1.0 Title Page

Clinical Study Protocol M11-617

A Phase 3, Prospective, Open-Label, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Paricalcitol Oral Solution for the Treatment of Secondary Hyperparathyroidism in Pediatric Subjects Ages 0 to 9 Years with Stage 5 Chronic Kidney Disease Receiving Peritoneal Dialysis or Hemodialysis

Incorporating Administrative Changes 1, 2, 3, 4, 5 and Amendment 1

AbbVie Investigational Product:	Paricalcitol Oral Solution
Date:	13 July 2023
Development Phase:	3
Study Design:	Open-label, single-arm, 24-week study
Investigator:	Investigator information on file at AbbVie Inc.
Sponsor:	AbbVie Inc.
Sponsor/Emergency Contact:	[redacted] MD [redacted] AbbVie Inc. [redacted] 1 North Waukegan Road North Chicago, IL 60064 Cell: [redacted] Fax: Emergency 24 hour Number: +1 (973)-784-6402

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	11 July 2019
Amendment 1	25 June 2020

The purpose of this protocol amendment is to correct minor clerical errors in the protocol, in addition to the following changes:

- Added BIW as a new abbreviation per Amendment 2.
- Updated Section 1.2, Synopsis: Updated the synopsis to accurately reflect the changes described below.

  Rationale: *This change is a clarification.*
- Updated Section 5.1, Overall Study Design and Plan and Section 5.5.4, Selection and Timing of Dose of Study Drug for Each Subject: Incorporated dose reduction instructions, if 0.25 mcg TIW dosing is to be held based on calcium, phosphorous or iPTH levels, then re-start study drug at 0.25 mcg per dose BIW or TIW is allowed at investigator's discretion, at the next scheduled visit.

  Rationale: *This change will provide additional flexibility to the investigators before discontinuing the study drug, if a subject needs a lower dose than 0.25 mcg TIW.*
- Updated Section 5.1, Overall Study Design Plan and Amended Figure 2 Flow Chart,
  a. Clarified the entire washout period is a minimum of 2 weeks and maximum of 12 weeks.
  b. Added in the minimum amount of time required for washout.

  Rationale: *This change is a clarification.*
- Updated Section 5.2.1, Inclusion Criteria and Appendix D, Age-Specific Limit for Phosphorus and Total Calcium: Adjusted upper limit of phosphorus value

for subjects 6-9 years (inclusive) from 5.8 mg/dL to 6.5 mg/dL for entry into washout and dosing period.

Rationale: *Older children with CKD stage 5 tend to have higher phosphate levels despite using different approaches to lower phosphate levels. The upper value of 5.8 mg/dL is for children without chronic kidney disease therefore, changing the limit to 6.5 mg/dL may support enrollment in Study M11-617.*

- Updated Section 5.2.2, Exclusion Criteria #1: Changed timeframe for kidney transplant from within 6 months to within 3 months of screening, and clarified reference is to living donor transplant.

  Rationale: *Exclusion criteria relaxed since primary timepoint for the study is Week 12 and kidney transplant from a living donor can be electively scheduled.*

- Updated Section 5.2.2, Exclusion Criteria # 2: Changed timeframe to discontinue hemodialysis (HD) or peritoneal dialysis (PD) from within 6 months to within 3 months of screening.

  Rationale: *Exclusion criteria relaxed to match the exclusion criteria for kidney transplant. HD and PD can only be discontinued if a subject receives kidney transplant.*

- Updated Section 5.2.3.1 and Section 5.4.1:
  - Changed the word "dose" to "systemic dose" for clarity.
  - Added "chronic use" to glucocorticoids
  - Added language to allow "short term use of high steroids"

  Rationale*: Updated to add clarity regarding route of administration for steroids that are prohibited, and clarified that only chronic use of high dose steroids are prohibited and would require study discontinuation. Short term use is allowed.*

- Updated Section 5.5.4 and Section 5.6.4, Changed the minimum number of subjects to be enrolled in Part 1 from 4 to 8 (to align with Section 5.1)

  Rationale: *Consistency in the minimum numbers of subjects required for Part 1 between Section 5.1, Section 5.5.4 and Section 5.6.4*

- Updated Section 5.5.2.1, Packaging and Labeling: Added further information on glass bottle fill volume and usable volume of Paricalcitol for clarity.

Rationale: *This change is a clarification.*

- Updated Section 6.1.1.1 and Section 7.0: Added language regarding COVID-19.

  Rationale: *Clarification added to capture COVID-19 protocol deviations and AEs.*

- Updated Section 6.1.5, Adverse Event Reporting: Changed physician contact information to [redacted], MD.

  Rationale: *Physician contact for the study has changed.*

- Updated Section 7.0, Protocol Deviations: Updated primary and alternate contacts.

  Rationale: *Primary and alternate contacts for the study have changed.*

- Updated Section 9.2, Ethical Conduct of the Study: Added a paragraph regarding performing protocol-specified procedures due to COVID-19.

  Rationale: *To provide guidance on contingent measures that could be implemented as a response to the COVID-19 pandemic with the aim to ensure continuity of protocol compliance and subject care.*

- Updated Section 10.2, Case Report Forms: Added a sentence regarding performing remote monitoring of data due to COVID-19.

  Rationale: *To clarify remote monitoring may be used due to COVID-19 pandemic.*

- Updated Appendix B, List of Protocol Signatories: Updated list of protocol signatories.

  Rationale: *Protocol signatories have changed.*

- Updated Appendix C, Study Activities: Added a footnote to the table stating that blood draws should be performed following completion of vital signs assessment and ECG and prior to start of dialysis.

