PROTOCOL: SHP634-402

TITLE:	A Phase 4, Open-Label, Single-Center Clinical Study of Extended use of rhPTH(1-84) in Hypoparathyroidism
DRUG:	rhPTH(1-84)
IND	076514
BLA:	125511
SPONSOR	Shire Human Genetic Therapies, Inc. 300 Shire Way, Lexington, MA 02421 USA
PRINCIPAL/ COORDINATING INVESTIGATOR:	[redacted], MD
PROTOCOL HISTORY:	Original Protocol: 27 May 2016

PROTOCOL SIGNATURE PAGE

Sponsor's (Shire) Approval

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

Investigator's Acknowledgement

I have read this protocol for Shire Study SHP634-402.

Title: A Phase 4, Open-Label, Single-Center Clinical Study of Extended use of rhPTH(1-84) in Hypoparathyroidism.

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

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

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

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

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

Investigator Name and Address: _____
(please hand print or type) _____

Signature: _____ **Date:** _____

SUMMARY OF CHANGES FROM PREVIOUS VERSION

Not applicable. This is Version 1.0 of the protocol.

EMERGENCY CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator must fax or e-mail the Shire Clinical Study Serious Adverse Event and Non-serious Adverse Events (AEs) Required by the Protocol Form within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department. Applicable fax numbers and e-mail address can be found on the form (sent under separate cover). A copy of this form must also be sent to the Shire Medical Monitor by fax or e-mail using the details below.

For protocol- or safety-related issues during normal business hours (9 am to 5 pm Eastern Standard Time), the investigator must contact the Shire Medical Monitor:

[redacted], MD
Email: [redacted]
Phone: [redacted]
Mobile: [redacted]

[redacted], MD
Email: [redacted]
Phone: [redacted]
Mobile: [redacted]

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Telephone numbers:

Shire

Lexington, MA (USA)

[redacted]

TABLE OF CONTENTS

PROTOCOL SIGNATURE PAGE 2
SUMMARY OF CHANGES FROM PREVIOUS VERSION 3
EMERGENCY CONTACT INFORMATION 4
PRODUCT QUALITY COMPLAINTS 5
TABLE OF CONTENTS 6
LIST OF TABLES 10
LIST OF FIGURES 10
LIST OF APPENDICES 10
ABBREVIATIONS 11
STUDY SYNOPSIS 13
STUDY SCHEDULE 16
1. BACKGROUND INFORMATION 18
1.1 Indication and Current Treatment Options 18
1.2 Product Background 19
1.2.1 Preclinical Information 19
1.2.2 Clinical Information 20
2. STUDY OBJECTIVES AND PURPOSE 22
2.1 Rationale for the Study 22
2.2 Study Objectives 22
2.2.1 Primary Objectives 22
2.2.2 Secondary Objectives 22
3. STUDY DESIGN 23
3.1 Study Design and Flow Chart 23
3.2 Duration and Study Completion Definition 25
3.3 Sites and Regions 25
3.4 Discussion of Study Design 25
4. STUDY POPULATION 27
4.1 Inclusion Criteria 27
4.2 Exclusion Criteria 27
4.3 Reproductive Potential 28
4.3.1 Female Contraception 28
4.3.2 Male Contraception 28
4.4 Discontinuation of Subjects 28
4.4.1 Subject Withdrawal Criteria 28
4.4.2 Reasons for Discontinuation 28

4.4.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit 29
5. PRIOR AND CONCOMITANT TREATMENT 30
5.1 Prior Treatment 30
5.2 Concomitant Treatment 30
5.2.1 Permitted Treatment 30
5.2.2 Prohibited Treatment 30
5.2.3 Active Vitamin D, Calcium, Native Vitamin D, and Magnesium Supplementation 30
5.2.3.1 Active Vitamin D 30
5.2.3.2 Native Vitamin D 30
5.2.3.3 Calcium 31
5.2.3.4 Magnesium 31
5.2.4 Thiazide Diuretics 31
6. INVESTIGATIONAL PRODUCT 32
6.1 Identity of Investigational Product 32
6.1.1 Blinding the Treatment Assignment 32
6.2 Administration of Investigational Product(s) 32
6.2.1 Allocation of Subjects to Treatment 33
6.2.2 Dosing 33
6.2.3 Unblinding the Treatment Assignment 33
6.3 Labeling, Packaging, Storage, and Handling 33
6.3.1 Packaging 33
6.3.2 Labeling 33
6.3.3 Storage 34
6.3.4 Special Handling 34
6.4 Drug Accountability 35
6.5 Subject Compliance 35
7. STUDY PROCEDURES 37
7.1 Study Schedule 37
7.1.1 Baseline Visit (Visit 1) 37
7.1.2 Treatment Period 38
7.1.2.1 Visit 2, (Month 6) 38
7.1.2.2 Visit 3 (Month 12) 38
7.1.2.3 Visit 4 (Month 18) 38
7.1.2.4 EOT Visit (Month 24) 38
7.1.3 Additional Care of Subjects after the Study 38
7.2 Study Evaluations and Procedures 38
7.2.1 Demographic and Other Baseline Characteristics 38

7.2.2 Efficacy 39
7.2.2.1 Biochemical Evaluations 39
7.2.2.2 Hypoparathyroidism Multisymptom Questionnaire 39
7.2.2.3 Cognition Tool 39
7.2.2.4 FACIT Fatigue Scale 39
7.2.2.5 HADS Assessment 39
7.2.2.6 Short Form Health Survey-36 39
7.2.2.7 Bone Mineral Density 40
7.2.2.8 Bone Biopsy 40
7.2.2.9 [redacted] 40
7.2.3 Safety 40
7.2.3.1 Adverse Event Collection 40
7.2.3.2 Clinical Laboratory Evaluations 41
7.2.3.3 Pregnancy Test 42
7.2.3.4 PTH Antibodies 42
7.2.3.5 Vital Signs 43
7.2.3.6 Physical Examination 43
8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT 44
8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events 44
8.1.1 Severity Categorization 44
8.1.2 Relationship Categorization 45
8.1.3 Outcome Categorization 45
8.1.4 Symptoms of the Disease Under Study 45
8.1.5 Clinical Laboratory and Other Safety Evaluations 45
8.1.6 Pregnancy 46
8.1.7 Abuse, Misuse, Overdose, and Medication Error 46
8.2 Serious Adverse Event Procedures 47
8.2.1 Reference Safety Information 47
8.2.2 Reporting Procedures 47
8.2.3 Serious Adverse Event Definition 48
8.2.4 Serious Adverse Event Collection Time Frame 48
8.2.5 Serious Adverse Event Onset and Resolution Dates 48
8.2.6 Fatal Outcome 49
8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting 49
9. DATA MANAGEMENT AND STATISTICAL METHODS 50
9.1 Data Collection 50
9.2 Clinical Data Management 50

9.3 Data Handling Considerations....50
9.4 Statistical Analysis Process....50
9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee....50
9.6 Sample Size Calculation and Power Considerations....51
9.7 Study Population....51
9.8 Efficacy Analyses....51
9.8.1 Primary Efficacy Endpoint....51
9.8.2 Secondary Efficacy Endpoints....51
9.8.3 Exploratory Efficacy Endpoints....51
9.9 Safety Analyses....52
9.10 Other Analyses....52
9.10.1 Health-related Quality of Life Analyses....53
10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES....54
10.1 Sponsor's Responsibilities....54
10.1.1 Good Clinical Practice Compliance....54
10.1.2 Public Posting of Study Information....54
10.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees....54
10.1.4 Study Suspension, Termination, and Completion....54
10.2 Investigator's Responsibilities....55
10.2.1 Good Clinical Practice Compliance....55
10.2.2 Protocol Adherence and Investigator Agreement....55
10.2.3 Documentation and Retention of Records....56
10.2.3.1 Case Report Forms....56
10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents....56
10.2.3.3 Audit/Inspection....56
10.2.3.4 Financial Disclosure....57
10.3 Ethical Considerations....57
10.3.1 Informed Consent....57
10.3.2 Institutional Review Board or Ethics Committee....57
10.4 Privacy and Confidentiality....58
10.5 Study Results / Publication Policy....59
11. REFERENCES....61

LIST OF TABLES

Table 1-1: Schedule of Study Assessments 16
Table 6-1: Recommended Adjustments for Active Vitamin D and Calcium Supplements 32

LIST OF FIGURES

Figure 3-1: Study Design Flow Chart 24

LIST OF APPENDICES

Appendix 1 Hypoparathyroidism Symptom Diary 62
Appendix 2 FACT-Cognitive Function ENG 67

ABBREVIATIONS

ACSC	albumin-corrected total serum calcium
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β-HCG	beta-human chorionic gonadotropin
BLA	Biologics License Application
CI	confidence interval
CRA	Clinical Research Associate
CRF	case report form
CRO	contract research organization
CSR	clinical study report
DXA	dual-energy x-ray absorptiometry
EC	Ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
eGRF	estimated Glomerular Filtration Rate
EMA	European Medicines Agency
EU	European Union
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-Cog	Functional Assessment of Cancer Therapy - Cognitive Function
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
HADS	Hospital Anxiety and Depression Scale
HIPAA	Health Insurance Portability and Accountability Act
HPT	Hypoparathyroidism
HRpQCT	high-resolution peripheral quantitative computerized tomography
ICF	informed consent form
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
MedDRA	Medical Dictionary of Regulatory Activities

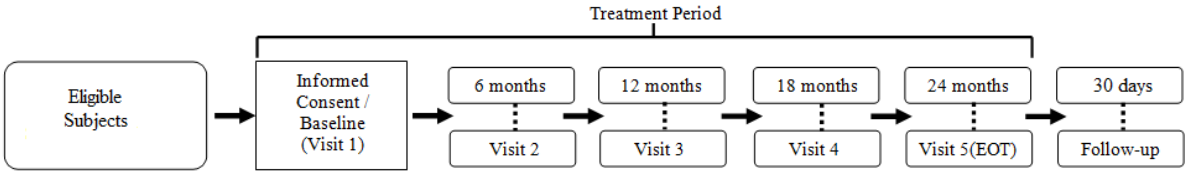
mmHg	millimeters of mercury
PTH	Parathyroid hormone
QD	once daily
RBC	red blood cell
rhPTH(1-84)	recombinant human parathyroid hormone
SAE	serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SC	subcutaneous
SF-36	36-item Short Form Health Survey
SOC	system organ class
TEAE	treatment-emergent adverse event
US	United States
WBC	white blood cell

STUDY SYNOPSIS

Protocol number: SHP634-402	**Drug:** rhPTH(1-84)
Title of the study: A Phase 4, Open-Label, Single-Center Clinical Study of Extended use of rhPTH(1-84) in Hypoparathyroidism	
Number of subjects (total and for each treatment arm): The subject population anticipated in this study is up to 50 subjects. All subjects are exclusively from the core study (HEXT: The Hypoparathyroidism Studies, EXTended: The Effect of PTH on the Skeleton in Hypoparathyroidism) Protocol AAAE0544 at Columbia University Medical Center, and will all receive active rhPTH(1-84) treatment.	
Investigator(s): Single site located at: Columbia University New York, NY 10032	
Site(s) and Region(s): Columbia University New York, NY 10032	
Study period (planned): 24 months	**Clinical phase:** 4
Objectives: **Primary:** • To evaluate albumin-corrected serum calcium while on rhPTH(1-84) treatment **Secondary:** • To evaluate urinary calcium excretion and serum phosphate while on rhPTH(1-84) treatment • To evaluate calcium and active vitamin D supplement doses while on rhPTH(1-84) treatment • To evaluate disease-related symptoms, perception of cognitive function, and health-related quality-of-life associated with long-term rhPTH(1-84) treatment • To evaluate the skeletal actions of rhPTH(1-84): bone turnover (markers), architecture, and histology (biopsy)	
Rationale: Chronic hypoparathyroidism (HPT) is a life-long and irreversible disease for which the chronic administration of rhPTH(1-84) is a potential treatment option. Thus, long-term safety and efficacy data are important in evaluating the proper use of this treatment option in clinical practice.	
Investigational product, dose, and mode of administration: rhPTH(1-84); 25, 50, 75, and 100 μg for once daily subcutaneous injection to the thigh via a multidose pen injector device. The dose will be individualized to achieve a serum calcium level in the lower half of the normal range.	

