Hypoparathyroidism Registry ”PARADIGHM”

Protocol PAR-R13-001

PARADIGHM (Physicians Advancing Disease Knowledge in Hypoparathyroidism): A Natural History Registry for Patients with Chronic Hypoparathyroidism

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SIGNATURE PAGE

PARADIGHM HYPOPARATHYROIDISM REGISTRY

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REGISTRY PROTOCOL SYNOPSIS

Title	PARADIGHM (Physicians Advancing Disease Knowledge in Hypoparathyroidism): A Natural History Registry for Patients with Chronic Hypoparathyroidism
Protocol Number	PAR-R13-001
Objectives	To characterize the natural history of chronic hypoparathyroidism, including such items as its treatment, clinical outcomes, comorbidity, and mortality in patients, under conditions of normal clinical practice, regardless of disease etiology and management.
Study Design	This is a prospective, observational, natural history registry, designed to collect data on patients with chronic hypoparathyroidism. It is designed to permit interested physicians to participate as investigators, and interested patients to enroll as study participants. No study-defined procedures will be required, and if available, a select set of data will be collected at baseline and at least annually.
Disease Management	Management of chronic hypoparathyroidism will be determined by the physician according to normal clinical practice; follow-up will be according to routine care by the patients' physicians.
Rationale	To date, limited data are available on the epidemiology of chronic hypoparathyroidism, including incidence, prevalence, risk factors, comorbidity, management modalities, and mortality. The objective of this registry is to characterize the natural history of chronic hypoparathyroidism under conditions of normal clinical practice. Results from the registry are intended to assist health care providers in optimizing their clinical decision-making, through enhanced understanding of the variability, progression, and natural history of chronic hypoparathyroidism. Patients with a diagnosis of chronic hypoparathyroidism will be eligible for inclusion into the registry, regardless of disease etiology and management..
Duration of Study	Approximately 5 years of recruitment and a minimum of 10 years of follow-up per patient
Patient Population and Key Selection Criteria	• Patients of any age or gender, with a diagnosis of chronic hypoparathyroidism before enrollment. • Signed informed consent and medical records release by the patient or a legally acceptable representative.
Number of Patients	Approximately 900 patients will be enrolled globally.

Study Procedures	All eligible patients will be invited to participate in the registry. After patients have signed the informed consent and medical records release, data will be entered into the registry (demographic and baseline data) using electronic data capture (EDC). Thereafter, information on disease status and management will be collected as the patients visit their physicians, according to normal practice. Laboratory tests and other clinical tests are not required and will be entered only if performed. No predetermined follow-up requirements will apply; however, investigators should update patient data in the registry at each patient visit, and will be reminded at least twice annually, with the expectation to update patient data at minimum every 12 months. Patients may enroll directly, in which case, data will be collected via review of medical records by sponsor/designee or via interview by sponsor/designee and entered into the registry using EDC.
Study Data to Be Collected	Following the signing of the Informed Consent Form, data such as the following will be collected, if available. Data is to be entered at minimum every 12 months for data collected since the last registry data entry, including: • Demographic information • Medical and family history • Height and weight • Patient-reported signs and symptoms • Social history (eg, alcohol/tobacco use, socioeconomic status) • Questionnaires (patient- or investigator-reported, eg, history of hospitalization, emergency room visits, sick leave) • Prior and concomitant medications (including over-the-counter medications) • Diagnosis details, including chronic hypoparathyroidism etiology and history • Management of chronic hypoparathyroidism • Comorbidities and outcomes • Laboratory and imaging evaluations • Vital statistics (via search of databases, eg, National Death Index)
Data Collection Procedures	Data will be collected using EDC.
Statistical Methods	Detailed statistical analysis methods will be conducted as described in the statistical analysis pan (SAP) for this study. Data will be summarized using descriptive statistics. Descriptive statistics will comprise the number of observations (n), mean, standard deviation, median, minimum, and maximum for continuous variables; and n and percent for categorical variables. Person-years of follow-up and incidence rates of prospective events will be calculated.
Sample Size	The planned sample size of approximately 900 chronic hypoparathyroidism patients is based upon feasibility rather than statistical considerations.
Analysis Populations	All analyses will be based upon the enrolled population.
Disposition and Baseline Data	Disposition, demographic, and baseline data will be summarized with descriptive statistics and presented in listings.
Prospective Data	Prospective data will be summarized with descriptive statistics and presented in listings.

INVESTIGATOR REGISTRY AGREEMENT PAGE

Protocol PAR-R13-001

I agree:

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

That I am aware of, and will comply with, the internationally recognized code of Good Pharmacoepidemiologic Practices (GPP), International Society for Pharmacoepidemiology standards, and all other applicable regulatory requirements to obtain written and dated approval from the Institutional or Central Review Board (IRB) or Independent Ethics Committee (IEC) for the study protocol and any amendments thereof, written informed consent or updates thereof, patient recruitment procedures (eg, advertisements), and any other written information to be provided to the patients, before initiating this registry,

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

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

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

To ensure that all persons assisting in this study are adequately informed about the protocol and their registry-related duties and functions,

To maintain copies of medical records, electronic case report forms, and study records, including but not limited to signed patient consent documents, for at least 15 years from registry termination/completion or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor.

