical testing will be conducted for this study. Summary statistics will be provided.

Continuous variables, including those assessed on a discrete scale, will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. For categorical variables, statistical summaries will include number of subjects and percentages.

For summary purposes, baseline will be defined as the last available pre-dose value, unless otherwise specified. End of treatment (EOT) time point, defined as the last determination of response or last available measurement during the treatment period (from the date of first dose to the date of last dose + 1 day), will be analyzed in addition to the scheduled visits. Visits will be summarized based on the analysis visit windows.

5.2. Adjustments for Covariates

No preselected covariates are selected for adjustments.

5.3. Visit Windows

5.3.1. Analysis Visit Windows

Analysis visit windows are defined in Table 4.

Table 5. 1 Analysis Visit Window Definition (1st 12 Month of Study)

Analysis Visit	Target Study Day	Analysis Visit Window
Baseline	1	See definition in Section 7.3.2
Week 4	29	[2, 42], and ≤last dose day + 1
Week 8	57	[43, 84], and ≤last dose day + 1
Week 16	113	[85, 140], and ≤last dose day + 1
Week 24	169	[141, 196], and ≤last dose day + 1
Week 32	225	[197, 252], and ≤last dose day + 1
Week 40	281	[253, 308], and ≤last dose day + 1
Week 48	337	[309, 350], and ≤last dose day + 1
Week 52	365	≥351, and ≤last dose day + 1 or <start date of the extension period

If there are more than one non-missing observations in the same analysis visit window, the following selection rules will be applied sequentially to determine which observation will be used for analysis:

- The observation that is closer to the target day will be used;
- If Observations are equal-distance in days from the target day, the later one based on measurement date and time will be used.

Analysis visit in the Long Term Extension period will be the same as the nominal visit in the CRF database. No derivation is necessary.

5.3.2. Definition of Baseline

For all data including baseline variables, efficacy endpoints, and safety endpoints, the baseline values are defined as follow:

- For subjects who previously completed the REPLACE and RELAY studies or completed only the REPLACE study, the baseline value of REPLACE study will be used as the baseline value for this study;
- For subjects who previously only completed RELAY study, the baseline value of RELAY study will be used as the baseline value for this study;
- For subjects who enrolled in REPLACE and dropped out during optimization and subjects who are new to the rhPTH[1-84] treatment, Visit 1 (BL visit) record of this study will be used as the baseline value.

5.4. Handling of Dropouts or Missing Data

5.4.1. Handling of Dropouts or Missing Data for Efficacy Analysis

The daily dose of calcium and vitamin D metabolite/analog will be computed based on both investigator prescribed data and subject diary data. The investigator prescribed data will be considered as the primary method for all efficacy analysis endpoints.

The daily dose of calcium and vitamin D metabolite/analog based on investigator prescription will be determined by using the latest prescribed dose prior to the assessment date of albumin corrected calcium for each analysis visit. To avoid the effect of potential fluctuation of the supplemental medication dose, the prescribed supplemental medication dose at Visit 1 (BL visit) will be excluded from the derivation of the baseline dose and the prescribed dose at the Visit 9 (week 52) for subjects who complete the treatment or Early Termination Visit. Subjects that discontinued early will be excluded from the derivation of the post-baseline prescribed dose.

The average daily dose of calcium and vitamin D metabolite/analog based on subject diaries will be calculated as the average daily dose of a 14-day interval. The 14-day interval for each current analysis visit includes the dose reported during the 14 days on or prior to the assessment date of albumin corrected calcium. However, this 14-day interval should not include or go beyond the assessment date of albumin corrected calcium for the previous analysis visit. If the number of days from the previous albumin corrected calcium date to the current assessment date is less than 14 days, the actual number of days during the two analysis visits will be used to calculate the average daily dose. If the number of days from the previous albumin corrected calcium date to the current assessment date is less than 9 days, the average daily dose will not be calculated and will be classified as missing. Diary data after the last dose date of study drug will be excluded from the derivation.