Methodology:

Subjects enrolled are currently or were previously enrolled in the core study (AAAE0544) and have maintained uninterrupted therapy with rhPTH(1-84). Study visits will be scheduled every 6 months up to the 24-month end of study visit. Specific procedures at each study visit are summarized in Table 1- 1. A schematic of the study design is provided below:



Inclusion and exclusion criteria:

Inclusion Criteria:

The subject must meet all of the following criteria to be eligible

1. Subjects that are currently or previously enrolled in the core study (AAAE0544) and have maintained uninterrupted therapy with rhPTH(1-84) (transient interruptions of up to 1 month continuously off treatment may be allowed).
2. Signed and dated informed consent form (ICF).
3. Adult men and women 18 to 85 years of age.
4. History of hypoparathyroidism for at least 12 months prior to rhPTH(1-84) treatment, defined by the requirement for supplemental calcium and/or active vitamin D to maintain serum calcium along with an undetectable or insufficient PTH concentration.
5. Able to perform daily subcutaneous self-injections of study medication (or have designee perform injection).
6. Willingness and ability to understand and comply with the protocol. Women must agree to pregnancy testing and acceptable methods of contraception, as detailed in the protocol.

Exclusion Criteria:

Subjects will be excluded from the study if **any** of the following exclusion criteria are met:

1. The subject is treated or has been treated with any investigational drug, aside from rhPTH(1-84), within 30 days of consent.
2. As assessed by the investigator, the subject has a safety or medical issue that contraindicates participation in the study.
3. The subject and/or the subject's parent(s) or legally-authorized representative(s) is unable to understand the nature, scope, and possible consequences of the study.
4. The subject is unable to comply with the protocol, eg, uncooperative with protocol schedule, refusal to agree to all of the study procedures, inability to return for evaluations, or is otherwise unlikely to complete the study, as determined by the investigator or the medical monitor.
5. The subject is pregnant or lactating.
6. Subjects who are at increased baseline risk for osteosarcoma such as subjects with Paget's disease of bone or unexplained elevations of alkaline phosphatase, subjects with hereditary disorders predisposing to osteosarcoma or subjects with a prior history of external beam or implant radiation therapy involving the skeleton.

Maximum duration of subject involvement in the study:

Each study visit has a threshold of ±1 month with a total treatment period of 24 months. A follow-up phone call to assess safety will occur 30 days after the end of treatment visit.

Endpoints and Statistical Analysis:

Primary Efficacy Endpoint:

- Albumin-corrected serum calcium over time

Secondary Efficacy Endpoint(s):

- Urinary calcium and serum phosphate over time
- Calcium and active vitamin D supplement doses over time
- HPT Disease-related symptoms (Multisymptom questionnaire), FACT-Cog assessment, FACIT (Fatigue Scale [Version 4]), and HADS (Hospital Anxiety and Depression Scale)
- Health-related quality-of-life measured with SF-36 survey over time
- Bone turnover (markers), architecture, and histology (biopsy) over time

Exploratory Efficacy Endpoint:

- [redacted]

Safety Endpoints:

- AEs including SAEs
- Symptoms of hypoparathyroidism
- Vital signs including body temperature, heart rate, respiratory rate, and blood pressure (systolic and diastolic)
- Estimated Glomerular Filtration Rate (eGFR) and creatinine clearance
- Measurements of antibodies to parathyroid hormone (PTH)
- Laboratory safety data (eg, clinical chemistry, hematology, and urinalysis)

Although no formal hypotheses are being tested, 95% confidence intervals (CI) will be provided as appropriate. 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.

Safety data, including laboratory tests and vital signs assessments, will be summarized by visit. AEs will also be collected and summarized. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from the SHP634-402 baseline, if applicable. Frequency counts will be compiled for classification of qualitative safety data (for example shift from baseline according to lab normal range, AEs related to treatment, level of severity, etc.).

Other Analyses:

A retrospective analysis of historical data captured from the medical records of subjects (eg, since the start of rhPTH(1-84) treatment) will be conducted. Data collected will include but is not limited to, medical history and clinical laboratory data. There are no formal hypotheses testing for the retrospective analysis. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from the pre-rhPTH(1-84) treatment baseline, if applicable.

Interim Analysis:

A retrospective analysis of historical data captured from the medical records of subjects (eg, since the start of rhPTH(1-84) treatment) will be conducted. Data collected will include but is not limited to, medical history and clinical laboratory data. There are no formal hypotheses testing for the retrospective analysis. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from the pre-rhPTH(1-84) treatment baseline, if applicable.

STUDY SCHEDULE

Table 1-1: Schedule of Study Assessments

Study Period	**Baseline**	**Maintenance Dosing Period**			**End of Treatment**
Visit	**Visit 1**	**Visit 2-4**			**EOT Visit[a]**
Study Month	**0**	**6**	**12**	**18**	**24**
Study Procedures		**±1 month**			
Informed Consent[b]	X				
Inclusion/Exclusion	X				
Medical history and demography	X				
Prior/concomitant medications	X	X	X	X	X
Physical examination	X		X		X
Vital signs[c]	X	X	X	X	X
Hematology	X				X
Serum chemistry[d]	X	X	X	X	X
Serum TSH	X				
Serum pregnancy test[e]	X				
Urine pregnancy test	X	X	X	X	X
FSH level[f]	X				
Serum PTH antibodies[g]	X	X	X	X	X
Serum 25-hydroxyvitamin D	X	X	X	X	X
Serum 1,25-dihydroxyvitamin D	X	X	X	X	X
Bone turnover markers	X	X	X	X	X
Urinalysis (dipstick)	X				X
24-hour urine[h]		X	X	X	X
Bone mineral density DXA	X	X	X	X	X
Bone mineral density HRpQCT	X	X	X	X	X
Bone biopsy (optional)			X		
HPT multisymptom questionnaire	X	X	X	X	X
FACT-Cog assessment	X	X	X	X	X
SF-36	X		X		X
FACIT Fatigue Scale	X	X	X	X	X
HADS assessment	X	X	X	X	X
[redacted]	X	X	X	X	X
AE/SAE monitoring	X	X	X	X	X
Dispense/Account for study drug	X	X	X	X	X
Collection of unused study drug & injection pen					X
Record any use of Calcium, Calcitriol, and/or Vitamin D supplements	X	X	X	X	X

Abbreviations: AE = Adverse event; DXA = dual-energy x-ray absorptiometry; HPT = Hypoparathyroidism; SAE=Serious adverse event; SF-36 = 36-Item Short Form Health Survey; HRpQCT = High-resolution peripheral quantitative computerized tomography.

[a] For subjects not continuing rhPTH[1-84] treatment, see Section 7.1.3.

[b] Remote consent allowed. Consent procedure must be complete prior to completing any Baseline assessments (can occur at Baseline Visit as long as complete prior to assessments).

[c] Vitals signs include: blood pressure, heart rate, body temperature, and respiration rate.

[d] Serum chemistry panel includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, calcium, phosphate, magnesium, albumin, ALT, AST, and ALP.

[e] Pregnancy tests for females of childbearing potential.

[f] FSH level required for newly menopausal women.

Table 1-1: Schedule of Study Assessments

Study Period	Baseline	Maintenance Dosing Period			End of Treatment
Visit	Visit 1	Visit 2-4			EOT Visit[a]
Study Month	0	6	12	18	24
Study Procedures		±1 month			

[g] Blood samples for antibody testing should be collected prior to dosing with PTH[1-84]. Any subject with newly developed PTH-specific antibodies at the end of treatment visit may require follow up. This will be discussed as necessary by the PI and medical monitor on a case-by-case basis.

[h] 24-hour urine collection includes urine calcium, creatinine, phosphate, magnesium and sodium analyses. Urine volume will be recorded. The 24-hour urine collections should generally be performed by the subject within 2 weeks prior to or within 2 days follow a study visit. These 24-hour urine collections may be analyzed in a local laboratory. To the greatest extent possible, the same laboratory should analyze the 24-hour urine collections throughout the study. Results from the last 24-hour urine collection obtained in Columbia protocol AAAE0544 will be used as the baseline assessment in this study. At the beginning of the study, the investigator should recommend an individualized target dietary (non-supplement) calcium intake for each subject to ingest consistently throughout the study on 24-hour urine collection days. When collecting 24-hour urine specimens subjects should be instructed to take their currently prescribed calcium, vitamin D (both parent and active) and rhPTH(1-84) doses.

1. BACKGROUND INFORMATION

Hypoparathyroidism (HPT) is a rare disorder characterized by hypocalcemia in the presence of inappropriately low or undetectable levels of circulating parathyroid hormone (PTH) (Avioli 1974; Haussler and Cordy 1982, Shoback 2008) The most frequent cause of hypoparathyroidism is resection of, or damage to, parathyroid glands during neck surgery (eg, thyroidectomy), although multiple other genetic, metabolic and congenital etiologies exist. Hypoparathyroidism occurs in about 0.9% to 6.6% of thyroidectomies, with higher rates associated with more complicated interventions (Shoback 2008; Thomusch et al. 2003; Zarnegar et al. 2003; Page and Strunski 2007). In 1 year spanning 2007-2008 (Powers et al. 2013) the incidence of chronic hypoparathyroidism (≥6 months) was said to be approximately 60,000 subjects in the United States (US), which rises to approximately 117,000 if the transient hypoparathyroid population is included (≤6 months). The same authors suggest that, of those 117,000 transient hypoparathyroid subjects, about 5% will become chronic.

Parathyroid hormone is an 84-amino acid protein that is secreted by the parathyroid glands. PTH has a variety of important physiological functions that are outlined below to explain the effects of absent or deficient PTH levels. Parathyroid hormone functions to help regulate bone metabolism and serum levels of calcium and phosphate. In general, if serum calcium concentrations decrease, the parathyroid glands consequently increase PTH secretion, and, if serum calcium concentrations increase, the parathyroid glands consequently reduce PTH secretion. The parathyroid glands sense the level of extracellular calcium at the surface of the parathyroid cell and adjust the synthesis and secretion of PTH accordingly.

Acute symptoms of hypoparathyroidism, linked mainly to the hypocalcemia, are generally reversible. The key symptoms associated with hypocalcemia involve mainly the neuromuscular system: numbness, paresthesias, twitching, and tetany. More serious and potentially life threatening effects of hypocalcemia such as seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm are also recognized in hypoparathyroidism (Behaghel and Donal 2011). Hypoparathyroidism has also been linked to effects on mood and ideation (Arlt et al. 2002; Velasco et al. 1999).

The kidneys are especially vulnerable in subjects with hypoparathyroidism. Circulating PTH promotes renal calcium reabsorption, especially at the level of the distal convoluted tubule (Blaine et al. 2015). In the absence of PTH, calcium can be over-excreted through the kidneys (Shoback 2008), leading to hypercalciuria which, together with a high-calcium-phosphate product, can potentially lead to nephrocalcinosis and kidney stones and, ultimately, to renal impairment (Blaine et al. 2015).

For further details see the recombinant human PTH (rhPTH[1-84]) investigator brochure.

1.1 Indication and Current Treatment Options

Prior to 2015, in the absence of an approved PTH replacement therapy, management of hypoparathyroidism consisted of supplemental oral calcium and active vitamin D in pharmacological doses sufficient to maintain the serum calcium level without the disabling symptoms of hypocalcemia. In order to improve the absorption of calcium from the

gastrointestinal tract, pharmacological supplementation with active forms of vitamin D (eg, 1,25-dihydroxyvitamin D_3 [$1,25(OH)_2D_3$], calcitriol, 1,25-dihydroxycholecalciferol or α-calcidol [$1(OH)D_3$]) is also required. Since PTH also functions in the kidney to stimulate the conversion of $25(OH)D_3$, the major circulating form of vitamin D, to the active vitamin D hormone ($1,25[OH]_2D_3$), the relative lack of circulating PTH results in a reduction of the production of active vitamin D. Thus, exogenous active vitamin D overcomes the synthetic block in endogenous production of the active vitamin D hormone in hypoparathyroidism. Together, supplemental oral calcium and active vitamin D have formed the mainstay of current treatment of subjects with hypoparathyroidism. The additional calcium load that results from supplementation with exogenous calcium and active vitamin D contributes to the hypercalciuria and renal risks often noted in patients with hypoparathyroidism.