Investigator (Print Name)	Date (DD MMM YYYY)

Investigator (Signature)

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation / Term	Equivalent Term / Definition
25(OH) vitaminD	25-hydroxyvitamin D, 25-hydroxycholecalciferol, or 25(OH) D_3-1-α (or alpha) hydroxylase
1,25-dihydroxyvitamin D	1,25-dihydroxycholecalciferol or calcitriol
BMD	Bone mineral density
CASR	Calcium-sensing receptor
eCRF	Electronic case report form
EDC	Electronic data capture
GPP	Good Pharmacoepidemiologic Practices
ICF	Informed Consent Form
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
NDI	National Death Index
NPS	NPS Pharmaceuticals, Inc.
PARADIGHM	Physicians Advancing Disease Knowledge in Hypoparathyroidism
PTH	Parathyroid hormone
rhPTH(1-84)	Recombinant human parathyroid hormone (1-84)
SAP	Statistical analysis plan

1 INTRODUCTION

1.1 Hypoparathyroidism

1.1.1 Disease Definition and Epidemiology

Hypoparathyroidism is a rare endocrine deficiency that is characterized by absent or inappropriately low circulating parathyroid hormone (PTH) levels, in association with hypocalcemia and often hyperphosphatemia (Bilezikian et al, 2011; Shoback, 2008). Hypoparathyroidism is listed as a rare disease by the Office of Rare Diseases Research of the National Institutes of Health, affecting less than 200,000 people in the US population.

The epidemiological estimates of the prevalence of hypoparathyroidism are few and range from approximately 65,000 to 100,000 patients in the US (Ruscio et al, 2012; Clarke et al, 2011).

1.1.2 Normal Function of Parathyroid Hormone

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 effect of deficient or absent PTH hormone on the body. It regulates metabolism and serum levels of calcium and phosphate: if serum calcium is low, the parathyroid glands increase PTH secretion, when serum calcium is high, PTH secretion decreases.

The parathyroid glands sense extracellular calcium at the surface of the parathyroid cell and adjust their synthesis and secretion of PTH accordingly. The relationship between ionized extracellular calcium and PTH secretion is a steep sigmoidal curve where small variations in calcium level lead to significant changes in PTH secretion. Calcium sensing is initiated by the binding of calcium to a "sensing" receptor (CASR for calcium-sensing receptor) that is present on the plasma membrane of parathyroid cells. The CASR, a member of the G-protein-coupled receptor superfamily, is activated by calcium binding to it that induces intracellular signals and, through largely unknown mechanisms, regulates the secretion of PTH. The net physiological effect is an increase in PTH when the extracellular calcium falls and a reduction in PTH when the extracellular calcium increases (Bilezikian et al, 2011).

The CASR is widely distributed throughout the human body which may help to explain how a fluctuation in serum calcium may lead to multiple and very diverse symptoms. Besides the parathyroid glands, the CASR has been detected in the kidney, the gastrointestinal tract, bone (in osteoblasts and osteoclasts), the nervous system (in the brain: subfornical organ, the hippocampus and in glial cells), the breast (normal and malignant tissue), in epidermal cells, and in the heart (in the myocytes, and endothelial cells of the cardiac microvasculature and

the aorta). The complete range of these effects is beyond this overview and has been described in detail elsewhere (Magno et al, 2011).

The main actions of PTH are on the kidney, the conversion of vitamin D in the kidney, and on the bone. It has an additional indirect action on the intestines through calcitriol or activated vitamin D.

In the kidney, PTH stimulates calcium reabsorption at the proximal tubule and calcium excretion at the distal nephron. The overall effect of increased PTH is a reduced excretion of calcium. Also in the kidney, PTH will stimulate the 25-hydroxyvitamin D_3-1αhydroxylase that converts 25(OH) vitamin D into 1,25-dihydroxyvitamin D (calcitriol) that will increase the absorption of calcium and phosphate from the intestine. Another contribution of the kidney is the regulation of phosphate excretion since PTH increases phosphate excretion. In the case of hypoparathyroidism and low or absent levels of PTH, hyperphosphatemia is frequent (Sikjaer et al, 2011).

In bone, PTH regulates calcium deposition and resorption (bone holds 99% of the calcium in the human body). The orderly process of bone formation and bone resorption is known as bone remodeling, an important feature of metabolically normal bone.