A missing daily dose of calcium and vitamin D from subject diaries will not be imputed. A minimum 9 days of non-missing data from the intervals is required, otherwise the average daily dose will be classified as missing. Because recordings of dose of calcium and vitamin D metabolite/analog may be missing on different days, different days within the interval may be used in the computation for the daily dose of calcium and for the daily dose of vitamin D metabolite/analog.

For determination of baseline supplemental medication dose, the derivation rules specified in this section will only be applicable when the value of Visit 1 (BL visit) of this study is used as the baseline value. For all other cases, as specified in section 7.3.2, baseline values will be obtained from the REPLACE or RELAY study. The detailed derivation rules are provided in the SAPs for REPLACE and RELAY studies accordingly.

5.4.2. Handling of Dropouts or Missing Data for Safety Analysis

Missing safety parameters will not be imputed.

5.4.3. Handling of Partial Dates

Complete dates will be imputed from partial dates of adverse events and medications solely for the purpose of defining treatment emergence for adverse events and prior/concomitant status for medications. Dates will be defined using the hierarchy of derivations below.

Adverse event or medication start date:

1. If year and month are known, and it is the month and year of the first dose date, use the first dose date.
2. If year and month are known, and it is the month and year of the informed consent, use the informed consent date.
3. If year and month are known, and the month is not the month and year of the first dose or informed consent, use the first day of the month.
4. If only year is known, and it is previous to the year of the informed consent, use June 30th of that year.
5. If only year is known, and it is the year of the informed consent, use the informed consent date.
6. Should any of the previous start dates created be after a complete stop date provided, use the stop date instead of the date that would otherwise be created.
7. Otherwise, if start date is unknown leave as missing.

Medication stop date:

1. If year and month are known and study medication stopped during that month and year, use the stop date of study medication.
2. If year and month are known and informed consent was provided during that month and year, use the date of informed consent.
3. If year and month are known and study medication stopped after the date of informed consent and not in the month that medication stopped, use the last day of the month.
4. If year and month are known and are prior to the month of informed consent, use the first day of the month.
5. If only year is known and study medication stopped during that year, use the stop date of study medication.
6. If only year is known and study medication stopped after that year, use December 31st of that year.
7. If only year is known and study medication stopped prior to that year, use the first day of the year.
8. Should any of the previous stop dates created be before a start date, either a complete date or an imputed one, use the (imputed) start date instead of the date that would otherwise be created.
9. Otherwise, if stop date is unknown leave as missing.

5.5. Interim Analyses and Data Monitoring

Two interim study reports will be completed: 3-year interim analyses to look at safety and efficacy compiled through 31 May, 2013; 5-year interim analyses to look at safety and efficacy compiled through 08 May 2017. There is no DSMB identified for this study.

5.6. Multicenter Studies

Center will not be used as a covariate factor in the analysis.

5.7. Multiple Comparisons/Multiplicity

Not applicable.

5.8. Active-Control Studies Intended to Show Non-inferiority or Equivalence

There is no active control in the current study

5.9. Examination of Subgroups

Subgroup analysis by gender will be performed for the primary efficacy endpoint. Additional subgroup analysis may be explored as appropriate. Subgroup results need to be interpreted with caution if there is insufficient number of subjects in a subgroup.

6. Statistical Analysis

6.1. Disposition of Subjects

Subject disposition will be summarized for all subjects enrolled as well as subjects in each analysis population.

The number and percentage of subjects assessed at each planned visit, subjects completing the treatment (based on the study exit CRF at Visit 9 (week 52), completing the study (based on the study exit CRF and finish the follow-up Visit 11 (week 56), and discontinuation by reasons will be summarized

6.2. Protocol Deviations

Protocol deviations will be identified programmatically as well as based on protocol deviations collected by the study monitors. A summary table and listing of all collected protocol deviations might be presented upon request.