In an effort to limit the extent and effect of hypercalciuria, thiazide diuretics can be helpful since they promote renal calcium reabsorption. However, thiazides are associated with their own adverse events (AEs) including hypokalemia and, more importantly, have no proven long-term effect to reduce hypercalciuria or kidney damage or improve the safety profile in this patient population (Shoback 2008). Although an accepted adjunct to the use of calcium and active vitamin D in hypoparathyroidism, thiazides are prescribed to only a minority of hypoparathyroid patients.

The investigational product (rhPTH[1-84]) is a recombinant human PTH that is identical in structure to endogenous human PTH, a single-chain polypeptide consisting of 84 amino acid residues and is manufactured using a strain of Escherichia coli modified by recombinant DNA technology. rhPTH(1-84) was approved for marketing in the US on 23 January 2015 under the brand name Natpara® as a once-daily injectable dose as an adjunct to calcium and vitamin D to control hypocalcemia in patients with hypoparathyroidism.

1.2 Product Background

1.2.1 Preclinical Information

A total of 46 in vivo studies in mouse, rat, rabbit, dog, and rhesus and cynomolgus monkeys have evaluated the pharmacokinetics, pharmacodynamics and toxicology of rhPTH(1-84) at doses ranging from 0.1 to 10,000 µg/kg given as single doses or as daily doses for up to 2 years. In the vast majority of studies, rhPTH(1-84) was administered by subcutaneous (SC) injection, the intended route of administration of rhPTH(1-84) in humans. A total of 7 in vitro pharmacology and toxicology studies have been performed.

In male and female rats, the administration of PTH was associated with an increase in the incidence of osteosarcoma. These data were interpreted as an increased risk for osteosarcoma in the clinic. Therefore, administration of rhPTH(1-84) should be avoided in subjects who are considered to be at increased risk for osteosarcoma (including those with Paget's disease of bone or unexplained elevations of alkaline phosphatase, subjects with hereditary disorders predisposing to osteosarcoma or subjects with a history of prior external beam or implant radiation therapy involving the skeleton).

Currently available results from animal reproductive toxicology studies suggest that rhPTH(1-84) is not associated with significant fetal or neonatal toxicity; however, the safety of rhPTH(1-84) in pregnant or nursing women is not established.

For full details see the rhPTH(1-84) investigator brochure.

1.2.2 Clinical Information

Study CL1-11-040 (REPLACE) was a double-blind, placebo controlled study of once daily (QD) SC administration of 50 μg to 100 μg of rhPTH(1-84). The 3-tiered primary endpoint included ≥ 50% reduction from baseline in oral calcium supplementation, ≥ 50% reduction from baseline in active Vitamin D, and albumin-corrected total serum calcium (ACSC) concentration maintained or normalized compared to baseline (not exceeding upper limit of normal). The 3-tiered endpoint was met in 54.8% of rhPTH(1-84) subjects compared to 2.5% of placebo subjects ($p<0.001$). Long-term, open-label studies have supported these findings with subjects maintaining the physiologic benefit derived from rhPTH(1-84) treatment. One extension study, PAR-C10-008 (RACE), is ongoing with some subjects receiving treatment for more than 3 years.

In clinical trials, rhPTH(1-84) significantly reduced the serum calcium-phosphate product. In these studies, hypercalciuria was defined as an excretion of calcium in the urine greater than 300mg per 24 hours. Data from the REPLACE Study and the long-term open label study, RACE, show that rhPTH(1-84) has a calcium-sparing effect, consistent with the reduction of urinary calcium excretion seen in a previous pharmacokinetic/pharmacodynamic study (C09-002) of single dose administration of rhPTH(1-84) in subjects with hypoparathyroidism in comparison with calcitriol administration.

The Phase 3 clinical study, REPLACE, was the largest, randomized, placebo controlled clinical study conducted in hypoparathyroidism population and was the pivotal study demonstrating that rhPTH(1-84) is effective in maintaining serum calcium levels and enabling significant decreases in active vitamin D and oral calcium doses. REPLACE also established the rhPTH(1-84) dose and dose titration and evaluated the physiologic effects of PTH replacement on serum calcium, serum phosphate, urinary calcium excretion and bone turnover markers. Eighty-four subjects were evaluated in the active treatment group and 40 subjects received placebo. Subjects received at a flexible dose range of 50 to 100 μg SC in the thigh once daily for 6 months. The study met the primary efficacy triple endpoint, with a statistically higher responder rate (54.8%) versus placebo (2.5%). To meet the primary endpoint a subject had to fulfill all 3 conditions as follows: a 50% or greater reduction in oral calcium requirement, a 50% or greater reduction in active vitamin D therapy and an ACSC concentration that was maintained within a range of 7.5 to 10.6 mg/dL.

A review of safety data across the hypoparathyroidism program indicated that rhPTH(1-84) administered in the dose range of 25 to 100 μg SC QD is safe for use for the treatment of hypoparathyroidism. Very common adverse reactions (ie, reported in at least 1 in every 10 subjects) included hypocalcemia, hypercalcemia, headaches, diarrhea, vomiting, and hypercalciuria. Common adverse reactions (ie, reported in at least 1 in every 100 subjects, but less than 1 in every 10 subjects) included hypomagnesemia, anxiety symptoms, palpitations, flushing, coughing and associated symptoms, neck pain, pollakiuria, chest pain, thirst, blood 25-hydroxycholecalciferol decreased, and blood alkaline phosphatase increased.

There was no suggestion that rhPTH(1-84) causes drug-induced liver injury in humans. There were no renal-related AEs or abnormalities in renal function tests or urinalysis tests in clinical studies apart from changes expected from the mechanism of action of rhPTH(1-84). Despite significant increases in total serum calcium levels and improved calcium homeostasis, treatment with rhPTH(1-84) did not result in worsening of hypercalciuria.

Because of the potential risk of osteosarcoma, rhPTH(1-84) is recommended only for subjects who cannot be well controlled on calcium supplements and active forms of vitamin D alone. Additional risks include extensions of the pharmacologic effects of PTH including hypercalcemia. Post-treatment hypocalcemia following the abrupt withdrawal of rhPTH(1-84) can be particularly problematic. Following sustained withdrawal of rhPTH(1-84), serum calcium levels must be carefully monitored with reinstatement of appropriate dosages of oral calcium and active vitamin D. No on-treatment events of hypocalcemia occurred following incidental missed doses of rhPTH(1-84) during any of the clinical studies, however subjects should be advised to take their rhPTH(1-84) dose as soon possible following a missed dose and to take oral calcium.

Always refer to the latest version of the rhPTH(1-84) investigator's brochure for the overall risk/benefit assessment and the most accurate and current information regarding the drug metabolism, pharmacokinetics, efficacy and safety of rhPTH(1-84).

2. STUDY OBJECTIVES AND PURPOSE

2.1 Rationale for the Study

Recombinant human parathyroid hormone has been developed as an adjunct to calcium and vitamin D to control hypocalcemia in hypoparathyroidism subjects who cannot be well controlled with calcium and vitamin D supplementation alone. Although the development of a novel therapeutic agent for the treatment of hypoparathyroidism is encouraging, it is important to gain knowledge about the efficacy and safety of long-term use of rhPTH(1-84) due to the chronic nature of the condition.

The AAAE0544 cohort has the longest known duration of rhPTH(1-84) therapy for the treatment of hypoparathyroidism to date. This protocol is designed to extend this experience and to provide additional data on the long-term safety and efficacy of rhPTH(1-84).

2.2 Study Objectives

2.2.1 Primary Objectives

- To evaluate albumin-corrected serum calcium while on rhPTH(1-84) treatment

2.2.2 Secondary Objectives

- To evaluate urinary calcium excretion and serum phosphate while on rhPTH(1-84) treatment
- To evaluate calcium and active vitamin D supplement doses while on rhPTH(1-84) treatment
- To evaluate disease-related symptoms, perception of cognitive function, and health-related quality-of-life associated with long-term rhPTH(1-84) treatment.
- To evaluate the skeletal actions of rhPTH(1-84): bone turnover (markers), architecture, and histology (biopsy)

3. STUDY DESIGN

3.1 Study Design and Flow Chart

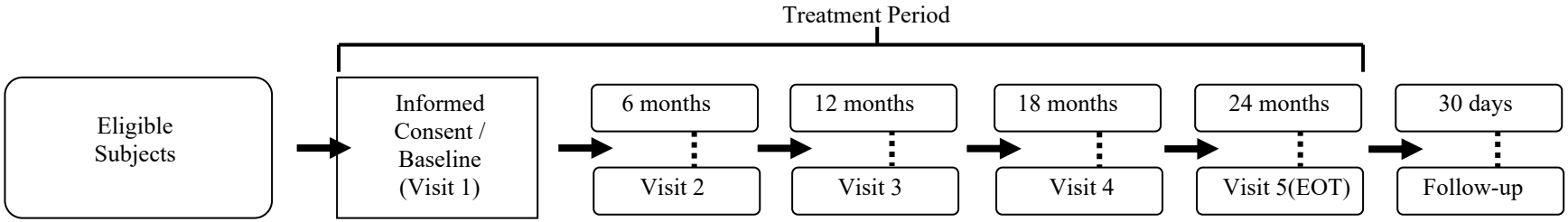
Protocol SHP634-402 is a single-center, open-label, single arm, Phase 4 study of rhPTH(1-84) treatment in adult subjects (up to 50 subjects) diagnosed with hypoparathyroidism.

Pre-study treatment, laboratory data, and medical history information for enrolled subjects will be verified.

Subjects will be treated with rhPTH(1-84) for a two-year treatment period with study visits scheduled every 6 (±1) months.

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

Figure 3-1: Study Design Flow Chart



3.2 Duration and Study Completion Definition

The subject's maximum duration of participation in the study is approximately 25 months. The study Completion Date is defined as the date the final subject completes their final protocol-defined assessment. Please note that this includes the follow-up phone contact 30 days following the EOT(Month 24) visit.

3.3 Sites and Regions

This is a single-center study that will be conducted at Columbia University Medical Center, New York, NY.

3.4 Discussion of Study Design

This protocol is only intended for those subjects who participated and were treated in the AAAE0544 study. Limiting enrollment to subjects from the core study (AAAE0544) will allow this study to provide long-term safety and efficacy data.

Administration via injection to the thigh has been shown to be a safe and effective delivery method of rhPTH(1-84). Dosing is based upon previous exposure and the recommended dosing in the rhPTH(1-84) package insert. The selected dose should reduce calcitriol and oral calcium (carbonate or citrate) supplementation to as low as safely possible while maintaining total serum calcium levels. All subjects will have their total serum calcium checked by a local laboratory as outlined in the Schedule of Study Assessments (Table 1-1). Subjects may have their rhPTH(1-84) dose increased in increments of 25 µg to a maximum of 100 µg SC QD by the investigator no more frequently than 4 week intervals 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 clinically appropriate. The rhPTH(1-84) dose may be adjusted downward at any time as needed to maintain appropriate serum calcium levels (approximately 8.0 to 9.0 mg/dL) or due to any safety concerns.

Adjustment of supplemental calcium and calcitriol regimens will be based on serum calcium levels, with the goal to be a reduction or removal of calcitriol treatment to the maximum degree clinically possible and to decrease the prescribed oral calcium supplementation to ≤ 500 mg daily.

Subjects generally should have blood draws to assess total serum calcium levels (which may be performed locally) 3 to 5 days after ANY dose adjustment of rhPTH(1-84), after any significant change in doses of calcium and/or and calcitriol supplements, or at any other time at the discretion of the investigator. Results of local total serum calcium levels will be entered on the electronic case report form (eCRF).