  Rationale: *This change is a clarification.*

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M11-617
Name of Study Drug: Paricalcitol	**Phase of Development:** 3
Name of Active Ingredient: Paricalcitol	**Date of Protocol Synopsis:** 13 July 2023
Protocol Title: A Phase 3, Prospective, Open-Label, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Paricalcitol Oral Solution for the Treatment of Secondary Hyperparathyroidism in Pediatric Subjects Ages 0 to 9 Years with Stage 5 Chronic Kidney Disease Receiving Peritoneal Dialysis or Hemodialysis	
Objective: To evaluate the safety, efficacy and pharmacokinetics of paricalcitol oral solution for the treatment of secondary hyperparathyroidism (SHPT) in pediatric subjects 0 to 9 years of age with stage 5 chronic kidney disease (CKD), receiving peritoneal dialysis (PD) or hemodialysis (HD).	
Investigator: Multicenter	
Study Sites: Approximately 12 sites in the United States (US) and in Puerto Rico (PR)	
Study Population: Approximately 16 pediatric male and female subjects between 0 to 9 years of age with SHPT associated with stage 5 CKD receiving PD or HD. A minimum of 4 subjects 0 to 5 years of age and a minimum of 4 subjects 6 to 9 years of age, inclusive at screening, will be enrolled in the study.	
Number of Subjects to be Enrolled: 16 minimum	
Methodology: This study is a Phase 3, 24 week, open-label, single-arm, multicenter study to evaluate the safety, efficacy and pharmacokinetics of paricalcitol oral solution for the treatment of SHPT in pediatric subjects with stage 5 CKD receiving PD or HD. The study will be conducted in four Periods: Screening Period, Washout Period, Dosing Period 1 and Dosing Period 2. The Screening Period may last up to 4 weeks in order to determine eligibility for entry into the Washout or Dosing Period, as applicable. Vitamin D Receptor Activator (VDRA) non-naïve subjects will require a washout period up to 12 weeks to achieve the appropriate laboratory criteria for entry into the Dosing Period. This 24-week study will include two 12-week dosing periods. Eligible subjects entering Dosing Period 1 will receive paricalcitol oral solution for 12 weeks and may continue into Dosing Period 2 for an additional 12 weeks. A minimum of 16 subjects will be required to complete the Dosing Period 1. Enrollment into Dosing Period 1 will occur in two consecutive parts: Part 1 will enroll only patients aged 2 to 9 years and Part 2 will open enrollment to subjects aged < 2 years. Part 2 will not enroll subjects < 2 years of age until after the data from subjects 2 to 9 years of age that complete Dosing Period 1 has been reviewed by the FDA. The initial paricalcitol dose in 2 to 9 years old subjects will be calculated using the last iPTH measurement in the screening or washout period prior to Day 1, based on the following formula: [redacted]. The paricalcitol dose can be decreased at any time. During Dosing Period 1, dose will be increased if needed, every 2 weeks, as determined by iPTH, calcium, and phosphorus levels. Following completion of Dosing Period 1, subjects who enter Dosing Period 2 will continue dosing with up-titration every 4 weeks (if needed) and calcium and phosphorus levels checks for a total of 12 weeks. Subjects will have a Follow-Up phone contact 30 – 35 days after their last dose of study drug.	

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

- Male or female subject between 0 and 9 years of age, inclusive at the time of initial Screening.
- Subject is currently diagnosed with and/or being treated for SHPT.
- Subject must be diagnosed with CKD stage 5 receiving PD or HD for at least 30 days prior to initial Screening.
- For entry into the Washout Period (for VDRA non-naïve subjects), the subject must meet the appropriate laboratory criteria based upon the subject's age:
  - **< 1 year**
    - A corrected calcium value ≥ 8.8 and ≤ 11.0 mg/dL
    - A phosphorus value ≥ 4.8 and ≤ 7.4 mg/dL
    - An iPTH value ≥ 200 pg/mL and ≤ 1,500 pg/mL
  - **1 – 5 years (inclusive)**
    - A corrected calcium value ≥ 9.4 and ≤ 10.8 mg/dL
    - A phosphorus value ≥ 4.5 and ≤ 6.5 mg/dL
    - An iPTH value ≥ 200 pg/mL and ≤ 1,500 pg/mL
  - **6 – 9 years**
    - A corrected calcium value ≥ 9.4 and ≤ 10.3 mg/dL
    - A phosphorus value ≥ 3.6 and ≤ 6.5 mg/dL
    - An iPTH value ≥ 200 pg/mL and ≤ 1,500 pg/mL
- For entry into the Dosing Period (for VDRA-naïve subjects or VDRA non-naïve subjects who have completed the Washout Period), the subject must meet the appropriate laboratory criteria based upon the subject's age:
  - **< 1 year**
    - A corrected calcium value ≥ 8.8 and ≤ 10.2 mg/dL
    - A phosphorus value ≥ 4.8 and ≤ 7.4 mg/dL
    - An iPTH value ≥ 400 pg/mL and ≤ 2,000 pg/mL
  - **1 – 5 years (inclusive)**
    - A corrected calcium value ≥ 8.8 and ≤ 10.2 mg/dL
    - A phosphorus value ≥ 4.5 and ≤ 6.5 mg/dL
    - An iPTH value ≥ 400 pg/mL and ≤ 2,000 pg/mL
  - **6 – 9 years**
    - A corrected calcium value ≥ 8.8 and ≤ 9.5 mg/dL
    - A phosphorus value ≥ 3.6 and ≤ 6.5 mg/dL
    - An iPTH value ≥ 400 pg/mL and ≤ 2,000 pg/mL

Diagnosis and Main Criteria for Inclusion/Exclusion (Continued): **Main Exclusion:** • Subject is scheduled to receive a living donor kidney transplant within 3 months of Screening or is a kidney transplant recipient. • Subject is expected to discontinue PD or HD within 3 months of the initial Screening visit. • Subject has had a parathyroidectomy within 12 weeks prior to Screening. • Subject is taking maintenance calcitonin, bisphosphonates, glucocorticoids (in a dose equivalent to more than > 0.16 mg/kg/day or 5 mg prednisone/day, whichever is lower), 4 weeks prior to Dosing. • Subject is receiving calcimimetics at the time of Screening or is expected to initiate calcimimetics at any time throughout the study.	
Investigational Product:	Paricalcitol Oral Solution – 2.5 mcg/mL
Initial Dose	[redacted]
Mode of Administration:	Oral
Reference Therapy:	Not applicable
Dose	Not applicable
Mode of Administration:	Not applicable
Duration of Treatment: up to 24 weeks	
Criteria for Evaluation: **Efficacy:** The proportion of subjects who achieve two consecutive ≥ 30% reductions from baseline in iPTH or two consecutive iPTH values in the target range between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 1. **Safety:** The proportion of subjects who develop hypercalcemia, defined as two consecutive, post-baseline, corrected calcium measurements above the subject's age-specific limit. Additionally, safety will be assessed through adverse events, changes from baseline in chemistry and hematology laboratory variables, ECG, and changes from baseline in vital signs and physical examinations.	

Statistical Methods:

Efficacy:

Primary: The proportion of subjects who achieve positive response, defined as having either two consecutive ≥ 30% reductions from baseline in iPTH or two consecutive iPTH values in the target range between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 1. The baseline iPTH is defined as the average of the last measurement in the screening or washout period and Day 1, if both are non-missing, otherwise the last non-missing measurement collected prior to the first dose of study drug. The point estimate of the positive response rate and its 95% exact confidence interval (CI) will be provided. The study is targeted to achieve a ≥ 50% positive response rate. If the observed response rate in the Dosing Period 1 is 50% or higher, the study is considered to meet the efficacy endpoint. With a sample size of 16 subjects and an assumed true underlying positive response rate of 65%, the study has an approximately 93% probability to meet the efficacy endpoint.

Secondary:

- Proportion of subjects who achieve a positive response (as defined for the primary endpoint) during Dosing Period 2.
- Proportion of subjects who achieve a positive response (as defined for the primary endpoint) during the Dosing Periods 1 and 2 combined (24 weeks).
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during Dosing Period 1.
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during Dosing Period 2.
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during the Dosing Periods 1 and 2 combined (24 weeks).
- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 1.
- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 2.
- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during the Dosing Periods 1 and 2 combined (24 weeks).

Pharmacokinetic:

Individual paricalcitol plasma concentrations during Dosing Period 1 at each visit will be tabulated and summarized with appropriate statistical methods. Population pharmacokinetic analyses may be performed if useful in the interpretation of the data.