6.3. Analysis Populations

The analysis populations to be used in this study are the Safety Population and the Intent-to-Treat (ITT) Population.

The Safety Population includes all subjects who received at least one dose of study drug with any follow-up information. All safety analyses will be conducted on this population.

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

6.4. Demographic and Other Baseline Characteristics

Demographic variables (such as sex, age, race, etc.) and medical history will be obtained; medical history will be reviewed and updated as necessary from the RELAY or REPLACE study, if available, for subjects previously enrolled in those studies.

Descriptive statistics will be used to summarize the baseline and demographic characteristics. Demographic and baseline characteristics to be presented include:

- age (in years, both as a continuous parameter and by categories of <45, 45-64, >=65)
- gender
- race
- ethnicity
- height (cm) at the baseline visit
- weight (kg) at the baseline visit
- body mass index (BMI) (kg/m^2) at the baseline visit

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [2], Version 13.0. The history will be summarized by system organ class (SOC) and preferred term (PT) within system organ class for the Safety Population, with both SOC and PT sorted alphabetically.

6.5. Measurements of Treatment Compliance

The data for study medication use are reported in the paper diary. Percent treatment compliance will be calculated as:

[100*doses administered / days on treatment], where days on treatment is calculated as (date of last dose - date of first dose) + 1.

Subjects will be considered compliant overall for study medication if the calculated compliance is ≥80% to ≤120%. Overall treatment compliance will be presented using descriptive statistics and the number and percentage of subjects who are ≥80% to ≤120% compliant will be presented for the Safety Population.

6.6. Extent of Exposure

6.6.1. Exposure during this (RACE) study

The extent of exposure is defined as the number of days on treatment, calculated as:

(date of last dose - date of first dose) + 1.

The date of the first dose is based on CRF entry. The date of the last dose will be based on information collected in the paper diary. The extent of exposure and the number of days that the dose was administered will be summarized. The extent of exposure will also be categorized into weeks (<1, 1-<4, 4-<8, 8-<16, 16-<24, 24-<32, 32-<40, 40-<48, 48-<52, ≥52) and tabulated. Exposure summaries will be presented for the Safety Population. Number of subjects at different dose level at EOT will be summarized as specified in section 8.7.2.

6.7. Analysis of Efficacy

All efficacy analyses will be conducted on the ITT Population.

Prescriptive analyses will be presented by visit in order to see how the status or value changes over time. The EOT status or value will be included as a separate time point in the summary.

Efficacy endpoints based on the calcium and/or calcitriol supplement will be derived using both the investigator prescribed data and subject diary data. Computation of daily calcium and calcitriol dose is specified in Section 7.4.1. Analysis based on the investigator prescribed data will be primary. Analysis based on the subject diary data will be considered as supportive.

6.7.1. Primary Analysis

As specified in the definition of efficacy endpoint, the subject must meet three conditions at Week 52 and/or EOT to be considered a responder. First, the subject's prescribed daily oral calcium supplementation should be reduced by at least 50% from baseline or an oral calcium dose of ≤ 500 mg; second, the subject's prescribed daily oral calcitriol supplementation dose should be reduced by at least 50% from baseline or an oral calcitriol dose of ≤ 0.25 µg. For the third condition, albumin-corrected total serum calcium concentration should be normalized or maintained compared to the baseline value (≥7.5 mg/dL) and does not exceed the ULN for the central laboratory. Different maintenance ranges for this third condition will be assessed in the sensitivity analysis (Section 8.7.5).

The calculation of daily calcium and calcitriol dose is specified in Section 7.4.1. The determination of responders using the subject diary dose data instead of prescribed dose will be used as one of the supportive analyses to the primary analysis.

The number and percentage of responder status will be presented. No formal statistical test will be done. A bar chart for percent of subjects who achieve responder status will be plotted. The percent of subjects who achieve calcium supplement response criterion, and the percent of subjects who achieve calcitriol supplement response criterion will also be plotted in a bar chart.