The net effect of increasing PTH levels is to increase serum calcium, decrease the urinary losses in calcium, and increase phosphate urinary excretion (lowering serum phosphate). The normal negative feedback mechanism is provided by the rise in serum calcium that inhibits PTH secretion and the increase in 1,25-dihydroxyvitamin D (calcitriol) that limits the activation by PTH on the 1-α-hydroxylase (Shoback, 2008). Parathyroid hormone may also play a role in the regulation of magnesium. Serum levels of magnesium and PTH depend on each other in several ways. PTH serves as a modulator of magnesium reabsorption by increasing influx of magnesium into the distal convoluted cell. Additional humoral factors (eg, calcitonin, vitamin D) and the CASR also play a role. In a reciprocal manner, magnesium acts as a negative regulator of PTH release from the parathyroid gland in a manner similar to calcium, and low levels of magnesium (< 0.5 mM) can cause a block of PTH secretion (Vetter and Lohse, 2002).

However, PTH enhances the uptake of phosphate from the intestine and mobilization from bones into the blood. In the bone, slightly more calcium than phosphate is released from the PTH-mediated bone metabolism. In the intestines, absorption of both calcium and phosphate is mediated by an increase in activated vitamin D. The absorption of phosphate is not as dependent on vitamin D as is that of calcium.

As a result the absence of PTH in hypoparathyroidism has direct implications on calcium and phosphate metabolism and their levels throughout the extracellular space. The affected

organs and body systems give rise to a wide range of symptoms that afflicts patients with hypoparathyroidism (Shoback, 2008).

1.1.3 Pathophysiology of Hypoparathyroidism and Related Symptoms

In patients with hypoparathyroidism, low or absent PTH levels frequently lead to a low level of serum calcium and a high serum level of phosphate, whereas, in the urine, there is increased calcium excretion and decreased phosphate excretion. Parathyroid hormone has been shown to cause acute changes in calcium and magnesium transport in the kidney when given in pharmacological doses, however the concentrations of serum magnesium are usually not abnormal, suggesting that PTH does not play an important physiological role in magnesium homeostasis (Rude and Ryzen, 1986).

Acute symptoms of hypoparathyroidism are linked mainly to the low serum calcium levels and are generally reversible. The key symptoms associated with hypocalcemia involve the neuromuscular system where irritability is evident: numbness, paresthesias, twitching, tetany. Difficulty in concentrating ("brain fog") is also commonly reported (Bilezikian et al, 2011). Besides effects on cognition, hypoparathyroidism has also been linked to effects on mood and ideation (Arlt et al, 2002; Velasco et al, 1999). 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).

Bone is another target organ affected by missing PTH (rather than the low serum levels of calcium). Bone serves a key structural role in the body that is normally capable of dynamic change and remodeling in response to physical stressors and metabolic demands. Bone is also a major reservoir of calcium for physiological processes. PTH is required for proper bone remodeling. Patients with hypoparathyroidism have low levels of bone turnover with suppression of biochemical markers of bone formation and resorption. In the setting of chronic hypoparathyroidism, patients develop abnormally increased bone mineral density (BMD). These abnormalities in BMD reflect pathological bone changes in hypoparathyroid patients as seen on bone biopsy and imaging studies. Hypoparathyroid patients have greater cancellous bone volume, greater trabecular and cortical bone widths, and markedly reduced mineralizing surface and bone formation rate as compared with normal subjects (Bilezikian et al, 2011; Rubin and Bilezikian, 2010; Rubin et al, 2011a; Rubin et al, 2011b; Sikjaer et al, 2011; Sikjaer et al, 2012).

Patients with hypoparathyroidism have disruption of normal vitamin D metabolism. As explained earlier, 1,25-dihydroxycholecalciferol is required to permit normal dietary calcium and phosphate absorption from the small intestine and to permit normal mineralization of the bone. Patients with hypoparathyroidism have low endogenous levels of 1,25-dihydroxycholecalciferol because the activity of the 1-alpha hydroxylase enzyme is PTH dependent. Therefore, due to deficient PTH levels, hypoparathyroid patients cannot

properly absorb dietary calcium and have associated impairment of vitamin D dependent bone and renal regulatory mechanisms (Brunton et al, 2011). As a result, in order for PTH to exert its full effects, it is desirable to maintain the serum levels of 25-hydroxycholecalciferol within the normal range.