Safety:

Primary: The incidence of hypercalcemia, defined as two consecutive, post-baseline, corrected calcium measurements above the subject's age-specific limit, during Dosing Period 1.

Secondary:

- The incidence of hypercalcemia during Dosing Period 2.
- The incidence of hypercalcemia during the Dosing Periods 1 and 2 combined (24 weeks).

Age (yrs.)	Age-Specific Limit for Total Calcium (mg/dL)[13]
< 1	11.0
1 – 5	10.8
6 – 9	10.3

The summary of adverse events will include "treatment-emergent" events (i.e., those that first occur or worsen after the first dose of study drug and with an onset date no more than 30 days after the last dose of study drug) and "observational" events (i.e., those that first occur or worsen after the first dose of study drug up to the last day in the study). Each adverse event will be mapped to a primary system organ class (SOC) and MedDRA preferred term according to the MedDRA adverse event-coding dictionary.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse Event
ATEMS	AbbVie Temperature Excursion Management System
BIW	Two Times Per Week
BUN	Blood Urea Nitrogen
°C	Celsius degrees
Ca	Calcium
Ca × P	Calcium × Phosphorus product
CD-ROM	Compact Disc Read-Only Memory
CKD	Chronic Kidney Disease
CFR	Code of Federal Regulations
COVID-19	Coronavirus disease 2019
CRF	Case report form
dL	Deciliter
DSUR	Development Safety Update Report
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic Data Capture
EDTA	Edetic acid (ethylenediaminetetraacetic acid)
EMEA	European Agency for the Evaluation of Medicinal Products
ESRD	End stage renal disease
EU	European Union
°F	Fahrenheit degrees
FDA	US Food and Drug Administration
g	grams
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HD	Hemodialysis
HEENT	Head, Eyes, Ears, Nose and Throat
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product

IPPN	International Pediatric Dialysis Network
iPTH	Intact Parathyroid Hormone
IRB	Institutional Review Board
IRT	Interactive Response Technology
KDIGO	Kidney Disease Improving Global Outcomes
KDOQI	Kidney Dialysis Outcomes Quality Initiative
Kg	Kilograms
L	Liter
LDH	Lactic Dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mcg	Micrograms
min	minutes
mL	milliliters
NKF KDOQI	National Kidney Foundation Kidney Dialysis Outcomes Quality Initiative
P	Phosphorus
PD	Peritoneal Dialysis
pg	picograms
PK	Pharmacokinetics
pmol	picomole
PMR	Post-Marketing Requirement
PR	Puerto Rico
PREA	Pediatric Research Equity Act
PTH	Parathyroid Hormone
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SHPT	Secondary Hyperparathyroidism
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TA MD	Therapeutic Area Medical Director
TIW	Three Times Per Week
ULN	Upper Limit of Normal
US	United States
VDRA	Vitamin D Receptor Activator

WHO	World Health Organization
WO	Washout

Definition of Terms

Corrected Calcium	Serum calcium results will be reported as corrected calcium results using the following formula for albumin levels < 4.0 g/dL: corrected calcium (mg/dL) = [(4.0 – subject's albumin level measured in g/dL) × 0.8] + serum total calcium (uncorrected) measured in mg/dL
VDRA Naïve Subjects	Subjects who have not received VDRAs within 4 weeks of the Screening visit.
VDRA non-Naïve Subjects	Subjects who have received VDRAs within 4 weeks of the Screening visit.

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3.0 Introduction

Chronic Kidney Disease (CKD) is characterized by a progressive reduction of renal function. The etiologies of CKD in children often differ from adults, and include congenital, hereditary, acquired or metabolic causes. Irrespective of the etiology, the clinical course of CKD involves a progression to End Stage Renal Disease (ESRD), requiring either dialysis or kidney transplant. The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) Clinical Practice Guidelines[1] divide the clinical course of progressive kidney disease into a continuum of 5 stages based on glomerular filtration rate (GFR), with CKD stage 5 defined as either GFR < 15 mL/min/1.73 m^2 or requiring dialysis.

Similar to adults, secondary hyperparathyroidism (SHPT), characterized by elevated parathyroid hormone (PTH) levels and parathyroid gland hyperplasia, is a common complication of CKD in children. The pathogenesis is mainly attributed to diminished calcitriol synthesis and phosphate retention, both of which result from decreased functional kidney mass. In CKD, the diseased kidneys progressively lose their ability to synthesize 1α, $25(OH)_2$ D_3 and to excrete phosphate, both of which cause hypocalcemia. Decreased levels of 1α, $25(OH)_2$ D_3, phosphate retention, and hypocalcemia, together or independently, stimulate PTH synthesis and secretion and cause hyperproliferation of parathyroid cells. Elevated PTH levels have been reported in patients with a GFR ≤ 70 mL/min/1.73 m^2.[2]

Associated clinical risks include bone pain and fracture, osteopenia, arthritis, resistance to erythropoietin caused by marrow fibrosis, growth failure in children, and extraskeletal calcification.[1,3,4] Studies have shown that 30% to 50% of CKD predialysis patients have histological evidence of osteitis fibrosa cystica.[5-9] The hyperactivity of bone remodeling causes bone to release calcium and phosphorus, leading to hypercalcemia and aggravation of hyperphosphatemia. Hyperphosphatemia, elevated Calcium × Phosphorus product (Ca × P) and chronically high levels of iPTH have been linked to vascular and visceral calcification and increased risk of cardiovascular death.[10-12] Thus, SHPT results in substantial morbidity and increased mortality in CKD patients. Treatment should be

initiated early in patients with mild to moderate degrees of CKD. The goal of therapy for childhood CKD mineral bone disorder is to normalize mineral metabolism with the aim of improving growth, reducing bone deformities and fragility, and minimizing the progression of extra-skeletal calcification. Biochemical markers of serum calcium, phosphorus, and PTH are primarily used to guide therapy; current therapeutic agents are targeted to maintain values in the normal range for stage of CKD.[2]

The NKF KDOQI Pediatric Subcommittee on Practice Guidelines for Bone Metabolism and Disease in Children with CKD, and the Kidney Disease Improving Global Outcomes (KDIGO) international workgroup recommend the clinical diagnosis and evaluation of bone disease should rely on circulating markers of bone turnover, such as iPTH and alkaline phosphatase as well as measures of linear growth.[13,14] Whereas it is generally accepted that serum calcium and phosphate levels should be kept within the range for age, current pediatric consensus guidelines differ with respect to the optimal PTH target range. International guideline committees have suggested different recommendations, with PTH targets ranging from normal in CKD stages 2 – 4 to 2- to 4-fold above the ULN in children on dialysis.[13-17] Because of growth potential, duration of CKD and associated morbidities, recent recommendations have targeted the lower end of PTH range for children. The International Pediatric Dialysis Network (IPPN) has recommended a PTH target range of 1.7 – 3 times the ULN (i.e., 100 – 200 pg/ml) in children undergoing chronic PD and 2 – 3 times the ULN for HD patients.[16-17] Pediatric guidelines from the NKF KDOQI have recommended maintaining serum PTH 3 – 5 times above the upper limit of normal (i.e., 200 – 300 pg/mL).[13]