No statistical testing will be conducted to compare between group differences.

6.7.2. Other Analyses

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

The absolute and percentage changes from baseline will be summarized at each visit. No formal statistical test will be done.

Proportion of subjects achieving the primary endpoint at each visit

The number and percentage of subjects achieving the primary efficacy endpoint will be presented by visit. No formal statistical test will be done.

Mean percentage change from baseline in 24-hour urine calcium excretion

The absolute and percentage changes from baseline will be summarized by visit. No formal statistical test will be done.

Impact of calcium source (carbonate vs. citrate) on response

The number and percentage of subjects meeting the criteria of being responders will be presented by visit and by calcium source (carbonate vs. citrate). No formal statistical test will be done.

Impact of calcium-sparing diuretics on serum and urinary calcium

The number and percentage of subjects who use at least one calcium-sparing diuretics during the study will be presented.

The urinary calcium will be listed for subjects who received calcium-sparing diuretics during the study. No formal statistical test will be done.

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

Calcium phosphate product will be classified as normal (35 - 55 mg^2/dL^2), or abnormal (including low and high). The number and percentage of subjects with maintenance of a calcium phosphate product in the normal range will be presented by visit. No formal statistical test will be done.

Distribution of subjects by rhPTH[1-84] doses at the End of Treatment Visit

The number and percentage of subjects at different dose levels at the EOT visit will be summarized. No formal statistical test will be done.

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, and osteocalcin), PTH and ECP antibodies, and BMD by DXA

The absolute and percentage changes from baseline will be summarized by visit. No formal statistical test will be done. For DEXA, Z-scores will also be presented and summarized.

6.7.3. Subset Analyses

Subgroup analyses will be done as specified in Section 7.9.

6.7.4. Exploratory Analyses

There is no exploratory analysis planned.

6.7.5. Sensitivity Analyses

There is no sensitivity analysis planned for this study.

6.8. Analysis of Safety

All safety analyses will be performed on the Safety Population. All values presented in summaries will be observed values. No formal statistical comparisons are planned.

6.8.1. Adverse Events

Adverse events will be coded using MedDRA Version 13.0. Adverse event listings will provide the verbatim term as well as SOC and PT for each recorded event. A separate listing may be produced to provide the SOC, high level term, PT, and lower level term that are associated with each verbatim term.

Treatment emergent adverse events (TEAEs) are defined as AEs whose onset occurs, severity worsens or intensity increases after receiving the study medication of this study and <= 30 days after last dose of study drug. If any AE records contain only partial dates, these will be handled by imputation, as described in Section 7.4.3. AEs which are not treatment emergent will be flagged in listings.

An overview of TEAEs will be summarized using the number and percentage of subjects. The number of events will also be presented except for summaries by highest category. Categories summarized will include any TEAEs, severity of TEAEs (any and highest category), relationship of TEAEs to treatment (any and highest category), treatment emergent serious AEs (TESAEs), severity of TESAEs, relationship of TESAEs to treatment, TEAEs leading to discontinuation, and TEAEs leading to death.

Treatment emergent AEs will be summarized using number and percentage of subjects. Subject incidence for AEs within each SOC and PT will be presented, and the number of events will also be summarized except for summaries by highest category. Categories summarized will be the same as those summarized overall, except that no summary table will be provided for TEAEs leading to death.

Summaries of TEAEs and TESAEs will also be presented by PT. These presentations will be sorted by descending incidence.

Listings will be provided for serious adverse events (SAEs), AEs leading to discontinuation, and AEs leading to deaths.

The incidence of hypocalcemia and hypercalcemia will be identified by clinical preview. Prevalence of hypocalcemia and hypercalcemia will be assessed at all visits on the date of visit. The number of subjects with hypocalcemia and hypercalcemia and the number of episodes of hypocalcemia and hypercalcemia will be assessed for the overall trial.