During the week following the last visit (End of Treatment or early termination visit), subjects who are discontinuing rhPTH(1-84) treatment (ie, those who are NOT continuing on commercial Natpara) will have oral calcium and/or active vitamin D adjusted to compensate for the cessation of rhPTH(1-84). Their total serum calcium levels will be checked locally 3 to 5 days after the last dose of study medication. Subjects will also be scheduled for a follow-up clinic visit at the end of this week in order to have serum calcium and phosphate checked.

Approximately 30 days following the End of Treatment visit, subjects will be contacted by telephone in order to assess AEs/serious AEs (SAEs).

4. STUDY POPULATION

Each subject must participate in the informed consent process and provide written informed consent before any procedures specified in the protocol are performed. Subjects in this protocol are restricted to those who were treated in the core study (AAAE0544). Approximately 50 subjects are expected to enroll in this study.

4.1 Inclusion Criteria

The subject must meet all of the following criteria to be eligible for the study:

1. Subjects that are currently or previously enrolled in the core study (AAAE0544) and have maintained uninterrupted therapy with rhPTH(1-84) (transient interruptions of up to 1 month continuously off treatment may be allowed).
2. Signed and dated informed consent form (ICF).
3. Adult men and women 18 to 85 years of age.
4. History of hypoparathyroidism for at least 12 months prior to rhPTH(1-84) treatment, defined by the requirement for supplemental calcium and/or active vitamin D to maintain serum calcium along with an undetectable or insufficient PTH concentration.
5. Able to perform daily SC self-injections of study medication (or have designee perform injection).
6. Willingness and ability to understand and comply with the protocol. Women must agree to pregnancy testing and acceptable methods of contraception, as detailed in the protocol.

4.2 Exclusion Criteria

Subjects will be excluded from the study if any of the following exclusion criteria are met:

1. The subject is treated or has been treated with any investigational drug, aside from rhPTH(1-84), within 30 days of consent.
2. As assessed by the investigator, the subject has any safety or medical issues that contraindicate participation in the study.
3. The subject and/or the subject's parent(s) or legally-authorized representative(s) are unable to understand the nature, scope, and possible consequences of the study.
4. The subject is unable to comply with the protocol, eg, uncooperative with protocol schedule, refusal to agree to all of the study procedures, inability to return for evaluations, or is otherwise unlikely to complete the study, as determined by the investigator or the medical monitor.
5. The subject is pregnant or lactating.
6. Subjects who are at increased baseline risk for osteosarcoma such as subjects with Paget's disease of bone or unexplained new elevations of alkaline phosphatase, subjects with hereditary disorders predisposing to osteosarcoma or subjects with a prior history of external beam or implant radiation therapy involving the skeleton.

4.3 Reproductive Potential

4.3.1 Female Contraception

Women who are postmenopausal (absence of menses for at least 1 year) and women who are surgically sterilized (eg, tubal occlusion, hysterectomy, bilateral salpingectomy) can be enrolled. Women of childbearing potential must have a negative pregnancy test and agree to use medically acceptable methods of contraception for the duration of the study with pregnancy testing at every scheduled visit.

Medically acceptable methods of contraception include: true sexual abstinence (not having any type of intercourse or sex play with a male partner); hormonal methods of contraception (oral, injected, vaginal rings, patch, implanted, etc.); placement of an intrauterine device or intrauterine system; barrier methods of contraception (condom or occlusive diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. Women whose partner is a woman or whose partner is a man with a history of vasectomy are exempt.

4.3.2 Male Contraception

Not Applicable.

4.4 Discontinuation of Subjects

A subject may withdraw from the study at any time for any reason without prejudice to their future medical care by the physician or at the institution. The investigator or sponsor may withdraw the subject at any time (eg, in the interest of subject safety). The investigator is encouraged to discuss withdrawal of a subject from investigational product [rhPTH(1-84)] with the medical monitor when possible.

If investigational product is discontinued, regardless of the reason, the evaluations listed for End of Treatment (EOT) Visit are to be performed as completely as possible. Comments (spontaneous or elicited) or complaints made by the subject must be recorded in the source documents and as AEs, as applicable. The reason for termination, date of stopping rhPTH(1-84) and the total amount of rhPTH(1-84) taken must be recorded in the electronic case report form (eCRF) and source documents.

Subjects who discontinue will not be replaced.

4.4.1 Subject Withdrawal Criteria

Subjects can withdraw from the study at any time for any reason.

4.4.2 Reasons for Discontinuation

The reason for withdrawal must be determined by the investigator and recorded in the subject's medical record and on the eCRF. If a subject is withdrawn for more than 1 reason, each reason should be documented in the source document and the most clinically relevant reason should be entered on the eCRF. Reasons for discontinuation include but are not limited to:

- Completed
- Adverse event
- Protocol deviation
- Withdrawal by subject
- Lack of efficacy
- Lost to follow-up
- Other (If "Other" is selected, the investigator must specify on the eCRF: Examples are provided below)
    - Death
    - Physician decision
    - Pregnancy
    - Site terminated by sponsor
    - Study terminated by sponsor

4.4.3 Subjects "Lost to Follow-up" Prior to Last Scheduled Visit

A minimum of 3 documented attempts must be made to contact any subject lost to follow-up at any time point prior to the last scheduled contact (office visit or telephone contact). At least 1 of these documented attempts must include a written communication sent to the subject's last known address via courier or mail (with an acknowledgement of receipt request) asking that they return to the site for final safety evaluations and return any unused investigational product.

5. PRIOR AND CONCOMITANT TREATMENT

All non-study treatment, including but not limited to herbal treatment, vitamins, behavioral treatment, non-pharmacological treatment (such as psychotherapy), as appropriate, received within 30 days prior to the Baseline Visit (Visit 1) (or pharmacokinetic equivalent of 5 half-lives, whichever is longer) and through the final study contact (including protocol defined follow-up period) must be recorded on the appropriate eCRF page.

5.1 Prior Treatment

Prior treatment includes all treatment, including but not limited to herbal treatment, vitamins, behavioral treatment, non-pharmacological treatment (such as psychotherapy), as appropriate as of the time of enrollment in Study SHP634-402. Prior treatment information must be recorded on the appropriate eCRF page. All available active vitamin D and calcium supplement doses from the beginning of rhPTH(1-84) will be recorded.

5.2 Concomitant Treatment

Concomitant treatment refers to all treatment taken between the dates of the first dose of rhPTH(1-84) and the end of the follow-up period in the SHP634-402 study, inclusive. Concomitant treatment information must be recorded on the appropriate eCRF page.

5.2.1 Permitted Treatment

Any treatment for an existing or obtained condition(s) will be permitted. Active vitamin D, native vitamin D, calcium and magnesium supplementation, and thiazide use are permitted. Prior treatment with rhPTH(1-84) is permitted.

5.2.2 Prohibited Treatment

The use of any other investigational product within 30 days prior to study enrollment or at any time during the trial is prohibited. Additionally, any medication that affects bone metabolism (eg, selective estrogen receptor modulators, calcitonin, bisphosphonates) and any other investigational products are prohibited while on rhPTH(1-84) treatment.

5.2.3 Active Vitamin D, Calcium, Native Vitamin D, and Magnesium Supplementation

5.2.3.1 Active Vitamin D

Subjects enrolled in this study may be taking active vitamin D to control serum calcium levels. Prior and concomitant prescribed doses of calcitriol will be entered on the appropriate eCRF.

5.2.3.2 Native Vitamin D

Subjects should receive native vitamin D to maintain the subject's serum 25(OH) vitamin D level in the normal range (≥ 30 ng/ml and ≤ the upper limit of normal for the laboratory). Prior and concomitant doses of native vitamin D must be recorded on the appropriate eCRF.

5.2.3.3 Calcium

Subjects enrolled in this study may be taking oral calcium supplements (either calcium carbonate or calcium citrate). Prior and concomitant 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 a diary.

5.2.3.4 Magnesium

Magnesium is required for normal parathyroid function and disordered magnesium levels can exacerbate hypoparathyroidism. Subjects with low serum magnesium may receive supplementation to keep the serum magnesium level in the normal range. Prior and concomitant doses of magnesium must be recorded on the appropriate eCRF.

5.2.4 Thiazide Diuretics

Subjects in this study may be taking thiazide diuretics (hydrochlorothiazide or chlorthalidone) to limit the extent and effect of hypercalciuria. Prior and concomitant prescribed doses of thiazide diuretics will be entered on the appropriate eCRF.

6. INVESTIGATIONAL PRODUCT

6.1 Identity of Investigational Product

The investigational product is rhPTH(1-84), which will be provided as a multiple dose, dual chamber, glass cartridge containing a sterile lyophilized powder and a sterile diluent for reconstitution at doses of 25µg, 50µg, 75µg, and 100µg. The investigational product in the cartridge must be mixed using the provided mixing apparatus, and only administered via the injector pen, which is also provided. Additional information related to the investigational product, including preparation and administration, is provided in the current rhPTH(1-84) investigator brochure, and in an investigational product preparation and administration manual that will be provided.

No additional investigational product will be supplied. It is expected that subjects will continue to take their own supplemental oral calcium and vitamin D (except when instructed to hold at the times indicated in the current protocol) and that any products required for emergency treatment, eg, fluid or calcium replacement, be provided by the study physician.

6.1.1 Blinding the Treatment Assignment

This is an open-label single-arm study where all subjects will be administered study drug; therefore, no blinding will occur.

6.2 Administration of Investigational Product(s)

The following instructions describe how to administer the investigational product:

Adjust dose of active vitamin D or calcium supplement or both based on serum calcium value and clinical assessment (ie, signs and symptoms of hypocalcemia or hypercalciuria). Suggested adjustments to active vitamin D and calcium supplement based on serum calcium levels are provided in Table 6-1.

Table 6-1: Recommended Adjustments for Active Vitamin D and Calcium Supplements

	Adjust First	Adjust Second
Serum Calcium	**Active Vitamin D Forms**	**Calcium Supplement**
Above the Upper Limit of Normal (10.6 mg/dL)	Decrease or Discontinue *	Decrease
Greater than 9 mg/dL and below the Upper Limit of Normal (10.6 mg/dL)	Decrease or Discontinue *	No change or decrease if active vitamin D has been discontinued
Less than or equal to 9 mg/dL and above 8 mg/dL	No change	No change
Lowers than 8 mg/dL	Increase	Increase

*Discontinue in patients receiving lowest available dose

6.2.1 Allocation of Subjects to Treatment

This is an open-label, single-center study where all subjects will receive rhPTH(1-84).

6.2.2 Dosing

The dose of rhPTH(1-84) will be individualized based on SCAC and 24-hour calcium urinary excretion. The recommended rhPTH(1-84) dose will be the minimum dose required to prevent both hypocalcemia and hypocalciuria. This dose will generally be the dose that maintains SCAC within the lower half of the normal range (ie, between 8 and 9 mg/dL) without the need for active forms of vitamin D and with calcium supplementation sufficient and individualized to meet the patient's daily requirements.

The doses of rhPTH(1-84), active vitamin D, and calcium supplements will be prescribed on an individual basis. Dosing guidelines found in the US package insert will be used but may be individualized at the discretion of the investigator.

Doses of active forms of vitamin D and calcium supplements will be adjusted when using rhPTH(1-84).

6.2.3 Unblinding the Treatment Assignment

Not Applicable.

6.3 Labeling, Packaging, Storage, and Handling

6.3.1 Packaging

The study site will receive open label supplies of investigational product, injection pens and mixing devices required for dosing.

Each subject will receive 2 pens for use during the study period and sufficient cartridges to provide daily doses for the duration of the study. Drug cartridges will be provided in kits containing 8 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 be provided by the CRO to the site.

6.3.2 Labeling

All clinical supplies will be manufactured, tested, labeled and released according to current legal and local country specific regulatory requirements and will comply with Good Manufacturing Practices.

A caution statement limiting the investigational product to the clinical trial will be appended as regionally required. For example, in the US the following statement will be appended "For clinical trial use only", and/or "CAUTION: New Drug - Limited by Federal (or US) Law to Investigational Use" and the statement "Keep out of the reach of children".