Vitamin D receptor activators (VDRAs) have been used for nearly half a century to treat SHPT and other biochemical abnormalities in both adults and children with similar therapeutic effects. The dosage of VDRAs needs careful titration based on trends and concurrent changes in serum calcium, phosphate and PTH.[13-17]

Paricalcitol (Zemplar®) capsules are approved and marketed for the prevention and treatment of SHPT associated with CKD stages 3 and 4, and CKD stage 5 receiving PD or HD in adults and pediatric patients 10 years and older.[18]

Use of paricalcitol capsules in this age group (≥ 10 years) is supported by evidence from adequate and well controlled studies in adults with CKD, a 12-week double-blind placebo-controlled randomized multicenter study in 36 pediatric subjects 10 to 16 years of age with CKD stages 3 and 4, and safety data from a 12-week open-label single-arm multicenter study in 13 pediatric subjects 10 to 16 years of age with CKD stage 5 receiving PD or HD. The pharmacokinetics of paricalcitol in stage 5 CKD pediatric subjects appear to be similar to those observed in stage 3 and 4 CKD pediatric subjects.

Adverse reactions reported in these pediatric studies are consistent with the known safety profile of paricalcitol capsules and with what has been reported in adult clinical studies.

Safety and effectiveness of paricalcitol capsules in pediatric subjects under the age of 10 years have not been established.

This study is being conducted to fulfill a post-marketing requirement (PMR) issued under the Pediatric Research Equity Act (PREA) to develop an age appropriate formulation (paricalcitol oral solution), and to determine the safety of the paricalcitol oral solution for the prevention and treatment of SHPT associated with CKD stage 5 in subjects ages 0 to 9 years receiving PD or HD.

3.1 Differences Statement

This is the first prospective clinical study to utilize paricalcitol oral solution in pediatric subjects aged 0 to 9 years with SHPT associated with CKD stage 5 who are receiving PD or HD.

3.2 Benefits and Risks

The potential benefit of paricalcitol in pediatric PD and HD subjects with SHPT is the reduction of iPTH levels without significant incidences of hypercalcemia; thus, further reducing the complications and manifestations of bone disease.

In completed clinical trials with paricalcitol capsules in adult subjects with CKD stage 5, the most common adverse reactions included diarrhea, gastroesophageal reflux, decreased

appetite, hypocalcemia, acne, breast tenderness, and dizziness. Symptoms of elevated calcium (feeling tired, unclear thinking, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination and weight loss) as well as the potential risk of excessive administration of vitamin D compounds including paricalcitol capsules to cause hypercalciuria, hyperphosphatemia, over suppression of PTH, and adynamic bone disease are possible risks associated with paricalcitol. The clinical trials with paricalcitol capsules in children 10 to 16 years of age had a similar safety profile to the adult populations.

4.0 Study Objective

The objective is to evaluate the safety, efficacy and pharmacokinetics of paricalcitol oral solution for the treatment of SHPT in pediatric subjects 0 to 9 years of age with CKD stage 5, receiving PD or HD.

Efficacy will be evaluated as the proportion of subjects who achieve two consecutive ≥ 30% reductions from baseline in iPTH or two consecutive iPTH values in the target range between 150 to 300 pg/mL (16.5 – 33.0 pmol/L). Safety will be evaluated as the incidence of hypercalcemia, defined as two consecutive, post-baseline, corrected calcium measurements above the subject's age-specific upper limit.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

This is a Phase 3, open-label, single-arm, multicenter study evaluating the safety, efficacy and pharmacokinetics of paricalcitol oral solution in pediatric subjects with SHPT associated with stage 5 CKD receiving PD or HD. Approximately 12 sites in the US and PR will be selected to enroll approximately 16 evaluable subjects aged 0 to 9 years in Dosing Period 1, of which at least 4 will be between 0 to 5 years of age and 4 between 6 to 9 years of age, inclusive at screening. Eligible subjects will receive paricalcitol oral solution three times a week (TIW) but no more frequently than every other day for 24 weeks, divided into two 12-week dosing periods (Dosing Period 1 followed by Dosing Period 2).

Enrollment of a minimum of 16 subjects to complete the 12-week Dosing Period 1 will occur in two consecutive parts (Part 1 and Part 2) that are summarized below.

- **Part 1** will enroll only subjects aged 2 to 9 years with the initial paricalcitol dose (in mcg) [redacted]
- **Part 2** will enroll subjects aged < 2 years. This part will not be initiated until after the data and results from Part 1 have been submitted to the FDA and were reviewed from approximately 12 subjects enrolled (age 2 to 9) with a minimum of 8 subjects and a maximum of 12 subjects who completed Dosing Period 1 in Part 1.

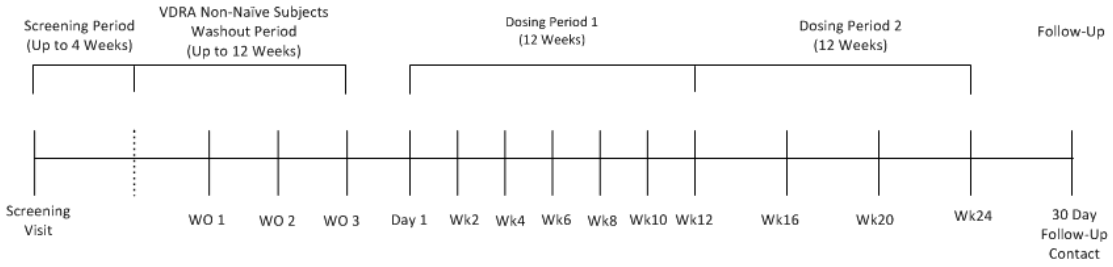
Based on the 2 to 9 year old data that will be submitted to the FDA for review, AbbVie will make a recommendation for the initial paricalcitol dose in subjects < 2 years of age based on a downward trend in iPTH levels while maintaining normal serum calcium levels (for their age) for the 12 week duration. While FDA reviews the data, enrollment will continue for children aged 2 to 9 years, up to a maximum of 14 children that complete Dosing Period 1. Depending on the overall number and age range of subjects enrolled in Study M11-617 when FDA's feedback on Part 1 is received, AbbVie anticipates having future discussions with the FDA to meet the enrollment target goals and complete the study.

The study consists of four Periods:

- Screening Period
- Washout Period (if applicable)
- Dosing Period 1 (Parts 1 and 2)
- Dosing Period 2

A schematic of the study design is shown in Figure 1.

Figure 1. Study Schematic



Screening Period

Potential subjects will undergo Screening procedures listed in Appendix C to determine eligibility for entry into the Washout or Dosing Period, as applicable. Tests for eligibility may be repeated within the subject's 4-week Screening Period.

Subjects who screen fail may be rescreened (minimum of 4 weeks between screening visits) at the discretion of the Investigator. If subjects are rescreened, they will maintain their original subject number.