6.8.2. Clinical Laboratory Evaluation

All laboratory parameters will be collected and processed via a central laboratory, with exception of all urine pregnancy tests and total serum calcium levels which will be done at investigator's local laboratories. Standard international (SI) units will be used for data presentation. Only scheduled lab parameters will be included in the lab summaries. All lab data will be included in the listings.

Quantitative results will be summarized for hematology, serum chemistry, thyroid function tests (levothyroxine and thyroid-stimulating hormone), creatinine clearance, urinary chemistries (24-hour urine calcium, phosphate, and sodium excretion), and selected urinalysis parameters (pH, specific gravity, and urobilinogen) by visit. Both actual values and change from baseline will be summarized. Additionally, shift tables will be presented, summarizing cross tabulations of low,

normal, and high based on the parameter normal range, from baseline to each post-baseline visit and EOT. Percentages for shift tables will be based on the number of subjects with both baseline and post-baseline values at each visit.

Categorical urinalysis findings and urine pregnancy results will be presented in appendix data listings only.

Estimated creatinine clearance rate will be re-calculated based on the Cockcroft-Gault (C-G) equation:

CLcr (mL/min) =[140 − age (years)]× weight (kg) {×0.85 for female subjects}/ (72 × serum creatinine (mg/dL)),

Estimated creatinine clearance rate will be summarized by stages as defined in Table 5.

Table 6. 1 Definition of the Stages of Clcr3

Stage	Description	CLcr (mL/min)
1	Control (normal) Glomerular filtration rate (GFR)	≥ 90
2	Mild decrease in GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	End Stage Renal Disease (ESRD)	<15 not on dialysis
		Requiring dialysis

The number and percentage of subjects with post-baseline results qualifying as markedly abnormal will be summarized by parameter. A listing of all values for the parameter which qualifies as markedly abnormal will be provided. Markedly abnormal laboratory criteria are defined in Table 6.

Table 6. 2 Markedly Abnormal Laboratory Criteria[4]

Lab parameter	Unit	Lower Limit	Upper Limit
Chemistry			
Albumin	g/L	<=20	>=90
Alkaline Phosphatase	U/L	NA	>2*ULN
ALT	U/L	NA	>3*ULN
Amylase	U/L	<=15	>=350
AST	U/L	NA	>3*ULN
Bilirubin	µmol/L	NA	>2*ULN
BUN	mmol/L	NA	>=10.7
Calcium (total)	mmol/L	<=2.1	>=3.0
Chloride	mmol/L	<=80	>=125
Cholesterol (total)	mmol/L	NA	>=12.9
Creatinine	µmol/L	NA	>=177
Creatinine clearance	ml/min	<=60	NA

Glucose	mmol/L	<=1.7	>=13.9
Gamma glutamyl transferase	U/L	NA	>=100
Phosphate	mmol/L	NA	>=2
Potassium	mmol/L	<=2.5	>=6.5
Sodium	mmol/L	<=120	>=165
Triglycerides	mmol/L	NA	>=5.6
Uric acid	µmol/L	NA	>=624 (males) >=505 (females)
Hematology			
Hematocrit	L/L	<=0.37 (males) <=0.32 (females)	>0.54 (males) NA (females)
Hemoglobin	g/L	<=115 (males) <=95 (females)	NA
Platelets	10^9/L	<=75	>=700
RBC count	10^{12}/L	<=2.5 (males) <=2.0 (females)	NA
WBC count	10^9/L	<=2.8	>=16.0
Basophils	L/L	NA	>=0.15
Eosinophils	L/L	NA	>=0.10
Lymphocytes	L/L	NA	>=0.80
Monocytes	L/L	NA	>=0.40
Neutrophils	L/L	<=0.15	NA
24-Hour urine			
Urine calcium	mg	NA	>300 for men >250 for women

NA=Not Applicable; ULN = Upper Limit of Normal

6.8.3. ECG Evaluations

The number and percentage of subjects with each type of ECG finding (Normal/Abnormal, Not Clinically Significant/Abnormal, and Clinically Significant) will be presented by visit.