Additional labels (eg, those used when dispensing marketed product) may, on a case-by-case basis, be applied to the investigational product in order to satisfy local or institutional requirements, and must not:

- Contradict the clinical study label
- Obscure the clinical study label
- Identify the study subject by name

Additional labels may not be added without the sponsor's prior full agreement.

Changes to sponsor-supplied packaging prior to dosing may not occur without full agreement in advance by the sponsor.

6.3.3 Storage

The dual-chamber medication cartridge should be stored between 2 – 8 °C. The reconstituted medication can be stored for up to 14 days at these conditions. The mixing device and empty delivery pen (ie, unloaded) can be stored at room temperature.

The investigator has overall responsibility for ensuring that investigational product is stored in a secure, limited-access location. Limited responsibility may be delegated to the pharmacy or member of the study team, but this delegation must be documented.

Investigational product must be stored in accordance with labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the investigational product is maintained within an established temperature range. The investigator is responsible for ensuring that the temperature is monitored throughout the duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in house system, a mechanical recording device such as a calibrated chart recorder, or by manual means, such that both minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required. Such a device (ie, certified min/max thermometer) would require manual resetting upon each recording. The sponsor must be notified immediately upon discovery of any excursion from the established range. Temperature excursions will require site investigation as to cause and remediation. The sponsor will determine the ultimate impact of excursions on the investigational product and will provide supportive documentation as necessary. Under no circumstances should the product be dispensed to subjects until the impact has been determined and the product is deemed appropriate for use by the sponsor.

The sponsor should be notified immediately if there are any changes to the storage area of the investigational product that could affect the integrity of the product(s), eg, fumigation of a storage room.

6.3.4 Special Handling

Do not freeze or shake. Do not use rhPTH(1-84) if it has been frozen or shaken.

6.4 Drug Accountability

The investigator will be provided with sufficient amounts of the investigational product to carry out this protocol for the agreed number of subjects. The investigator or designee will acknowledge receipt of the investigational product, documenting shipment content and condition. Accurate records of all investigational product dispensed, used, returned, and/or destroyed must be maintained as detailed further in this section.

The investigator has overall responsibility for administering/dispensing investigational product. Where permissible, tasks may be delegated to a qualified designee (ie, a pharmacist) who is adequately trained in the protocol and who works under the direct supervision of the investigator. This delegation must be documented in the applicable study delegation of authority form.

The investigator or his/her designee (as documented by the investigator in the applicable study delegation of authority form) will dispense the investigational product only to subjects included in this study following the procedures set out in the study protocol. Each subject will be given only the investigational product carrying his/her treatment assignment. All dispensed study drug will be documented on the eCRFs and/or other investigational product record. The investigator is responsible for assuring the retrieval of all study supplies from subjects.

No investigational product stock or returned inventory from a Shire-sponsored study may be removed from the site where originally shipped without prior knowledge and consent by the sponsor. If such transfer is authorized by the sponsor, all applicable local, state, and national laws must be adhered to for the transfer.

At the end of the study, or as instructed by the sponsor, all unused stock, subject returned investigational product, and empty/used investigational product packaging are to be sent to a nominated contractor on behalf of the sponsor. Investigational products being returned to the sponsor's designated contractors must be counted and verified by clinical site personnel and the sponsor (or designated contract research organization [CRO]). For unused supplies where the original supplied tamper-evident feature is verified as intact, the tamper-evident feature must not be broken and the labeled amount is to be documented in lieu of counting. Shipment return forms, when used, must be signed prior to shipment from the site. Returned investigational products must be packed in a tamper-evident manner to ensure product integrity. Contact the sponsor for authorization to return any investigational product prior to shipment. Shipment of all returned investigational products must comply with local, state, and national laws.

Based on entries in the site drug accountability forms, it must be possible to reconcile investigational products delivered with those used and returned. All investigational products must be accounted for and all discrepancies investigated and documented to the sponsor's satisfaction.

6.5 Subject Compliance

Subjects will be instructed to bring their unused investigational product and empty/used investigational product packaging to every visit. Drug accountability will be assessed at the container/packaging level for unused investigational product that is contained within the original tamper-evident sealed container (eg, bottles, trays, vials) or at the individual count level for

opened containers/packaging. The pharmacist/nominated person will record details on the drug accountability form.

7. STUDY PROCEDURES

7.1 Study Schedule

See Table 1-1 for a complete list of study procedures. Site visits will be conducted at 6-month intervals until the end of treatment (EOT) visit at month 24.

A core set of study procedures, conducted at each site visit, are defined as the following:

- Prior/concomitant medications
- Vital signs
- Serum chemistry (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, calcium, phosphate, magnesium, albumin, ALT, AST and ALP).
    - Should be drawn fasting, prior to administration of calcium or vitamin D supplements or rhPTH(1-84) administration . If in the opinion of the investigator, it is necessary for a subject to take calcium and/or active vitamin D supplements prior to traveling for blood work, the doses of the pre-draw supplements and their timing with respect to the blood draw should be consistent throughout the study to the greatest extent possible.
- Urine pregnancy test
- Serum 25-hydroxyvitamin D
- Serum 1,25-dihydroxyvitamin D
- Bone turnover markers
- Serum PTH antibodies (blood samples should be drawn prior to dosing)
- 24-hour urine for calcium, creatinine, phosphate, sodium excretion. Total urinary volume will be recorded.
- HPT multisymptom questionnaire
- FACT-Cog (Functional Assessment of Cancer Therapy - Cognitive Function) assessment
- FACIT (Functional Assessment of Chronic Illness Therapy) Fatigue Scale
- HADS (Hospital Anxiety and Depression Scale) assessment
- [redacted]
- AE/SAE monitoring
- 24-hour urine
- Bone mineral density DXA (dual-energy x-ray absorptiometry)
- Bone mineral density HRpQCT (High-resolution peripheral quantitative computerized tomography)
- Dispense/Account for study drug

7.1.1 Baseline Visit (Visit 1)

All study procedures outlined in Table 1-1 will be conducted at the baseline visit with the exception of ‘Collection of unused study drug & injection pen. Additionally, the bone biopsy is an optional procedure, performed once any time during the study, depending on subject history and consent.

7.1.2 Treatment Period

7.1.2.1 Visit 2, (Month 6)

The core set of study procedures will be conducted at this visit.

7.1.2.2 Visit 3 (Month 12)

The core set of study procedures will be conducted at this visit. In addition to the core study procedures, the following procedures will be performed:

- Physical Examination
- SF-36 (36-Item Short Form Health Survey)

7.1.2.3 Visit 4 (Month 18)

The core set of study procedures will be conducted at this visit.

7.1.2.4 EOT Visit (Month 24)

All study procedures outlined in Table 1-1 will be performed at this visit except for the following:

- Informed consent
- Inclusion/exclusion
- Medical history and demography
- Serum thyroid stimulating hormone (TSH)
- Serum pregnancy test
- Follicle-stimulating hormone (FSH) level

7.1.3 Additional Care of Subjects after the Study

After the EOT visit or early termination visit, subjects who will not continue rhPTH[1-84] treatment will have 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 according to guidelines followed in the US package insert. 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 30 days ± 7 days after EOT visit. After the 30-day follow-up phone call, further management of hypoparathyroidism will occur as part of the subject's long-term non-study medical care.

7.2 Study Evaluations and Procedures

7.2.1 Demographic and Other Baseline Characteristics

Demographic characteristics will be recorded at the Baseline visit including date of birth, sex, and race on the eCRF for each subject.

Medical history including etiology of hypoparathyroidism and duration of hypoparathyroidism will be recorded on the eCRF for each subject.

Pre-study rhPTH(1-84) treatment will be recorded on the eCRF for each subject.

Pre-study laboratory data will be recorded on the eCRF for each subject.

7.2.2 Efficacy

7.2.2.1 Biochemical Evaluations

Biochemical evaluation including serum calcium, PTH, albumin, phosphate, alkaline phosphatase, urine calcium, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D will be collected at the time points specified in Table 1-1 to assess efficacy and bone turnover.

7.2.2.2 Hypoparathyroidism Multisymptom Questionnaire

The Hypoparathyroidism Symptom Diary is a 15-item tool describing the subject's experience related to hypoparathyroidism during the past 24 hours (Appendix 1).

7.2.2.3 Cognition Tool

The FACT-Cog assessment is a 37-item tool (Cella 1997). It includes 4 subscales: perceived cognitive impairments, impact of perceived cognitive impairments on quality of life, comments from others and perceived cognitive ability.

7.2.2.4 FACIT Fatigue Scale

FACIT fatigue questionnaire contains 13 fatigue-related questions (Cella 1997). The responses to the 13 items on the FACIT fatigue questionnaire are each measured on a 4-point Likert scale. Thus, the total score ranges from 0 to 52. High scores represent less fatigue.

7.2.2.5 HADS Assessment

The HADS is a 14-item scale that generates ordinal data (Zigmond and Snaith 1983). Seven of the items relate to anxiety and seven relate to depression. The scale is designed to avoid reliance on aspects of conditions that are also common somatic symptoms of illness. Each item on the questionnaire is scored from 0-3, therefore, a person can score between 0 and 21 for either anxiety or depression. Data returned from the HADS is ordinal.

7.2.2.6 Short Form Health Survey-36

The SF-36 is a validated questionnaire that questions subjects about perceived physical and mental health and function. The SF-36 consists of 8 scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight; the lower the score the more disability. The higher the score the less disability ie, a score of zero is equivalent to maximum disability and a score of 100 is equivalent to no disability. The eight sections included in the SF-36 assessment are vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health (Ware and Sherbourne 1992).

7.2.2.7 Bone Mineral Density

DUAL-ENERGY X-RAY ABSORPTIOMETRY

Dual-energy X-ray absorptiometry scans will be performed at Baseline, Month 6, Month 12, Month 18, Month 24, and at the EOT visit, if it is greater than 3 months since the previous DXA scan. These scans will evaluate bone mineral density and T-scores of the lumbar spine (vertebra L1-L4), hip (total and femoral neck), and ⅓ distal radius (arm).

Please note: DXA will NOT be completed at baseline if subject had a scan performed in the previous study.

HIGH-RESOLUTION PERIPHERAL QUANTITATIVE COMPUTERIZED TOMOGRAPHY

High-resolution peripheral quantitative computerized tomography will be performed at Baseline, Month 6, Month 12, Month 18, Month 24, and at the EOT visit. HRpQCT analyses includes Individual Trabecula Segmentation (ITS) analysis and finite element modeling.

7.2.2.8 Bone Biopsy

An optional transiliac bone biopsy will be performed for willing subjects, at the discretion of the investigator a maximum of one time during the duration of the study.

Subjects who agree to have the bone biopsy, and have selected to participate in the procedure on the Informed Consent Form, will receive two 3-day courses of tetracycline with a 12-day window between the first and second course. The bone biopsy must occur 4 to 6 days after the second tetracycline course. Subjects should be instructed to avoid food and drink for 6 hours before the procedure, although small amounts of clear fluids are allowed.

The incision will be made at the iliac crest, and a bone biopsy needle used to aspirate 1 to 2 samples of bone from the hip. Investigators will follow their institutional procedures, and use the same techniques and equipment if possible.

Subjects should be observed for at least 1 hour postoperatively and advised to abstain from vigorous exercise until 1 week post-procedure.

7.2.2.9 [redacted]

[redacted]

7.2.3 Safety

7.2.3.1 Adverse Event Collection

At each study visit, subjects will be questioned in a general way to ascertain if AEs have occurred since the previous visit (ie, “Have you had any health problems since your last visit?”).

Adverse events will be collected from the time informed consent is signed. (Please refer to Section 8, Adverse and Serious Adverse Events Assessment.)

7.2.3.2 Clinical Laboratory Evaluations

All clinical laboratory assays will be performed according to the laboratory's normal procedures. Reference ranges are to be supplied by the laboratory and will be used to assess the clinical laboratory data for clinical significance and out-of-range pathological changes. The investigator should assess out-of-range clinical laboratory values for clinical significance, indicating if the value(s) is/are not clinically significant or clinically significant. Abnormal clinical laboratory values, which are unexpected or not explained by the subject's clinical condition, maybe repeated as soon as possible until confirmed, explained, or resolved, at the discretion of the investigator or sponsor.