Washout Period

VDRA non-naïve subjects will discontinue treatment with VDRA compounds at the start of washout period, within 4 weeks of the qualifying Screening visit to clear any biological effects of VDRAs.

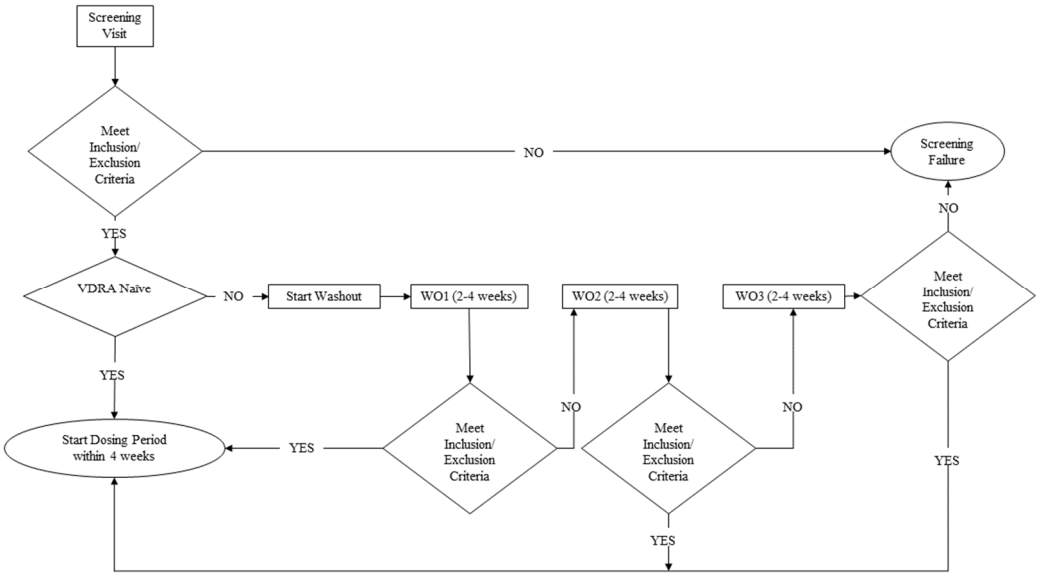
All subjects washing out of VDRAs may complete up to 3 Washout visits to determine eligibility for entry into the Dosing Period. It is at the investigator's discretion to determine the timing of the Washout visits, with a minimum of 2 weeks and a maximum of 4 weeks between visits. The entire Washout Period is a minimum of 2 weeks and a maximum of 12 weeks.

Procedures to be performed at each Washout visit are outlined in Appendix C.

Subjects who do not meet the criteria for entry into the Dosing Period after completing up to 12 weeks of Washout will be screen failed. Subjects who screen fail may be rescreened at the discretion of the Investigator.

Washout visits can be conducted at either the clinical site or the subject's home by a qualified home health nurse.

Figure 2. Flow Chart Screening and Washout



Dosing Period 1

Eligible subjects should be enrolled into Dosing Period 1 within 4 weeks of the qualifying Screening or Washout visit, as applicable. Dosing Period 1 will include 2 parts, Part 1 will enroll only subjects 2 to 9 years of age and after FDA's review of the data and agreement, Part 2 will be initiated to also enroll subjects < 2 years of age. During Dosing Period 1, subjects will receive paricalcitol oral solution TIW (or adjusted to BIW per

Section 5.5.4) for 12 weeks, with up-titration every 2 weeks, and will attend seven scheduled study visits (Day 1, Weeks 2, 4, 6, 8, 10 and 12).

- **Day 1 Visit:** The Investigator or designee will provide dose instructions (Appendix E, Instructions for Use) to subject's parents or legal guardian who will administer the first dose of study drug at the site with supervision by study staff.
- **Week 2 – 10 Visits:** All subjects are required to complete visits at Weeks 2, 4, 6, 8 and 10. Blood samples for limited chemistries and iPTH will be collected at every visit in order to make dose adjustment decisions of study drug, as detailed in Section 5.5.4. If a subject misses a regularly scheduled visit, every attempt should be made to reschedule a visit within that week to obtain labs, preferably within ± 3 days of the regularly scheduled visit. The subject will then resume their original visit schedule. If a subject is unable to reschedule a missed visit within the week, the subject is to maintain their dose of study drug and return at the next regularly scheduled visit. In the event that a subject cannot come to the site because of the COVID-19 pandemic, study visits may be conducted virtually by site staff (e.g., by phone or video) and by a qualified home health nurse at subject's home. AbbVie should be notified if the visit is not conducted at the site and the respective COVID-19 eCRFs should be completed. Any visits conducted virtually or partially should be recorded as such on the respective COVID-19 eCRFs.
- **Week 12 Visit:** At the end of Dosing Period 1, subjects will complete the Week 12 Visit.

Dosing Period 2

- **Week 16 – 20 Visits:** After completing Dosing Period 1, subjects will continue into Dosing Period 2. All subjects are required to complete visits at Weeks 16 and 20. Blood samples for limited chemistries and iPTH will be collected at every visit in order to make dose adjustment decisions of study drug, as detailed in Section 5.5.4. If a subject misses a regularly scheduled visit, every attempt should be made to reschedule a visit within that week to obtain labs, preferably within ± 3 days of the regularly scheduled visit. The

subject will then resume their original visit schedule. If a subject is unable to reschedule a missed visit within the week, the subject is to maintain their dose of study drug and return at the next regularly scheduled visit. In the event that a subject cannot come to the site because of the COVID-19 pandemic, study visits may be conducted virtually by site staff (e.g., by phone or video) and by a qualified home health nurse at subject's home. AbbVie should be notified if the visit is not conducted at the site and the respective COVID-19 eCRFs should be completed. Any visits conducted virtually or partially should be recorded as such on the respective COVID-19 eCRFs.

- **Week 24 Visit:** At the end of the Dosing Period 2, subjects will complete the Week 24 Visit. Following completion from the study, the subject will be treated in accordance with the Investigator's best clinical judgment.

Follow-up contact

All subjects will have a Follow-Up phone contact between 30 – 35 days after their last dose of study drug.

Unscheduled Visits

After reviewing the laboratory results following each scheduled visit, the Investigator may need to contact the subject to conduct an unscheduled visit for the collection of limited chemistry labs and iPTH if needed. Unscheduled visits for study drug dose adjustments may take place at the Investigator's discretion if iPTH, calcium and/or phosphorus values are out of range (Section 5.5.4).

Unscheduled visits can be conducted at either the site or the subject's home by qualified home health nurses.

Premature Discontinuation Visit

If the subject prematurely discontinues from the study the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably 7 days (± 3 days) following the last dose of study drug (Section 5.4.1).

The procedures to be performed at each study visit are outlined in Appendix C.

5.2 Selection of Study Population

Subjects will be male and female pediatric subjects who meet all of the inclusion criteria and none of the exclusion criteria.