1.1.4 Disease Etiology

Hypoparathyroidism has numerous recognized causes, the most frequent being injury to the parathyroid glands or their blood supply during surgery to the neck (Rubin et al, 2010; Bilezikian et al, 2011; Sikjaer et al 2011). The most typical surgical setting for the occurrence of hypoparathyroidism is thyroidectomy. This procedure is often performed in thyroid cancer patients, as total thyroidectomy is an effective and generally curative approach. Recent research also shows that the extent of the neck explorations (unilateral or bilateral) plays an important role in the incidence of hypoparathyroidism (Giordano et al, 2012). Thyroid resection for benign thyroid disease (eg, goiter), parathyroidectomy for the treatment of hyperparathyroidism or neck dissection procedures for head and neck carcinomas are similarly associated with surgical hypoparathyroidism. Hypoparathyroidism occurs in about 0.9% to 6.6% of thyroidectomies, with the higher rates being associated with more complicated interventions (Shoback, 2008; Thomusch et al, 2003; Zarnegar et al, 2003; Page and Strunski, 2007). Other causes of hypoparathyroidism occur more rarely, and include congenital absence of the parathyroid glands, autoimmune conditions, genetic mutations (eg, activating mutations of the CASR gene), iron overload syndromes (thalassemia), and radiation damage. These were reviewed in Shoback, 2008 and Bilezikian et al, 2011.

The important consequence of the surgical etiology of hypoparathyroidism is that the majority of the patients are in their thirties or forties when they become hypoparathyroid and will suffer from the disease and its consequences for the rest of their life. This reinforces the importance of preventing complications of hypoparathyroidism or of the administration of high doses of calcitriol or calcium that could occur over the course of an entire lifespan or the remaining life expectancy of 30 to 40 years.

1.1.5 Unmet Medical Need in Hypoparathyroidism

Current management of patients with hypoparathyroidism is limited to the moderation of symptoms of hypocalcemia by increasing intestinal calcium absorption and serum calcium levels. While use of these supplements increases intestinal calcium absorption and serum calcium levels, they do not eliminate the primary cause of the symptoms or alleviate non-symptomatic complications caused by the lack of PTH.

Although oral calcium and calcitriol/alphacalcidol supplementation increases serum calcium, maintenance of stable serum calcium levels at the desired level is essential for the avoidance of complications. The kidneys are especially vulnerable in patients with hypoparathyroidism because the filtered load of calcium increases directly with increases in the serum calcium level. In the absence of PTH to promote renal calcium reabsorption, the additional calcium absorbed must be excreted through the kidneys (Shoback, 2008). High levels of serum calcium can lead to hypercalciuria and ultimately renal failure in chronic cases.

Active vitamin D supplementation raises calcium and phosphate serum levels without normalization of calcium and phosphate metabolism. Furthermore, increasing serum calcium and phosphate levels (ie, raising the calcium phosphate product) worsen ectopic calcification of the kidney and brain in patients treated in this manner. Hypoparathyroidism occurring over a long period of time potentiates the accumulation of these calcifications in the brain and the kidneys leading to irreversible and severe damages (Goswami et al, 2012).

In the absence of PTH, patients with hypoparathyroidism have low endogenous levels of 1,25-dihydroxyvitamin D due to an inability to convert native 25(OH) vitamin D into the active state. This is one of the paramount reasons that hypoparathyroid patients cannot properly absorb dietary calcium.

Therefore, besides the long-term consequences of PTH deficiency and excessive supplementation with calcium and calcitriol on mineral metabolism and the brain and kidney, excessive supplementation does not correct the defective bone metabolism. Recent publications have investigated through bone biopsies the skeleton in patients with hypoparathyroidism and concluded it presented markedly unusual structural and dynamic properties (Rubin et al, 2008). Another recent study assessed the impact of hypoparathyroidism in postmenopausal women, in regard to BMD and the frequency of subclinical vertebral fractures (Mendonca et al, 2013). The results suggested that vertebral fragility occurs in patients with hypoparathyroidism despite normal or even high BMD.

Daily consumption of large oral doses of calcium and vitamin D leads to more complaints and symptoms and is not always effective in preventing clinical signs and symptoms. In addition, since there are currently no formal management guidelines, treatment is based on experience and clinical judgment (Bilezikian et al, 2011). Balancing the administration of supplementation is challenging, depending on a variety of intrinsic and extrinsic factors leading to symptom instability from day to day.

Hypoparathyroidism and its treatment with large doses of calcium and active vitamin D carry a large burden of disease including renal abnormalities and basal ganglia calcifications. An account of the long-term follow-up of 120 patients with hypoparathyroidism was recently published (Mitchell et al, 2012). This diagnosis was confirmed by documented hypocalcemia

with a simultaneous low or inappropriately normal PTH level for at least 1 year. The mean age at onset of hypoparathyroidism was 35 ± 21 years and the mean duration of the disease was 17 (±16) years. To ascertain the level of control of serum calcium in the patients of this cohort, time-weighted average serum calcium measurements were computed for all patients and were between 7.5 and 9.5 mg/dL for 88% of the patients. Of those with a 24-hour urine collection for calcium (n = 53), 38% had at least one measurement over 300 mg/day. Of those with renal imaging (n = 54), 31% had renal calcifications, and 52% of those with head imaging (n = 31) had basal ganglia calcifications. Rates of chronic kidney disease Stage 3 or higher were 2- to 17-fold greater than age-appropriate norms.