Lab assessments will be performed during the site visit with the exception of the 24-hour urine collection, which will be collected at a local laboratory. The collection of urine may occur up to 2 weeks before the study visit.

The following clinical laboratory assessments will be performed:

CHEMISTRY

Blood samples for serum chemistry will be collected at the time points described in Table 1-1 and will include:

Sodium	Phosphate	β-HCG [a,b]
Potassium	Magnesium	FSH [a,b]
Blood urea nitrogen	Total CO_2 (Bicarbonate)	
Creatinine	Albumin	
Calcium	Aspartate transaminase	
Chloride	Alanine transaminase	
Thyroid stimulating hormone (TSH)[a]	Alkaline phosphatase	
25-hydroxyvitamin D	1,25-dihydroxyvitamin D	

Creatinine clearance and glomerular filtration rate will be estimated (eGFR) by the laboratory.
β-HCG=beta-human chorionic gonadotropin; FSH=follicle-stimulating hormone; T3=triiodothyronine; TSH=thyroid stimulating hormone.
[a] Baseline only.
[b] Females only.

HEMATOLOGY

Blood samples for hematology will be collected at the time points described in Table 1-1 and will include:

Hemoglobin	Platelet count
Hematocrit	White blood cell (WBC) count
Red blood cells (RBC)	

URINALYSIS

A urine sample for urinalysis will be collected at the time points described in Table 1-1 and will include:

pH	Blood	Nitrites
Glucose	Ketones	Leukocyte esterase
Protein	Bilirubin	Specific gravity
Calcium		

Microscopic examination will be conducted if protein, leukocyte esterase, and/or blood is/are detected during urinalysis. At a minimum the microscopic examination will consist of red blood cells, white blood cells, casts, and bacteria.

24-HOUR URINE

At the beginning of the study, the investigator should recommend an individualized target dietary (non-supplement) calcium intake for each subject to ingest consistently throughout the study on 24-hour urine collection days. The 24-hour urine collections should generally be performed by the subject within 2 weeks prior to or within 2 days follow a study visit. These 24-hour urine collections may be analyzed in a local laboratory. To the greatest extent possible, the same laboratory should analyze the 24-hour urine collections throughout the study. Results from the last 24-hour urine collection obtained in Columbia protocol AAAE0544 will be used as the baseline assessment in this study.

When collecting 24-hour urine specimens subjects should be instructed to take their currently prescribed calcium, vitamin D (both parent and active) and rhPTH(1-84) doses.

A 24-hour urine sample will be collected at the time points described in Table 1-1 and will include:

Calcium	Sodium
Creatinine	Total Volume
Phosphate	
Magnesium	

7.2.3.3 Pregnancy Test

A serum and urine pregnancy test will be performed on all females of childbearing potential at the Baseline Visit (Visit 1). Additionally, a urine pregnancy test will be performed at all scheduled study visits.

7.2.3.4 PTH Antibodies

A blood sample for PTH antibodies will be collected at the time points described in Table 1-1. Blood samples for antibody testing should be collected prior to dosing with PTH[1-84]. Any subject with newly developed PTH-specific antibodies at the end of treatment visit may require follow up. This will be discussed as necessary by the PI and medical monitor on a case-by-case basis.

7.2.3.5 Vital Signs

Vital signs include blood pressure, heart rate, body temperature, and respiration rate. Blood pressure should be determined by cuff (using the same method, the same arm, and in the same position throughout the study). Any clinically significant deviations from Baseline (Visit 1) vital signs which are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

7.2.3.6 Physical Examination

A physical examination including height and weight will be conducted at Baseline, Month 12, and Month 24. Abnormalities identified at the Baseline Visit (Visit 1) will be documented in the subject's source documents and on the medical history eCRF. Any clinically significant deviations from Baseline (Visit 1) in physical examination findings which are deemed clinically significant in the opinion of the investigator are to be recorded as an AE.

8. ADVERSE AND SERIOUS ADVERSE EVENTS ASSESSMENT

8.1 Definition of Adverse Events, Period of Observation, Recording of Adverse Events

An AE is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidance E2A 1995).

All AEs are collected from the time the informed consent is signed until the defined follow-up period stated in Section 7.1.3. This includes events occurring during the screening phase of the study, regardless of whether or not investigational product is administered. Where possible, a diagnosis rather than a list of symptoms should be recorded. If a diagnosis has not been made, then each symptom should be listed individually. All AEs should be captured on the appropriate AE pages in the eCRF and in source documents. In addition to untoward AEs, unexpected benefits outside the investigational product indication should also be captured on the AE eCRF.

All AEs must be followed to closure (the subject's health has returned to his/her baseline status or all variables have returned to normal), regardless of whether the subject is still participating in the study. Closure indicates that an outcome is reached, stabilization achieved (the investigator does not expect any further improvement or worsening of the event), or the event is otherwise explained. When appropriate, medical tests and examinations are performed so that resolution of event(s) can be documented.

8.1.1 Severity Categorization

The severity of AEs must be recorded during the course of the event including the start and stop dates for each change in severity. An event that changes in severity should be captured as a new event. Worsening of pre-treatment events, after initiation of investigational product, must be recorded as new AEs (for example, if a subject experiences mild intermittent dyspepsia prior to dosing of investigational product, but the dyspepsia becomes severe and more frequent after first dose of investigational product has been administered, a new AE of severe dyspepsia [with the appropriate date of onset] is recorded on the appropriate eCRF).

The medical assessment of severity is determined by using the following definitions:

Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Moderate: A type of AE that is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject.

Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

8.1.2 Relationship Categorization

A physician/investigator must assess the relationship to investigational product for each AE. The investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. If there is no valid reason for suggesting a relationship, then the AE should be classified as "not related". Otherwise, if there is any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should be considered "related". The causality assessment must be documented in the source document.

The following additional guidance may be helpful:

Term	Relationship Definition
Related	The temporal relationship between the event and the administration of the investigational product is compelling and/or follows a known or suspected response pattern to that product, and the event cannot be explained by the subject's medical condition, other therapies, or accident.
Not Related	The event can be readily explained by other factors such as the subject's underlying medical condition, concomitant therapy, or accident and no plausible temporal or biologic relationship exists between the investigational product and the event.

8.1.3 Outcome Categorization

The outcome of AEs must be recorded during the course of the study on the eCRF. Outcomes are as follows:

- Fatal
- Not Recovered/Not Resolved
- Recovered/Resolved
- Recovered/Resolved With Sequelae
- Recovering/Resolving
- Unknown

8.1.4 Symptoms of the Disease Under Study

Symptoms of the disease under study should not be classed as AEs as long as they are within the normal day-to-day fluctuation or expected progression of the disease and are part of the efficacy data to be collected in the study; however, significant worsening of the symptoms should be recorded as an AE.

8.1.5 Clinical Laboratory and Other Safety Evaluations

A change in the value of a clinical laboratory or vital signs assessment can represent an AE if the change is clinically relevant or if, during treatment with the investigational product, a shift of a parameter is observed from a normal value to an abnormal value, or a further worsening of an already abnormal value. When evaluating such changes, the extent of deviation from the reference range, the duration until return to the reference range, either while continuing treatment

or after the end of treatment with the investigational product, and the range of variation of the respective parameter within its reference range, must be taken into consideration.

If, at the end of the treatment phase, there are abnormal clinical laboratory or vital signs values which were not present at the pre-treatment value observed closest to the start of study treatment, further investigations should be performed until the values return to within the reference range or until a plausible explanation (ie, concomitant disease) is found for the abnormal values.

The investigator should decide, based on the above criteria and the clinical condition of a subject, whether a change in a clinical laboratory or vital signs parameter is clinically significant and therefore represents an AE.

8.1.6 Pregnancy

All pregnancies are to be reported from the time informed consent is signed until the defined follow-up period stated in Section 7.1.3.

Any report of pregnancy for any female study participant must be reported within 24 hours to the Shire Global Pharmacovigilance and Risk Management Department using the Shire Investigational and Marketed Products Pregnancy Report Form. A copy of the Shire Investigational and Marketed Products Pregnancy Report Form (and any applicable follow-up reports) must also be sent to the CRO/Shire Medical Monitor using the details specified in the emergency contact information section of the protocol. The pregnant female study participant must be withdrawn from the study.

Every effort should be made to gather information regarding the pregnancy outcome and condition of the infant. It is the responsibility of the investigator to obtain this information within 30 calendar days after the initial notification and approximately 30 calendar days postpartum.

Pregnancy complications such as spontaneous abortion/miscarriage or congenital abnormality are considered SAEs and must be reported using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form. Note: An elective abortion is not considered an SAE.

In addition to the above, if the investigator determines that the pregnancy meets serious criteria, it must be reported as an SAE using the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form as well as the Shire Investigational and Marketed Products Pregnancy Report Form. The test date of the first positive serum/urine β-HCG (beta-human chorionic gonadotropin) test or ultrasound result will determine the pregnancy onset date.

8.1.7 Abuse, Misuse, Overdose, and Medication Error

Abuse, misuse, overdose, or medication error (as defined below) must be reported to the sponsor according to the SAE reporting procedure whether or not they result in an AE/SAE as described in Section 8.2. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors unless these result in an SAE.

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

Abuse – Persistent or sporadic intentional intake of investigational product when used for a non-medical purpose (eg, to alter one's state of consciousness or get high) in a manner that may be detrimental to the individual and/or society

Misuse – Intentional use of investigational product other than as directed or indicated at any dose (Note: this includes a situation where the investigational product is not used as directed at the dose prescribed by the protocol)

Overdose – Intentional or unintentional intake of a dose of an investigational product exceeding a pre-specified total daily dose of 250 µg of the product.

Medication Error – An error made in prescribing, dispensing, administration, and/or use of an investigational product. For studies, medication errors are reportable to the sponsor only as defined below.

- Cases of subjects missing doses of the investigational product are not considered reportable as medication errors.
- Medication errors should be collected/reported for all products under investigation.
- The administration and/or use of an expired investigational product should be considered as a reportable medication error.

Acute accidental overdosage of rhPTH(1-84) can result in transient hypercalcemia and hypercalciuria. Treatment of suspected overdose should include temporary discontinuation of rhPTH(1-84), monitoring of serum calcium, and implementation of appropriate, supportive measures such as hydration. Due to the relatively short duration of the pharmacological activity of rhPTH(1-84), further measures should not be necessary.

8.2 Serious Adverse Event Procedures

8.2.1 Reference Safety Information

The reference for safety information for this study is the investigators brochure, which the sponsor has provided under separate cover to all investigators.

8.2.2 Reporting Procedures

All initial and follow-up SAE reports must be reported by the investigator to the Shire Global Pharmacovigilance and Risk Management Department and the Shire Medical Monitor within 24 hours of the first awareness of the event. Note: The 24-hour reporting requirement for SAEs does not apply to reports of abuse, misuse, overdose, or medication errors (see Section 8.1.7) unless they result in an SAE.

The investigator must complete, sign, and date the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form and verify the accuracy of the information recorded on the form with the corresponding source documents (Note: Source documents are not to be sent unless requested) and fax or e mail the form to the Shire Global Pharmacovigilance and Risk Management Department. A copy of the Shire Clinical Study Serious Adverse Event and Non-serious AEs Required by the Protocol Form (and any applicable follow-up reports)

must also be sent to the Shire Medical Monitor using the details specified in the emergency contact information section of the protocol.

8.2.3 Serious Adverse Event Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence (whether considered to be related to investigational product or not) that at any dose:

- Results in death
- Is life-threatening. Note: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it was more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization. Note: Hospitalizations, which are the result of elective or previously scheduled surgery for pre-existing conditions, which have not worsened after initiation of treatment, should not be classified as SAEs. For example, an admission for a previously scheduled ventral hernia repair would not be classified as an SAE; however, complication(s) resulting from a hospitalization for an elective or previously scheduled surgery that meet(s) serious criteria must be reported as SAE(s).
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Is an important medical event. Note: 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 and may require medical or surgical intervention to prevent 1 of the 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 inpatient hospitalization; or the development of drug dependency or drug abuse.