5.2.1 Inclusion Criteria

A subject will be eligible for study participation if he/she meets the following:

1. Male or female subject between 0 and 9 years of age, inclusive at the time of Screening.
2. Subject is currently diagnosed with and/or being treated for SHPT.
3. Subject must be diagnosed with CKD stage 5 receiving PD or HD for at least 30 days prior to Screening.
4. If taking phosphate binders, the subject has been on a stable dose, type and regimen for at least 4 weeks prior to initial Screening (excluding dose adjustments for weight gain).
5. If taking nutritional vitamin D, calcium or phosphorus supplementation, the subject has been on a stable dose, type and regimen for at least 4 weeks prior to initial Screening (excluding dose adjustments for weight gain).
6. Subject has stable dialysate calcium content for at least 4 weeks prior to Day 1.
7. If receiving recombinant growth hormone, subject must be receiving it for at least 3 months prior to initial Screening and is expected to remain on a stable dose and regimen throughout the study (excluding dose adjustments for weight gain).
8. For entry into the Washout Period (for VDRA non-naïve subjects), the subject must meet the appropriate laboratory criteria based upon the subject's age:
   - **< 1 year**
     - A corrected calcium value ≥ 8.8 and ≤ 11.0 mg/dL

- A phosphorus value ≥ 4.8 and ≤ 7.4 mg/dL
- An iPTH value ≥ 200 pg/mL and ≤ 1,500 pg/mL

- **1 – 5 years (inclusive)**
  - A corrected calcium value ≥ 9.4 and ≤ 10.8 mg/dL
  - A phosphorus value ≥ 4.5 and ≤ 6.5 mg/dL
  - An iPTH value ≥ 200 pg/mL and ≤ 1,500 pg/mL
- **6 – 9 years (inclusive)**
  - A corrected calcium value ≥ 9.4 and ≤ 10.3 mg/dL
  - A phosphorus value ≥ 3.6 and ≤ 6.5 mg/dL
  - An iPTH value ≥ 200 pg/mL and ≤ 1,500 pg/mL

9. For entry into the Dosing Period (for VDRA-naïve subjects or VDRA non-naïve subjects who have completed the Washout Period), the subject must meet the appropriate laboratory criteria based upon the subject's age:

- **< 1 year**
  - A corrected calcium value ≥ 8.8 and ≤ 10.2 mg/dL
  - A phosphorus value ≥ 4.8 and ≤ 7.4 mg/dL
  - An iPTH value ≥ 400 pg/mL and ≤ 2,000 pg/mL
- **1 – 5 years (inclusive)**
  - A corrected calcium value ≥ 8.8 and ≤ 10.2 mg/dL
  - A phosphorus value ≥ 4.5 and ≤ 6.5 mg/dL
  - An iPTH value ≥ 400 pg/mL and ≤ 2,000 pg/mL
- **6 – 9 years (inclusive)**
  - A corrected calcium value ≥ 8.8 and ≤ 9.5 mg/dL
  - A phosphorus value ≥ 3.6 and ≤ 6.5 mg/dL
  - An iPTH value ≥ 400 pg/mL and ≤ 2,000 pg/mL

10. The subject has provided voluntary assent, if applicable, and the subject's parent or legal guardian has voluntarily signed and dated an informed consent form, approved by an Institutional Review Board (IRB), after the nature of the study has

been explained and the subject and parent or legal guardian has had the opportunity to ask questions.

Rationale for Inclusion Criteria:

1 to 9	To select the adequate subject population with appropriate disease severity for the evaluation
10	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will not be eligible for study participation if he/she meets any of the following criteria:

1. Subject is scheduled to receive, living donor kidney transplant within 3 months of Screening or is a kidney transplant recipient.
2. Subject is expected to discontinue PD or HD within 3 months of the initial Screening visit.
3. Subject has a history of an allergic reaction or significant sensitivity to paricalcitol or other VDRAs.
4. Subject has undergone parathyroidectomy within 12 weeks prior to the initial Screening visit.
5. Subject has chronic gastrointestinal disease, which in the Investigator's opinion may cause significant gastrointestinal malabsorption.
6. Subject is taking maintenance calcitonin, bisphosphonates, glucocorticoids (in a dose equivalent to more than 0.16 mg/kg or 5 mg prednisone/day, whichever is lower), within 4 weeks prior to Dosing.
7. Subject is receiving calcimimetics at the time of the initial Screening visit or is expected to initiate calcimimetics at any time throughout the study.

8. Subject has a current malignancy or clinically significant liver disease, in the opinion of the investigator.
9. Subject has a history of Hepatitis B and/or C.
10. Subject is known to be HIV positive.
11. Subject has evidence of poor compliance with diet or medication that may interfere, in the Investigator's opinion, with adherence to the protocol.
12. Subject has received any investigational drug within 30 days or 5 half-lives, whichever is longer, prior to the initial Screening visit; or is currently enrolled in an interventional clinical study.
13. Subject has any condition which affects iPTH/calcium/phosphorus axis from a congenital bone metabolism disorder (i.e., nephropathic cystinosis, hypophosphatemic rickets, or other rare disorders including metabolic disorders that the Investigator will need to assess).
14. Subject is unable to take oral medications.
15. Subjects who have reached the onset of puberty will be excluded from the study.
16. For any reason, subject is considered by the Investigator to be an unsuitable candidate to receive paricalcitol oral solution or is put at risk by the study procedures.

Rationale for Exclusion Criteria:

1 to 2, 8 to 10, 13 to 16	To exclude an inappropriate subject population
6 to 7, 11, 12	To avoid bias for the evaluation of safety by underlying conditions or concomitant use of other medications
3 to 5, 9 to 10	To ensure safety of the subjects throughout the study

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving within 4 weeks prior to screening or receives during the study, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

If the subject is taking nutritional Vitamin D, calcium or phosphorus supplementation (at a stable dose prior to screening), phosphate binders, and/or receiving growth hormone, as noted in the Inclusion Criteria, the subject should continue these therapies at the same dose throughout the Washout and Dosing Period. Any changes should be noted in EDC.

The AbbVie Therapeutic Area Medical Director (TA MD) should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prohibited Therapy

Subject must not take calcitonin, bisphosphonates, chronic use of glucocorticoids (in a systemic dose equivalent to more than 0.16 mg/kg/day or 5 mg/day prednisone, whichever is lower), or other drugs that may affect calcium, vitamin D or bone mineral metabolism (except for stable phosphate binder or nutritional supplementation) from 4 weeks prior to the Dosing Period, and throughout the study.

Subject must not take calcimimetics from the time of the initial Screening visit and at any time throughout the study.

Short term use of high dose steroids is allowed; the AbbVie therapeutic area medical director (TA MD) should be contacted if there are any questions regarding concomitant or prior therapies.

5.3 Efficacy and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

Informed Consent

Signed informed consent and assent, if applicable, will be obtained before any Screening or study procedures are undertaken or medications discontinued. Informed consent can be collected up to 30 days prior to Screening. Details about how informed consent will be obtained and documented are provided in Section 9.3.