The table below outlines the most significant comorbidities associated with hypoparathyroidism. Of these, current therapy addresses only serum calcium levels.

Complications of Hypoparathyroidism	**Symptoms Mitigated by Calcium & Active Vitamin D Supplementation**
Decreased serum calcium levels	✔
Decreased renal calcium reabsorption	
Increased serum phosphate	
Increased calcium-phosphate product	
Lack of endogenous 1,25-dihydroxyvitamin D production	
Increased bone mineral density	
Decreased bone turnover	

Replacement of absent endogenous PTH hormone with recombinant human parathyroid hormone (1-84) (rhPTH[1-84]) is a logical strategy to fulfill the current unmet medical need in hypoparathyroidism treatment. Oral calcium and active vitamin D do not address the multiple abnormalities in physiological processes that occur in the absence of PTH in hypoparathyroidism. Parathyroid hormone replacement therapy will normalize/stabilize both serum calcium and phosphate, while concomitantly controlling renal calcium and phosphate handling, returning autonomous vitamin D activation and reactivating suppressed bone turnover and improving abnormal bone structure. In parallel, hormone replacement prevents the propensity for unfavorable alterations in serum calcium-phosphate dynamics so as not to increase the risk of soft tissue calcification.

1.2 Rationale for the Registry

To date, limited data are available on the epidemiology of chronic hypoparathyroidism, including incidence, prevalence, risk factors, comorbidity, management modalities, and mortality. The objective of this registry is to characterize the natural history of chronic hypoparathyroidism, including treatment, clinical outcomes, comorbidity, and mortality in

patients, under conditions of normal clinical practice, regardless of disease etiology and management.

Results from the registry are intended to assist health care providers in optimizing their clinical decision-making, through enhanced understanding of the variability, progression, and natural history of chronic hypoparathyroidism. Patients with a diagnosis of chronic hypoparathyroidism will be eligible for inclusion into the registry, regardless of disease etiology and management.

2 OBJECTIVES AND STUDY VARIABLES

2.1 Objectives

The objectives of this registry are:

- To characterize the natural history of chronic hypoparathyroidism, including such items as its treatment, clinical outcomes, comorbidity, and mortality in patients, under conditions of normal clinical practice, regardless of disease etiology and management.

2.2 Registry Data to be Collected

Specific variables to be collected are listed in Appendix 1 and include the following information. Laboratory and other clinical tests are not required and will be entered only if performed.

- Demographic information
- Patient-reported signs and symptoms
- Social history (eg, alcohol/tobacco use)
- Prior and concomitant medications (including over-the-counter medications)
- Diagnosis details, including hypoparathyroidism etiology and history
- Comorbidities and outcomes
- Laboratory and imaging evaluations

3 REGISTRY STUDY DESIGN

3.1 Overall Design of the Registry Study

This is a prospective, observational, natural history registry, designed to collect data on patients with chronic hypoparathyroidism. It is designed to permit interested physicians to participate as investigators, and interested patients to enroll as study participants. Patients will be enrolled at participating study centers or can directly enroll if their physician declines.

If patients directly enroll, data will be collected via review of medical records by sponsor or designee or via interview by sponsor/designee.

If possible, patients also will be identified/contacted by sponsor/designee, in accordance with applicable privacy regulations, through organizations that have access to claims and/or electronic medical records to identify additional hypoparathyroid patients.

No study-defined procedures will be required, and if available, a select set of data will be collected at baseline and at least annually, as indicated in Appendix 1.

Patients who participated or are currently enrolled in NPS Pharmaceuticals, Inc. (NPS) rhPTH(1-84) studies are eligible for registry entry. Registry safety data for patients in current NPS rhPTH(1-84) studies will be subject to ongoing pharmacovigilance assessment, as appropriate, and according to the procedures followed in the clinical studies.

3.2 Study Duration

The registry is planned for approximately 5 years of patient recruitment and a minimum of 10 years of follow up for each chronic hypoparathyroidism patient.

3.3 Patient Recruitment and Follow-up

3.3.1 Patient Recruitment

To minimize bias, all patients with chronic hypoparathyroidism, regardless of disease etiology and management are eligible to enroll in this registry. Patients will be enrolled at participating study centers or can directly enroll if their physician declines. If patients directly enroll, data will be collected via review of medical records by sponsor/designee or via interview by sponsor/designee.

3.3.2 Patient Follow-up

During the informed consent process the patient will be asked to supply personal contact and identifiable (ie, social security number) information, permission to contact new treating physicians, and permission to search the US National Death Index (NDI) and other available health status databases to ascertain their vital status, all procedures to reduce lost to follow-up.

Specifically, the patients will be asked for their contact information and to identify a "contact" person so that the sponsor and/or designee or investigator can contact the patient as needed for registry follow-up.