8.2.4 Serious Adverse Event Collection Time Frame

All SAEs (regardless of relationship to study) are collected from the time the subject signs the informed consent until the defined follow-up period stated in Section 7.1.3, and must be reported to the Shire Global Pharmacovigilance and Risk Management Department and the Shire Medical Monitor within 24 hours of the first awareness of the event.

In addition, any SAE(s) considered "related" to the investigational product and discovered by the investigator at any interval after the study has completed must be reported to the Shire Global Pharmacovigilance and Risk Management Department within 24 hours of the first awareness of the event.

8.2.5 Serious Adverse Event Onset and Resolution Dates

The onset date of the SAE is defined as the date the event meets serious criteria. The resolution date is the date the event no longer meets serious criteria, the date the symptoms resolve, or the event is considered chronic. In the case of hospitalizations, the hospital admission and discharge dates are considered the onset and resolution dates, respectively.

In addition, any signs or symptoms experienced by the subject after signing the ICF, or leading up to the onset date of the SAE, or following the resolution date of the SAE, must be recorded as an AE, if appropriate.

8.2.6 Fatal Outcome

Any SAE that results in the subject's death (ie, the SAE was noted as the primary cause of death) must have fatal checked as an outcome with the date of death recorded as the resolution date. For all other events ongoing at the time of death that did not contribute to the subject's death, the outcome should be considered not resolved, without a resolution date recorded.

For any SAE that results in the subject's death or any ongoing events at the time of death, unless another investigational product action was previously taken (eg, drug interrupted, reduced, withdrawn), the action taken with the investigational product should be recorded as "dose not changed" or "not applicable" (if the subject never received investigational product). The investigational product action of "withdrawn" should not be selected solely as a result of the subject's death.

8.2.7 Regulatory Agency, Institutional Review Board, Ethics Committee, and Site Reporting

The sponsor and/or CRO is responsible for notifying the relevant regulatory authorities/US central Institutional Review Boards (IRBs) of related, unexpected SAEs.

In addition, the sponsor and/or CRO is responsible for notifying active sites of all related, unexpected SAEs occurring during all interventional studies across the SHP634-402 program.

The investigator is responsible for notifying the local IRB, local Ethics Committee (EC), or the relevant local regulatory authority of all SAEs that occur at his or her site as required.

9. DATA MANAGEMENT AND STATISTICAL METHODS

9.1 Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A study monitor will visit each site in accordance with the monitoring plan and review the eCRF data against the source data for completeness and accuracy. Discrepancies between source data and data entered on the eCRF will be addressed by qualified site personnel. When a data discrepancy warrants correction, the correction will be made by authorized site personnel. Data collection procedures will be discussed with the site at the site initiation visit and/or at the investigator's meeting. It is expected that site personnel will complete the eCRF entry within approximately 3 business days of the subject's visit.

9.2 Clinical Data Management

Data are to be entered into a clinical database as specified in the study data management plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

9.3 Data Handling Considerations

Not Applicable.

9.4 Statistical Analysis Process

The statistical analysis plan (SAP) will provide the statistical methods and definitions for the analysis of the efficacy and safety data, as well as describe the approaches to be taken for summarizing other study information such as subject disposition, demographics and baseline characteristics, study treatment exposure, and prior and concomitant medications. The SAP will also include a description of how missing, unused and spurious data will be addressed.

All statistical analyses will be performed using Statistical Analysis System (SAS®) (SAS Institute, Cary, NC, USA) version 9.3 or higher.

9.5 Planned Interim Analysis, Adaptive Design, and Data Monitoring Committee

A retrospective analysis of historical data captured from the medical records of subjects (eg, since the start of rhPTH(1-84) treatment) will be conducted. Data collected will include but is not limited to, medical history and clinical laboratory data. There are no formal hypotheses testing for the retrospective analysis. Descriptive statistics will be calculated for quantitative safety data as well as for the difference from the pre-rhPTH(1-84) treatment baseline, if applicable.

9.6 Sample Size Calculation and Power Considerations

No formal sample size calculation was performed.

9.7 Study Population

The **Safety Population** will be used for all analysis in this study and consists of all subjects who receive at least 1 dose of rhPTH(1-84).

9.8 Efficacy Analyses

9.8.1 Primary Efficacy Endpoint

- Albumin-corrected serum calcium over time

The primary efficacy endpoint is defined as the albumin-corrected serum calcium concentration over time at each study visit (ie, every 6 months). The Baseline serum calcium concentration is the final measurement taken prior to initiating treatment.

The change and percentage changes from baseline will be summarized at each visit. No formal statistical test will be conducted. 95% confidence intervals (CI) will be provided as appropriate.

9.8.2 Secondary Efficacy Endpoints

The secondary endpoints are defined as follows:

- Urinary calcium and serum phosphate over time
- Calcium and active vitamin D supplement doses over time
- HPT Disease-related symptoms (Multisymptom questionnaire), FACT-Cog assessment, FACIT (Fatigue Scale [Version 4]), and HADS
- Health-related quality-of-life measured with SF-36 survey over time
- Bone turnover (markers), architecture, and histology (biopsy) over time

For continuous variables, the change and percent changes from baseline will be summarized using descriptive statistics including number of subjects, mean, median, standard deviation, maximum, and minimum. The same analysis using core study (AAAE0544) baseline will be performed. CIs of 95% will be provided as appropriate. For categorical variables, statistical summaries will include number of subjects and percentages.

9.8.3 Exploratory Efficacy Endpoints

- [redacted]

Exploratory endpoints will be summarized with descriptive statistics or frequency counts and percentage as appropriate.

9.9 Safety Analyses

Safety analysis will be conducted on the safety population as defined in Section 9.7. The following safety variables constitute the safety endpoints measured in this study:

- AEs including SAEs
- Symptoms of hypoparathyroidism
- Vital signs including body temperature (°C/°F), heat rate (beats per minute), respiratory rate, and blood pressure (systolic and diastolic [mmHg])
- Estimated Glomerular Filtration Rate (eGFR) and creatinine clearance
- Measurement of PTH antibody
- Laboratory safety data (eg, clinical chemistry, hematology and urinalysis)

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number of events, incidence, and percentage of treatment-emergent adverse events (TEAEs) will be calculated overall, by system organ class (SOC), by preferred term, and by treatment group. TEAEs will be further summarized by severity and relationship to investigational product. AEs related to investigational product, AEs leading to withdrawal, SAEs, and deaths will be similarly summarized/listed. Clinical laboratory tests and vital signs findings will be summarized by treatment group and visit. Potentially clinically important findings will also be summarized or listed.

9.10 Other Analyses

Historical laboratory and medical history data on each subject will be summarized.

Any available historical data will be collected in the following order of priority:

Priority 1:

- Serum calcium and albumin
- Urine calcium excretion (to include 24 hour urine collections or estimates of 24 hour excretion based on 2 hour collections)
- Serum phosphate
- Serum creatinine•SF-36 results

Priority 2:

- Calcium and Vitamin D supplement doses
- Serum magnesium
- DXA bone density results
- HRpQCT results•24 hour urine creatinine, volume

Priority 3:

- 25-OH Vitamin D and 1,25-dihydoxy-Vitamin D levels
- Medical History/[redacted]
- Bone Turnover Markers
- Vital signs (body temperature, heat rate, respiratory rate, and blood pressure (systolic and diastolic)
- Electrocardiogram (ECG) parameters (atrial and ventricular rates and PR, QRS, and QTc intervals)
- Laboratory safety data (eg, clinical chemistry, hematology, and urinalysis)
- 24 hour urine phosphate, sodium
- Bone histology and histomorphometry results
- Descriptive statistics will used to evaluate the historical data, if applicable.

9.10.1 Health-related Quality of Life Analyses

SF-36 endpoints will be measured. For each endpoint, the change in Quality of Life score from baseline to the end of treatment will be measured relative to those measured just prior to beginning rhPTH(1-84) treatment and relative to Visit 1 in this study.

10. SPONSOR'S AND INVESTIGATOR'S RESPONSIBILITIES

This study is conducted in accordance with current applicable regulations, International Conference on Harmonisation (ICH), European Union (EU) Directive 2001/20/EC and its updates, and local ethical and legal requirements.

The name and address of each third party vendor (ie, CRO) used in this study will be maintained in the investigator's and sponsor's files, as appropriate.

10.1 Sponsor's Responsibilities

10.1.1 Good Clinical Practice Compliance

The study sponsor and any third party to whom aspects of the study management or monitoring have been delegated will undertake their assigned roles for this study in compliance with all applicable industry regulations, ICH GCP Guideline E6 (1996), European Union (EU) Directive 2001/20/EC, as well as all applicable national and local laws and regulations.

Visits to sites are conducted by representatives of the study sponsor and/or the company organizing/managing the research on behalf of the sponsor to inspect study data, subjects' medical records, and eCRFs in accordance with current Good Clinical Practice (GCP) and the respective local and (inter)national government regulations and guidelines. Records and data may additionally be reviewed by auditors or by regulatory authorities.

The sponsor ensures that local regulatory authority requirements are met before the start of the study. The sponsor (or a nominated designee) is responsible for the preparation, submission, and confirmation of receipt of any regulatory authority approvals required prior to release of investigational product for shipment to the site.

10.1.2 Public Posting of Study Information

The sponsor is responsible for posting appropriate study information on applicable websites. Information included in clinical study registries may include participating investigators' names and contact information.

10.1.3 Submission of Summary of Clinical Study Report to Competent Authorities of Member States Concerned and Ethics Committees

The sponsor will provide a summary of the clinical study report (CSR) to the competent authority of the member state(s) concerned as required by regulatory requirement(s) and to comply with the Community guideline on GCP. This requirement will be fulfilled within 6 months of the end of the study completion date for pediatric studies and within 1 year for non-pediatric studies as per guidance.

10.1.4 Study Suspension, Termination, and Completion

The sponsor may suspend or terminate the study, or part of the study, at any time for any reason. If the study is suspended or terminated, the sponsor will ensure that applicable sites, regulatory agencies and IRBs/ECs are notified as appropriate. Additionally, the discontinuation of a

registered clinical study which has been posted to a designated public website will be updated accordingly.

10.2 Investigator's Responsibilities

10.2.1 Good Clinical Practice Compliance

The investigator must undertake to perform the study in accordance with ICH GCP Guideline E6 (1996), EU Directive 2001/20/EC, and applicable regulatory requirements and guidelines.

It is the investigator's responsibility to ensure that adequate time and appropriately trained resources are available at the site prior to commitment to participate in this study. The investigator should also be able to estimate or demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

The investigator will maintain a list of appropriately qualified persons to whom the investigator has delegated significant study-related tasks, and shall, upon request of the sponsor, provide documented evidence of any licenses and certifications necessary to demonstrate such qualification. Curriculum vitae for investigators and sub investigators are provided to the study sponsor (or designee) before starting the study.

If a potential research subject has a primary care physician, the investigator should, with the subject's consent, inform them of the subject's participation in the study.

A coordinating principal investigator is appointed to review the final CSR for multicenter studies. Agreement with the final CSR is documented by the signed and dated signature of the principal investigator (single-site study) or coordinating principal investigator (multicenter study), in compliance with Directive 2001/83/EC as amended by Directive 2003/63/EC and ICH Guidance E3 (1995).

10.2.2 Protocol Adherence and Investigator Agreement

The investigator and any co-investigators must adhere to the protocol as detailed in this document. The investigator is responsible for enrolling only those subjects who have met protocol eligibility criteria. Investigators are required to sign an investigator agreement to confirm acceptance and willingness to comply with the study protocol.

If the investigator suspends or terminates the study at their site, the investigator will promptly inform the sponsor and the IRB/EC and provide them with a detailed written explanation. The investigator will also return all investigational product, containers, and other study materials to the sponsor. Upon study completion, the investigator will provide the sponsor, IRB/EC, and regulatory agency with final reports and summaries as required by (inter)national regulations.

Communication with local IRBs/ECs, to ensure accurate and timely information is provided at all phases during the study, may be done by the sponsor, applicable CRO, investigator, or for multicenter studies, the coordinating principal investigator according to national provisions and will be documented in the investigator agreement.