Medical History

A complete medical history from the time of birth will be obtained at the initial Screening visit. Full date of birth will be collected as part of the complete medical history. Renal replacement therapy data (e.g., type of dialysis, frequency, adequacy and dialysate calcium content) will be collected. An updated medical history will be obtained prior to study drug administration.

Physical Examination

Physical examinations will be performed at the initial Screening visit, Day 1, Week 12, Week 24 and Premature Discontinuation visits. A symptom-directed physical examination will be performed when necessary. The last physical examination prior to the first dose of study drug will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after dosing will be recorded as adverse events.

Height/Length

Length (for infants < 2 years of age or incapable for standing independently), or height without shoes (for children ≥ 2 years of age and that are capable of standing independently) will be measured at the initial Screening visit, Day 1, Week 12, Week 24 and Premature Discontinuation visits.

Weight

Weight with lightweight clothing and no shoes will be measured for all subjects at Screening and at each visit during the Dosing Periods and Premature Discontinuation visits, preferably at the termination of a regular dialysis session.

Vital Signs

Vital signs measurements (blood pressure, heart rate, respiratory rate and body temperature) will be collected at Screening and at each visit during the Dosing Periods and Premature Discontinuation visits, prior to dialysis and any scheduled blood draws or ECGs. Blood pressure and heart rate will be collected after the subject has been sitting or in the supine position for at least 5 minutes, if possible. Blood pressure will be measured using the same method, either auscultatory or oscillometric, throughout the study.

12-Lead Electrocardiogram (ECG)

A 12-lead resting ECG will be collected at Screening, Day 1 visit, at Week 12, Week 24 and Premature Discontinuation visits. ECGs should be conducted after vital signs are measured and prior to all blood draws. ECGs will be recorded after the subject has been in the supine position for at least 5 minutes, if possible.

Clinical Laboratory Tests

A central laboratory will be utilized for the required clinical laboratory tests as listed in Appendix C and detailed in Table 1. Blood draw should be performed following

completion of vital signs assessment and ECG, subjects should have their blood drawn prior to the start of their dialysis session.

Laboratory test results obtained at the Day 1 visit will serve as the baseline clinical assessment except for baseline iPTH which is defined for the Efficacy endpoint analysis as the average of the last measurement in the screening or washout period and Day 1, if both are non-missing, otherwise the last non-missing measurement collected prior to the first dose of study drug (Section 8.1).

Table 1. Clinical Laboratory Tests

Hematology	Complete Chemistry	Limited Chemistry
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands Lymphocytes Monocytes Basophils Eosinophils Platelet count	Albumin Alkaline Phosphatase Bicarbonate Blood Urea Nitrogen (BUN) Calcium[a] Chloride Creatinine Sodium Potassium Phosphorus Uric acid Total protein Glucose Magnesium Lactic Dehydrogenase (LDH)	Albumin Calcium[a] Phosphorus **Hormonal Test** iPTH

a. All serum calcium results will be corrected to an albumin level of 4.0 g/dL if the subject's reported albumin level is < 4.0 g/dL (40 g/L). Corrected calcium will be reported to the investigator by the central laboratory and all clinical decisions will be made based on the corrected calcium value.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Prior to the start of dialysis, blood samples for assay of paricalcitol, i.e., all PK samples, will be obtained according to the schedule in Appendix C. Refer to the study specific

laboratory manual for detailed instructions on sample collection, sample volume, processing, and shipment.

The date and time of each blood sample collection will be noted, and the date and time of the two previous doses of study drug will be recorded to the nearest minute on the appropriate site source documentation.

5.3.2.2 Measurement Methods

Plasma concentrations of paricalcitol will be determined by the Bioanalysis Department at AbbVie using a validated method. Plasma concentrations of possible metabolite(s) from paricalcitol may be determined with validated or non-validated methods.

5.3.3 Efficacy Variables

Primary:

- The proportion of subjects who achieve a positive response, defined as having two consecutive ≥ 30% reductions from baseline in iPTH or two consecutive iPTH values in the target range between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 1.

Secondary:

- Proportion of subjects who achieve a positive response (as defined for the primary endpoint) during Dosing Period 2.
- Proportion of subjects who achieve a positive response (as defined for the primary endpoint) during the Dosing Periods 1 and 2 combined (24 weeks).
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during Dosing Period 1.
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during Dosing Period 2.
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during the Dosing Periods 1 and 2 combined (24 weeks).

- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 1.
- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 2.
- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during the Dosing Periods 1 and 2 combined (24 weeks).

5.3.4 Safety Variables

The primary safety variable is the incidence of hypercalcemia, defined as two consecutive, post-baseline, corrected calcium measurements above the normal subject's age-specific upper limit (Appendix D), during Dosing Period 1.

Secondary:

- The incidence of hypercalcemia during Dosing Period 2.
- The incidence of hypercalcemia during the Dosing Periods 1 and 2 combined (24 weeks).

Safety will also be assessed through adverse events, changes from baseline in chemistry and hematology laboratory variables, ECG, and changes from baseline in vital signs and physical examinations.

5.3.5 Pharmacokinetic Variables

Individual paricalcitol plasma concentrations at each visit starting with Study Day 1 through Week 12 of Dosing Period 1 will be tabulated and summarized with appropriate statistical methods.

Population pharmacokinetic analyses may be performed if useful in the interpretation of the data.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Study subjects and/or their parent or legal guardian have the right to prematurely withdraw from the study at any time.

The investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns, or failure to comply with the protocol.

Subjects will be discontinued from study drug administration immediately if any of the following occur:

- Subject requires a dose increase of study drug beyond the maximum allowable paricalcitol dose (16 mcg per dose TIW)
- Subject receives a kidney or any other solid organ transplant
- Subject is enrolled in another interventional investigational study
- Subject begins taking calcitonin, bisphosphonates, calcimimetics, newly initiated growth hormone, chronic use of glucocorticoids (in a systemic dose equivalent to more than > 0.16 mg/kg/day or 5 mg prednisone/day, whichever is lower) or other drugs known to affect calcium or bone metabolism.
- Subject who needs a study drug interruption lasting more than 2 weeks
- Subject has reached the onset of puberty.
- Subject is lost to follow-up, non-compliant with the protocol, or experiences an adverse event that requires the subject to discontinue from the study
- Investigator believes it is in the best interest of the subject
- Subject or subject's parent or legal guardian request withdrawal from the study

Subjects who have had study drug interruption for any reason other than the above should be encouraged to restart study drug as soon as practically and medically appropriate at the discretion of the Investigator. The dates of study drug interruption and restart, and the reason for study drug interruption should be documented in the source document and eCRF(s). Study drug interruption should last no longer than 2 weeks.

In order to minimize missing data for assessments, subjects who discontinue study drug treatment should continue to be followed for all regularly scheduled visits and procedures, unless subjects and their parent or legal guardian have decided to discontinue study participation entirely (withdrawal of informed consent). At a minimum, for subjects who discontinue study drug but do not withdraw consent, the Investigator will monitor each subject for AEs, including hypercalcemia, hyperphosphatemia, and low iPTH values, at 12 weeks after initial dose of study drug (for AEs: or 30 days after last dose of study drug, whichever is later) if discontinued during Dosing Period 1 and 24 weeks after initial dose of study drug (for AEs: or 30 days after last dose of study drug, whichever is later) if discontinued during Dosing Period 2. Subjects and their parent or legal guardian should be advised on the continued scientific importance of their data even if they discontinue study participation or study drug early.