It is expected that some patients will transfer their medical care to a new physician over the course of their participation in the study. If this occurs, contact information for the new treating physician will be requested, and the new treating physician may be invited to

participate in the study. If the new treating physician is not willing to participate in the study, the patient will be asked to sign a medical release form requesting and permitting the new treating physician to provide copies of the patient's medical records for abstraction of study data.

The sponsor/designee will search the US NDI and other available health status databases in order to ascertain the vital status and cause of death of US patients who are lost to follow-up. Likewise, for chronic hypoparathyroidism patients from other regions of the world ascertainment of vital status will be done where similar vital status databases exist.

3.4 Registry Reports

Confidential study center-specific and aggregate reports will be provided to participating investigators and/or regulatory authorities on a periodic basis. Patient specific data will be anonymized. Annual reports will include, but not be limited to accrual rates; summary demographic, and clinical data; and total person-years of follow-up. In addition, these data may be summarized periodically for presentation at professional conferences and sessions, as appropriate. Publications on findings from this registry will be prepared as appropriate per sponsor publication policies and procedures.

4 PATIENT SELECTION AND PARTICIPATION

4.1 Number of Patients

Approximately 900 chronic hypoparathyroidism patients will be enrolled globally.

4.2 Inclusion Criteria

A patient must meet all of the following criteria to be eligible for participation in the study:

1. Patients of any age or gender, with a diagnosis of chronic hypoparathyroidism before enrollment.

   Chronic hypoparathyroidism, defined as one of the following:

   a. PTH value unequivocally low in the presence of low serum calcium for at least 6 months prior to enrollment

   b. Post surgery (thyroid, parathyroid, neck) occurrence of hypoparathyroidism which is currently treated with calcium/calcitriol supplements to maintain a low/normal calcium (if absence of PTH level) for at least 6 months prior to enrollment

   c. Post surgery (thyroid, parathyroid, neck), both serum PTH and calcium low for at least 6 months post surgery and continues to enrollment

d. Non-surgical hypoparathyroidism requiring calcium/calcitriol supplements to maintain a low/normal calcium (if no PTH level available) for at least 6 months prior to enrollment

2. Signed informed consent and medical records release by the patient or a legally acceptable representative

4.3 Exclusion Criteria

A patient who meets any of the following criteria is not eligible for participation in the study:

1. Transient hypoparathyroidism within 6 months of enrollment

4.4 Patient Withdrawal

Patients may participate as long as the registry is active and may withdraw from the registry at any time for any reason, without prejudice to their current or subsequent care.

If a patient withdraws, the reason should be documented in the electronic case report form (eCRF) and all applicable data collected up until the time the patient withdraws their consent will be entered into the eCRF.

Patients who withdraw from the registry will be allowed to re-enter upon re-consenting. If consented, the data during the time period the patient was not enrolled in the registry will be entered into the eCRF upon re-enrollment.

5 MANAGEMENT PLAN

Management of chronic hypoparathyroidism will be determined by the physician according to usual clinical practice. This is a prospective, natural history registry, and no study procedures will be required; patient care and follow-up will be according to routine care by the patients' physicians.

6 STUDY DATA AND PROCEDURES

6.1 Schedule of Data Collection

The schedule for data collection is summarized in Appendix 1.

6.2 Description of Study Procedures

All patients with chronic hypoparathyroidism will be invited to participate in the registry. After patients have signed the informed consent and medical records release, data, if available, will be entered into the registry using electronic data capture (EDC).

Information, as available, will be recorded at Visit 1 (baseline); the data fields are documented in Appendix 1.

During follow-up, information on disease status and management will be collected as the patients visit their study center, according to usual practice. No predetermined follow-up requirements will be required; however, investigators should update patient data in the registry at each patient visit, and will be reminded at least twice annually, with the expectation to update patient data at minimum every 12 months.

7 DATA MANAGEMENT

All data collected in this study will be stored and evaluated in accordance with Good Pharmacoepidemiologic Practices (GPP), local regulatory requirements and applicable guidance for electronic records.

7.1 Methods of Data Collection

Electronic case report forms will be used. Data will be abstracted from the patient's medical record and entered into the eCRFs according to the schedule presented in Appendix 1. Patients will be identified by use of the identification (ID) number assigned to them when they enroll in the registry. This ID will consist of a 4 digit study center (site) number plus a 4-digit patient number (xxxx-xxxx). If the patient has previously been enrolled in an NPS-sponsored rhPTH(1-84) study, the same ID should be assigned to the patient.

Before the first patient's medical record is abstracted, the sponsor/designee will train the investigator and the study center's personnel on recording the data on the eCRFs if the patient is enrolled through the study center. If patients directly enroll, data will be collected via review of medical records by sponsor/designee or via interview by sponsor/designee and recorded into the eCRF using the EDC system.

7.2 Electronic Case Report Forms

Only authorized personnel will have access to the EDC system. Data will be entered into eCRFs in accordance with instructions from the sponsor and/or designee. The investigator or designee will be responsible for the accurate and timely recording of patient data and resolution of missing data.