10.2.3 Documentation and Retention of Records

10.2.3.1 Case Report Forms

Case report forms (CRFs) are supplied by the CRO and should be handled in accordance with instructions from the sponsor.

The investigator is responsible for maintaining adequate and accurate medical records from which accurate information is recorded onto eCRFs, which have been designed to record all observations and other data pertinent to the clinical investigation. CRFs must be completed by the investigator or designee as stated in the site delegation log.

All data sent to the sponsor must be endorsed by the investigator.

The clinical research associate (CRA)/study monitor will verify the contents against the source data per the monitoring plan. If the data are unclear or contradictory, queries will be sent for corrections or verification of data.

10.2.3.2 Recording, Access, and Retention of Source Data and Study Documents

Original source data to be reviewed during this study will include, but are not limited to: subject's medical file, original clinical laboratory reports, and histology and pathology reports.

All key data must be recorded in the subject's medical records.

The investigator must permit authorized representatives of the sponsor, the respective national, local, or foreign regulatory authorities, the IRB/EC, and auditors to inspect facilities and to have direct access to original source records relevant to this study, regardless of media.

The CRA/study monitor (and auditors, IRB/EC or regulatory inspectors) may check the eCRF entries against the source documents. The consent form includes a statement by which the subject agrees to the monitor/auditor from the sponsor or its representatives, national or local regulatory authorities, or the IRB/EC, having access to source data (eg, subject's medical file, appointment books, original laboratory reports, X-rays etc).

These records must be made available within reasonable times for inspection and duplication, if required, by a properly authorized representative of any regulatory agency (eg, the US Food and Drug Administration (FDA), European Medicines Agency (EMA), UK Medicines and Healthcare Products Regulatory Agency) or an auditor.

Essential documents must be maintained according to ICH GCP requirements and may not be destroyed without written permission from the sponsor.

10.2.3.3 Audit/Inspection

To ensure compliance with relevant regulations, data collected for and generated by this study must be available for inspection upon request by representatives of, for example, the US FDA (as well as other US national and local regulatory authorities), the EMA, the Medicines and Healthcare Products Regulatory Agency, other regulatory authorities, the sponsor or its representatives, and the IRB/EC for each site.

10.2.3.4 Financial Disclosure

The investigator is required to disclose any financial arrangement during the study and for 1 year after, whereby the outcome of the study could be influenced by the value of the compensation for conducting the study, or other payments the investigator received from the sponsor. The following information is collected: any significant payments from the sponsor or subsidiaries such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation or honoraria; any proprietary interest in investigational product; any significant equity interest in the sponsor or subsidiaries as defined in 21 CFR 54 2(b) (1998).

10.3 Ethical Considerations

10.3.1 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from all study subjects prior to any study-related procedures including screening assessments. All consent documentation must be in accordance with applicable regulations and ICH GCP. The Informed Consent procedure has been modified to allow remote consenting of subjects for this phase 4 study. A member of the study team will send the Informed Consent document by mail or e-mail to the subject and discuss the document by telephone. Each subject or the subject's legally-authorized representative, as applicable, is requested to sign and date the subject informed consent form or a certified translation if applicable, after the subject has received and read (or been read) the written subject information and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences, and the subject's rights and responsibilities. The subject will return their signed informed consent document to the site. Upon receipt of the subject's consent, the authorized consenter who performed the remote informed consent procedure will physically sign and date the consent document as well. A copy of the informed consent documentation (ie, a complete set of subject information sheets and fully executed signature pages) must be given to the subject or the subject's legally-authorized representative, as applicable. This document may require translation into the local language. Signed consent forms must remain in each subject's study file and must be available for verification at any time.

The principal investigator provides the sponsor with a copy of the consent form which was reviewed by the IRB/EC and which received their favorable opinion/approval. A copy of the IRB/EC's written favorable opinion/approval of these documents must be provided to the sponsor, prior to the start of the study unless it is agreed to and documented (abiding by regulatory guidelines and national provisions) prior to study start that another party (ie, sponsor or coordinating principal investigator) is responsible for this action. Additionally, if the IRB/EC requires modification of the sample subject information and consent document provided by the sponsor, the documentation supporting this requirement must be provided to the sponsor.

10.3.2 Institutional Review Board or Ethics Committee

It is the responsibility of the investigator to submit this protocol, the informed consent document (approved by the sponsor or their designee), relevant supporting information and all types of subject recruitment information to the IRB/EC for review, and all must be approved prior to site initiation.

Responsibility for coordinating with IRBs/ECs is defined in the investigator agreement.

Prior to implementing changes in the study, the sponsor and the IRB/EC must approve any revisions of all informed consent documents and amendments to the protocol unless there is a subject safety issue.

Investigational product supplies will not be released until the sponsor/CRO has received written IRB/EC approval of and copies of revised documents.

The investigator is responsible for keeping the IRB/EC apprised of the progress of the study and of any changes made to the protocol, but in any case at least once a year; for sites within the EU, this can be done by the sponsor, the investigator or for multicenter studies the coordinating principal investigator, according to national provisions. The investigator must also keep the local IRB/EC informed of any serious and significant AEs.

10.4 Privacy and Confidentiality

All US-based sites and laboratories or entities providing support for this study, must, where applicable, comply with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. A site that is not a covered entity as defined by HIPAA must provide documentation of this fact to the CRO/sponsor.

The confidentiality of records that may be able to identify subjects will be protected in accordance with applicable laws, regulations, and guidelines.

After subjects have consented to take part in the study, the sponsor and/or its representatives reviews their medical records and data collected during the study. These records and data may, in addition, be reviewed by others including the following: independent auditors who validate the data on behalf of the sponsor; third parties with whom the sponsor may develop, register, or market rhPTH(1-84); national or local regulatory authorities; and the IRB(s)/EC(s) which gave approval for the study to proceed. The sponsor and/or its representatives accessing the records and data will take all reasonable precautions in accordance with applicable laws, regulations, and guidelines to maintain the confidentiality of subjects' identities.

Subjects are assigned a unique identifying number; however, their initials and date of birth may also be collected and used to assist the sponsor to verify the accuracy of the data (ie, to confirm that laboratory results have been assigned to the correct subject).

The results of studies – containing subjects' unique identifying number, relevant medical records, and possibly initials and dates of birth – will be recorded. They may be transferred to, and used in, other countries which may not afford the same level of protection that applies within the countries where this study is conducted. The purpose of any such transfer would include: to support regulatory submissions, to conduct new data analyses to publish or present the study results, or to answer questions asked by regulatory or health authorities.

10.5 Study Results / Publication Policy

Shire will endeavor to publish the results of all qualifying, applicable, and covered studies according to external guidelines in a timely manner regardless of whether the outcomes are perceived as positive, neutral, or negative. Additionally, Shire adheres to external guidelines (eg, Good Publication Practices 2) when forming a publication steering committee, which is done for large, multicenter Phase 2-4 and certain other studies as determined by Shire. The purpose of the publication steering committee is to act as a non-commercial body that advises or decides on dissemination of scientific study data in accordance with the scope of this policy.

All publications relating to Shire products or projects must undergo appropriate technical and intellectual property review, with Shire agreement to publish prior to release of information. The review is aimed at protecting the sponsor's proprietary information existing either at the commencement of the study or generated during the study. To the extent permitted by the publisher and copyright law, the principal investigator will own (or share with other authors) the copyright on his/her publications. To the extent that the principal investigator has such sole, joint or shared rights, the principal investigator grants the sponsor a perpetual, irrevocable, royalty free license to make and distribute copies of such publications.

The term "publication" refers to any public disclosure including original research articles, review articles, oral presentations, abstracts and posters at medical congresses, journal supplements, letters to the editor, invited lectures, opinion pieces, book chapters, electronic postings on medical/scientific websites, or other disclosure of the study results, in printed, electronic, oral or other form.

Subject to the terms of the paragraph below, the investigator shall have the right to publish the study results, and any background information provided by the sponsor that is necessary to include in any publication of study results, or necessary for other scholars to verify such study results. Notwithstanding the foregoing, no publication that incorporates the sponsor's confidential information shall be submitted for publication without the sponsor's prior written agreement to publish, and shall be given to the sponsor for review at least 60 days prior to submission for publication. If requested in writing by Shire, the institution and principal investigator shall withhold submission of such publication for up to an additional 60 days to allow for filing of a patent application.

If the study is part of a multicenter study, the first publication of the study results shall be made by the sponsor in conjunction with the sponsor's presentation of a joint, multicenter publication of the compiled and analyzed study results. If such a multicenter publication is not submitted to a journal for publication by the sponsor within an 18-month period after conclusion, abandonment, or termination of the study at all sites, or after the sponsor confirms there shall be no multicenter study publication of the study results, an investigator may individually publish the study results from the specific site in accordance with this section. The investigator must; however, acknowledge in the publication the limitations of the single site data being presented.

Unless otherwise required by the journal in which the publication appears, or the forum in which it is made, authorship will comply with the International Committee of Medical Journal Editors

(ICMJE) current standards. Participation as an investigator does not confer any rights to authorship of publications.

11. REFERENCES

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APPENDIX 1 HYPOPARATHYROIDISM SYMPTOM DIARY

Hypoparathyroidism Symptom Diary

For each of the following questions, please choose the one answer that best describes your experiences related to hypoparathyroidism during the past 24 hours.

1. How would you rate any muscle cramps you experienced during the past 24 hours?

0	1	2	3	4	5	6	7	8	9	10
No muscle cramps										Worst possible muscle cramps

2. How would you rate any tingling you experienced during the past 24 hours?

. None
Mild
Moderate
Severe
Very severe

3. How would you rate any numbness you experienced during the past 24 hours?

None
Mild
Moderate
Severe
Very severe

4. How would you rate any muscle spasms or twitching you experienced during the past 24 hours?

None
Mild
Moderate
Severe
Very severe

5. How would you rate any feelings of heaviness you experienced in your arms or legs during the past 24 hours?

None
Mild
Moderate
Severe
Very severe

6. How would you rate any physical fatigue you experienced during the past 24 hours?

None
Mild
Moderate
Severe
Very severe

7. How would you rate any slowed or confused thinking, sometimes called brain fog, you experienced during the past 24 hours?

None
Mild
Moderate
Severe
Very severe

8. How would you rate any anxiety you felt during the past 24 hours?

None
Mild
Moderate
Severe
Very severe

9. How would you rate any sadness or depression you felt during the past 24 hours?

None
Mild
Moderate
Severe
Very severe

10. How did your hypoparathyroidism impact your sleep last night?

Not at all
Somewhat
Very much

11. How did your hypoparathyroidism impact your ability to exercise in the past 24 hours?

Not at all
Somewhat
Very much

12. How did your hypoparathyroidism impact your ability to complete your work (for example, at school, at home or at a job) in the past 24 hours?

Not at all
Somewhat
Very much

13. How did your hypoparathyroidism impact your relationships with your family members in the past 24 hours?

Not at all
Somewhat
Very much

APPENDIX 2 FACT-COGNITIVE FUNCTION ENG

FACT-Cognitive Function (Version 3)

Below is a list of statements that other people with your condition have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PERCEIVED COGNITIVE IMPAIRMENTS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

FACT-Cog (Version 3)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	COMMENTS FROM OTHERS	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogO1	Other people have told me I seemed to have trouble remembering information	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble speaking clearly	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble thinking clearly	0	1	2	3	4
CogO4	Other people have told me I seemed confused	0	1	2	3	4

FACT-Cog (Version 3)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	PERCEIVED COGNITIVE ABILITIES	Not at all	A little bit	Some-what	Quite a bit	Very much
Cog PCI	I have been able to concentrate	0	1	2	3	4
Cog PVI	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PMI	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PFI	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PCH 1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PCH 2	My memory is as good as it has always been	0	1	2	3	4
Cog PMT 1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PMT 2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	IMPACT ON QUALITY OF LIFE	Not at all	A little bit	Some-what	Quite a bit	Very much
CogQ35	I have been upset about these problems	0	1	2	3	4
CogQ37	These problems have interfered with my ability to work	0	1	2	3	4
CogQ38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
CogQ41	These problems have interfered with the quality of my life	0	1	2	3	4