Actual value and change from baseline for each ECG parameters (HR, PR, QRS, QT, QTcB, QTcF) will be presented by visit.

Potentially clinically significant QTc finding criteria are defined in Table 7. The number and percentage of subjects with post-baseline results qualifying as potentially significant will be summarized by parameter. A listing will present all values for a subject and parameter for cases where at least one value for that parameter was potentially significant.

Table 6. 3 Potentially Clinically Significant Post-Baseline ECG[5,6]

ECG Parameter	Potentially Clinical Significant Criterion
QTcB	≥ 500 ms
QTcF	≥ 500 ms
QTcB	An increase from Baseline of ≥ 60 ms or ≥ 30 ms
QTcF	An increase from Baseline of ≥ 60 ms or ≥ 30 ms

6.8.4. Vital Signs, Physical Findings, and Other Observations Related to Safety

In general, other by-visit safety findings will be analyzed and presented in a way similar to laboratory variables.

6.8.4.1. Vital Signs

Vital signs to be analyzed include sitting blood pressure, sitting heart rate, and body temperature.

Observed vital signs and changes from baseline will be summarized by visit.

The number and percentage of subjects with post-baseline results qualifying as markedly abnormal will be summarized by parameter. A listing will present all values for a subject and parameter for cases where at least one value for that parameter was markedly abnormal. Post-baseline markedly abnormal vital signs criteria are defined in Table 8.

Table 6. 4 Markedly Abnormal Post-Baseline Vital Signs[7]

Vital Sign Parameter	Abnormally Low	Abnormally High
Systolic blood pressure (mmHg)	A decrease from Baseline of ≥ 20 to a value ≤ 90	An increase from Baseline of ≥ 20 to a value ≥ 180
Diastolic blood pressure (mmHg)	A decrease from Baseline of ≥ 15 to a value ≤ 50	An increase from Baseline of ≥ 15 to a value ≥ 105
Heart Rate (bpm)	A decrease from Baseline of ≥ 15 to a value ≤ 50	An increase from Baseline of ≥ 15 to a value ≥ 120
Temperature (°C)	N/A	Value ≥ 38.3°C and ≥0.8°C increase from Baseline

6.8.4.2. Body Weight

The observed values and changes from baseline for body weight and BMI will be summarized at each visit.

6.8.4.3. Serum 25-Hydroxyvitamin D and Serum 1,25-dihydroxyvitamin D

The observed value and change from baseline in serum vitamin D levels (Serum 25-hydroxyvitamin D and Serum 1,25 vitamin D) will be summarized descriptively by visit.

6.8.4.4. Physical Examination Findings

Physical examination results will be presented in appendix data listings only.

6.8.4.5. PTH and ECP Antibodies

The number and percentage of subjects classified as having antibodies to PTH and ECP at baseline, Visit 5 (Week 24), Visit 7 (Week 40), and EOT will be tabulated for each treatment group.

If any subject tests positive for PTH-specific antibodies at the final visit, they will have follow-up blood draws for PTH antibody analysis at Months 2, 3, and 6 post-study. 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 investigator 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.

Subjects may remain on study if they develop PTH-specific antibodies during the study, providing that there are no concurrent AEs related to immunogenicity.

The number and percentage of subjects classified as having antibodies to PTH during the follow up period will also be provided, if applicable.

6.8.5. Concomitant Medications

Prior and concomitant medications will be coded to indication-specific ATC (Anatomic Therapeutic Chemical classification) and preferred name using the 1Q2010 version of the World Health Organization (WHO) Drug Dictionary.

Prior medications are defined as medications taken prior to the first dose of study medication in this study (RACE). Medications ongoing at the end of the previous study will be considered as prior medications. Concomitant medications are defined as medications that are taken during the treatment period of this study. Partial date imputation for medications is described in Section 7.4.3.