Data collected during the study will be recorded in the patient's eCRF by study center personnel or sponsor designee. The study center personnel or sponsor designee will keep records of the patient's visit in the files considered as source documents for that study center/patient, eg, hospital chart, research chart, etc.

Online logic checks will be built into the system, so that missing or illogical data are not submitted. In the event that inconsistent data persist, queries may be issued electronically to the clinical study center and answered electronically by that study center's personnel. The identifying information (assigned user name, date, and time) for both the originator of the query and the originator of the data change (if applicable), as well as the investigator's approval of all changes performed on the data, will be collected.

The investigator will be responsible for reviewing eCRFs, resolving data queries generated by the Sponsor and/or designee via the system, providing missing or corrected data, approving all changes performed on the patient data, and endorsing these data within the EDC system. This approval method will include applying an electronic signature, a uniquely assigned user name, and a password that together will represent a traditional handwritten signature.

To ensure quality control and source data verification of eCRFs, 10% of study centers will be visited by a monitor from the sponsor/designee, who will notify the investigator/designee regarding questions or missing data. Additional study center monitoring may be done based on the periodic review of data.

7.3 Record Retention

The investigators will maintain medical records, copies of eCRFs and study records, including but not limited to signed patient consent documents for at least 15 years from registry termination/completion or until instructed in writing by the sponsor that records may be destroyed or forwarded to the sponsor. Records will be retained according to local regulations. The sponsor/designee will retain study related documents and data according to applicable sponsor's record retention schedules, local regulations, or 15 years from registry termination/ completion whichever is longer.

8 STATISTICAL METHODOLOGY AND SAMPLE SIZE

Detailed statistical analysis methods will be conducted as described in the statistical analysis plan (SAP) for this study.

Data will be summarized with tabulated descriptive statistics comprising the number of observations (n), mean, standard deviation, median, minimum, and maximum for continuous variables; and n and percent for categorical variables. Person-years of follow-up and incidence rates of prospective events will be calculated.

8.1 Demographic and Baseline Data

Medical history will be coded using the Medical Dictionary for Regulatory Activities.

Disposition, demographic, and baseline data will be summarized with descriptive statistics and presented in listings.

8.2 Prior and Concomitant Medications

Prior and concomitant medications will be coded using the World Health Organization Drug Dictionary with regard to drug class and drug name. The number and percentage of patients with specific medications will be summarized with descriptive statistics.

8.3 Prospective Data

Tabulated descriptive statistics and graphical data displays will be used to summarize prospectively collected study data. Person-years of follow-up and incidence rates of prospective events will be calculated.

8.4 Analysis Population

All analyses will be based upon the enrolled population.

8.5 Statistical/Analytical Issues

8.5.1 Adjustments for Covariates

Descriptive statistics will be presented without adjustments. Statistical analyses may be adjusted for age, gender, and other selected variables using multivariate techniques.

8.5.2 Handling of Dropouts or Missing Data

Analyses will be conducted using an observed case approach. In general, missing results will not be imputed. Persons lost to follow-up will have their person-time contribution to the registry included in analyses.

8.5.3 Interim Analyses and Data Monitoring

Data will be analyzed periodically for purposes of regulatory reporting and publication. No adjustment will be made for multiple analyses.

8.5.4 Examination of Subgroups

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

8.6 Sample Size

The planned sample size of approximately 900 chronic hypoparathyroidism patients is based upon feasibility rather than statistical considerations.

8.7 Changes to Planned Statistical Analyses

Deviations from the SAP (if any) will be described and justified in the final study report.

9 ADMINISTRATIVE AND ETHICAL REQUIREMENTS

9.1 Declaration of Helsinki and Ethical Review

This protocol will be conducted in accordance with the internationally recognized code of GPP as described by the International Society for Pharmacoepidemiology.

In accordance with guidelines, the protocol and any amendments thereof, advertisements, informed consent forms (ICFs) and updates thereof, and any other written information to be provided to the patients will be reviewed and approved by the Institutional Review Board/Independent Ethics Committee (IRB/IEC). The sponsor will supply relevant material for the investigator to submit to the IRB/IEC for the protocol's review and approval. Written and dated verification of the IRB/IEC approval of the protocol and the written ICF will be forwarded to the sponsor/designee.

The investigator or sponsor/designee will inform the IRB/IEC of subsequent protocol amendments (and any safety finding that results in an unanticipated problem). Approval for protocol amendments will be transmitted in writing to the investigator.

The investigator or sponsor/designee will provide the IRB/IEC with progress reports at appropriate intervals (not to exceed 1 year) and a study summary report following the completion or discontinuation of the study, if requested.

9.2 Patient Information and Consent

In accordance with GPP and applicable guidelines, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the patient or legally authorized representative before entry into the registry. A consent form model will be provided by the sponsor/designee and adapted by the investigator to meet study center, state, and country ethical guidelines, as appropriate.