Prior and concomitant medication use will be summarized by level 2 ATC and preferred term using the number and percentage of subjects. Medications will be sorted alphabetically by ATC and preferred term within ATC. Subjects with multiple occurrences of a medication in ATC and preferred term will only be counted once within each ATC and preferred term. Since medications are coded to ATC by indication, preferred terms may appear under multiple ATCs.

7. Programming Conventions for Outputs

Partial dates should be presented as - -NOV1999 or - - - - - 1999 as needed.

Partial times should be presented as --:30 or 14:-- as needed.

Listings should be sorted according to the order of the columns.

8. Mock Tables, Listings and Graphs (TLG)

The mock TLGs will be provided in a separate document and will follow the numbering scheme described in ICH, E3, Guideline for Industry, "Structure and Content of Clinical Study Reports" for tables, subject data listings and graphs.

9. References

1. SAS Institute, Inc. SAS OnlineDoc Version Eight. SAS Institute, Inc, Cary, NC, 1999.

2. Medical Dictionary for Regulatory Activities (MedDRA), Version 13.0. IFPMA, International Committee on Harmonization. Geneva, Switzerland. 2010.

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4. Data on File. ACM Global Central Laboratory April 2010.

5. FDA Guidance Industry on E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs, October 2005; 9-11.

6. Data on File. ERT Cardiac Solutions 2012.

7. Prohealthsys.com Canada: Bates Physical Assessment and Web MD [updated 2010].

10. Appendix I: Summary of Changes Made to SAP version 1.0 Dated October 24, 2011

Changes that are editorial in nature (to correct typographical errors, errors in formatting, or to modify the language) are not included.

Section No.	SAP Version 1.0	SAP Amendment 1	Change Justification
Title	A **12-Month** Open-label Study …	A **Long Term** Open-label Study …	In compliance to Protocol Amendment 3, Version 4.0
Section 5.1		Add a bullet 'At the end of Week 52, subjects will be invited to extend their study drug regimen until at least October 2013. During this time, subjects will return to the clinic for interim visits every 2 months (Months 14, 16, 18, etc).	In compliance to Protocol Amendment 3, Version 4.0
Section 5.1		Reordering of study visits to accommodate the long-term extension.	In compliance to Protocol Amendment 3, Version 4.0
Section 5.1	Figure 1	Replaced by Figure 1.1 and Figure 1.2	In compliance to Protocol Amendment 3, Version 4.0
Section 5.3	Approximately 40 subjects are anticipated to be enrolled.	Approximately 50 subjects are anticipated to be enrolled.	In compliance to Protocol Amendment 3, Version 4.0
Section 6.1	Table 1 Schedule of Study Evaluations and Procedures	Replaced by Table 1, Table 2, and Table 3	In compliance to Protocol Amendment 3, Version 4.0
Section 6.1		Add lab assessments 'Serum 1,25-dihydroxyvitamin D levels' and ECP antibody	In compliance to Protocol Amendment 3, Version 4.0
Section 6.2	Section header: Primary Efficacy Endpoint	Section header; Efficacy Endpoint	There is no primary efficacy endpoint defined in protocol.
Section 6.2	The proportion of subjects in whom the following three conditions are fulfilled at Week 52 (Visit 9):	The proportion of subjects in whom the following three conditions are fulfilled at Week 52 (Visit 9) and at the End of Treatment:	In compliance to Protocol Amendment 3, Version 4.0
Section 6.3	Section header: Secondary Efficacy Endpoints	Section header: Other Efficacy Endpoints	There is no secondary efficacy endpoints defined in protocol.
Section 7.5	An interim database with a cut off date of December 31, 2011 will be used to provide the NDA safety updates.	An interim study report will be completed to look at safety and efficacy compiled through 31 May 2013.	Project team decision.