The investigator (or designee) will explain to the patient the nature of the study. The patient will be informed that participation is voluntary and that he or she can withdraw from the study at any time, without prejudice to their current or subsequent care.

If the patient wishes to participate, but their physician declines participation, the sponsor/designee will obtain a medical records release from the patient.

9.3 Patient Data Protection

Patients should be informed in writing that their data will be stored and analyzed , with confidentiality maintained. This includes personal health information that is de-identified in datasets used for statistical analyses and that may be accessible to non-study personnel. Data protection and confidentiality will be done in accordance with GPP, national and local legislation. Study center-specific information must be added to the ICF as appropriate.

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

The investigator is responsible for keeping a patient identification list of all patients screened and enrolled which includes the following information: patient number, full name, and a secondary unique identifier (ie, hospital/clinic number). A list of patients with a very limited set of data who declined participation must also be maintained and be available for inspection.

For US patients who are lost to follow-up during the course of the registry, the sponsor/ designee will conduct a search of the US NDI and other available health status databases to ascertain their vital status and in the case of a participants death, the cause of death. Likewise, for chronic hypoparathyroid patients from other regions of the world ascertainment of vital status will be done where similar vital status data sources exist.

To facilitate this vital status search, patients will be asked to provide identifiable information (ie, social security number) at the time of enrollment along with their permission to do the search. Patients who decline this permission will be permitted to enroll with no consequence or change to their registry participation. All personal contact information will be maintained in a secure, password protected file and will be destroyed at the conclusion of the registry. Only the patient ID number, outcome of the search, and cause of death will be reported. Where possible, the study center personnel will be requested to perform the vital status search without disclosure of any patient identifying information.

9.4 Changes to the Protocol

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

approval by the IRB/IEC and the regulatory authorities before implementation. Local regulatory requirements must be followed.

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

9.5 Investigator Obligations

Each investigator must provide the following, at minimum, to the sponsor/designee prior to the start of the study:

- A current (within 2 years) signed and dated curriculum vitae for the investigator, including a current office address
- A copy of the original approval for conducting the study from the IRB/IEC. Renewals must be submitted at yearly intervals if the study is ongoing, or as required by the institution.
- A Statement of Investigator (ie, FDA-1572 Form) (for US investigators only)
- A copy of the IRB/IEC-approved ICF
- Financial disclosure for the investigator
- IRB/IEC membership list or Department of Health and Human Services General Assurance Number, which must be maintained current during the study
- The "Investigator Registry Agreement Page" of this protocol must be signed and dated by the investigator.

9.6 Confidentiality/Publication of the Study

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

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

9.7 Scientific Steering Committee

The Scientific Steering Committee will be comprised of key opinion leaders and relevant sponsor individuals who are responsible for making scientific and ethical policy decisions related to the registry.

9.8 Registry Discontinuation

The sponsor reserves the right to discontinue the registry at any time.

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APPENDIX 1 DATA FIELDS TO BE COLLECTED

	Visit 1 (Baseline)[a]	Follow-up[b]
Informed Consent and Medical Records Release	X	
Inclusion/Exclusion Criteria[d]	X	
Patient Demographics[d, e] (eg, Birth date, Gender, Ethnicity, Race, Zip code)	X	
Hypoparathyroidism Etiology (Primary Cause)[d] (eg, Genetic mutation, Surgery induced, Autoimmune, Radiation, Idiopathic, Other)	X	
Family History[d, e]	X	
Chronic Hypoparathyroidism Diagnosis[d, e] (eg, Diagnosis date, Lab evaluations)	X	
Significant Medical History[d, e]	X	
New Concomitant Diseases[d, e] (Comorbidities)		X
Chronic Hypoparathyroidism Management[d]	X[f]	X
Prior and Concomitant Medications[d, e] (Including over-the-counter medications)	X[f]	X
Height, Weight[d]	X	X
Lab Evaluations[d]	X[f]	X
Other Medical Procedures[d] (eg, Imaging)	X	X
Patient Questionnaire[d, e] (eg, Signs and symptoms)	X	X
Other Questionnaires[d, e] (eg, History of Emergency room visits/Hospitalizations, Sick leave, Socioeconomic status, Alcohol/Tobacco use)	X	X
US National Death Index and other vital status database searches[d]		X[c]

[a] Baseline data to be entered as available. No additional measures or tests will be mandated or required.

[b] Investigators will be prompted to enter comprehensive information according to the patient's visit to the clinic and other pertinent health care visits. It is expected that patients will visit their physician more frequently for follow-up, eg, changes in pharmacological treatment. Data should be entered at each patient's visit or at least every 12 months for data collected since the last registry data entry.

[c] Search intervals to be determined

[d] Investigator/Sponsor/Designee reported

[e] Patient reported

[f] Within the past 12 months