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Premature Discontinuation visit should be completed as soon as possible, preferably 7 days (± 3 days) after their last dose of study drug and preferably prior to the initiation of another VDRA therapy or kidney/major organ transplant. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the Investigator feels are necessary to treat the subject's condition. In addition, the procedures outlined for the Follow-Up contact must be completed between 30 – 35 days after their last dose of study drug. Following completion or withdrawal from the study, the subject will be treated in accordance with the Investigator's best clinical judgment.

Subjects who prematurely discontinue from the study during Dosing Period 1 may be replaced at the discretion of the sponsor. The date of last dose of study drug and reason for premature discontinuation will be recorded in the site source document and the eCRF.

Every effort will be made to retain all enrolled subjects in the study. All subjects that are unreachable after at least three documented attempts, including attempts to contact the subject's primary contact via phone, email, certified letter, and/or to attempt to reach the

subject's secondary contact that was provided on the informed consent, will be considered lost to follow-up.

For subjects who are lost to follow-up during the study, the Sponsor will take reasonable actions to ascertain the subjects' vital status at the end of the study. The Sponsor will make every effort to encourage investigational sites to use a public information source (such as county records) to obtain information about survival status only, as appropriate per local regulations.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination. Advance notice is not required by either party if the study is stopped due to safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.5 Treatments

5.5.1 Treatments Administered

All subjects will receive open-label paricalcitol oral solution for 24 weeks. Paricalcitol oral solution is to be administered with an oral dispenser by mouth only.

5.5.2 Identity of Investigational Product

The study drug information is presented in the table below.

Table 2. Identity of Investigational Product

Study Drug	Formulation	Manufacturer
Paricalcitol Oral Solution	2.5 mcg/mL	AbbVie Inc.

5.5.2.1 Packaging and Labeling

Paricalcitol in liquid solution form (2.5 mcg/mL) will be filled in amber glass bottles containing a 30 mL fill volume (25 mL usable volume) of paricalcitol. Paricalcitol oral solution is a combination product that will be packaged as a kit in a carton box with bottle adapters, 1 mL and 10 mL plastic dispensers for oral administration. The clinical study combination pack that includes the paricalcitol oral solution, 2.5 mcg/mL kit and each of its components will be labeled. Each paricalcitol oral solution study kit will contain a unique kit number and include the following:

- (1) Clear plastic zip lock bag containing 2 bottle adapters (Adapta-Cap®)
- (1) Clear plastic zip lock bag containing 15 (1 mL) oral dispensers
- (1) Clear plastic zip lock bag containing 15 (10 mL) oral dispensers
- (1) Paricalcitol oral solution (2.5 mcg/mL) glass bottle containing a 30 mL fill volume (25 mL usable volume) with a child-resistant cap
- (1) Instructions for Use - Paricalcitol oral solution (Appendix E)

Each study kit and its components will be labeled per local requirements and each label must remain affixed. AbbVie will not supply any other investigational drug or device components outside of those that are provided in the paricalcitol oral solution, 2.5 mcg/mL kit(s).

5.5.2.2 Storage and Disposition of Study Drug

The paricalcitol oral solution (2.5 mcg/mL) bottle must be stored between 2° and 25°C (36° and 77°F), kept away from excessive heat and in an upright position. Daily minimum/maximum temperature monitoring is required by the site. If the temperature falls outside this range, the excursion must be reported immediately, either by contacting

AbbVie directly, or through the AbbVie Temperature Excursion Management System (ATEMS) module of the Interactive Response Technology (IRT) system. In the event of a temperature excursion, affected study drug should be quarantined and should not be dispensed until notification of the final assessment and disposition is received.

The Investigator agrees to not supply study drug to any persons except to those subjects enrolled in the study. The investigational product kit(s) are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to AbbVie or destroyed on site as appropriate. Under circumstances related to COVID-19, sites will be allowed to ship study drug kits to the subject's house. The site must discuss options with AbbVie to ensure the courier has appropriate capabilities to monitor temperature excursions during shipment of the study drug kits.

- Sites will be responsible for meeting IRB reporting requirements and submitting the booking form (which will be provided) to the local IRB (as applicable).
- The investigator must discuss the direct-to-patient (DTP) process with the subject's parent or legal guardian.
- Obtain consent to provide delivery information to Marken and/or local courier and document this in the source.
- Review required safety laboratory results before registering subject dispensation of study drug in IRT.
- Confirm that the subject's parent or legal guardian will be available to accept delivery.
- The site will follow up with the subject's parent or legal guardian after shipment is received.
- Th subject's parent or legal guardian should maintain the study drug kits, as well as any unused drug for return to site.
- Sites will be required to retain documentation of the shipment for the study drug kit accountability and monitoring.

5.5.3 Method of Assigning Subjects to Treatment Groups

All subjects will receive an open-label paricalcitol oral solution, 2.5 mcg/mL kit(s). There is no randomization for this study. All subjects will be assigned a unique subject identification number by IRT at the screening visit. At this visit, IRT will trigger an initial shipment of study drug to the site. Upon receipt of study kit(s), the site will acknowledge receipt in the IRT system.

Subjects who are enrolled will retain their subject number assigned at the screening visit throughout the study. Each kit(s) will contain a unique kit number. The kit number is assigned to a subject via IRT and encodes the study kit(s) to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before dispensing to subjects.

Contact information and user guidelines for IRT use will be provided to each site.

Study drug will be dispensed at the study visits according to the schedule in Appendix C. Returned study drug should not be re-dispensed to the subject.

5.5.4 Selection and Timing of Dose of Study Drug for Each Subject

Initial dose of study drug:

The selection of the initial dose of the paricalcitol oral solution is based on pharmacokinetic/pharmacodynamic modeling that was developed using data from CKD subjects aged 10 to 16 years (Studies M10-149 and M11-612). Clinical trial simulations were then conducted for different dosing strategies of paricalcitol (initial dose and dose adjustments) in CKD stage 5 subjects 2 to 9 years of age. Based on the safety and efficacy results from these simulations, an initial paricalcitol dose of [redacted] was selected. Because reliable clinical simulations could not be performed on ages < 2 years, subjects in this age range will not be enrolled until at least 8 subjects in the 2 to 9 year age range have completed 12 weeks of dosing and the pharmacokinetic, iPTH and calcium results are analyzed and reviewed by FDA (see

Section 5.1 for details.) The initial dose of paricalcitol oral solution will be provided by IRT, and will be calculated using the last iPTH measurement in the screening or washout period prior to Day 1, as applicable, based on the following formula:

The minimum allowable dose of study drug will be 0.25 mcg per dose TIW (or BIW if re-starting study drug, per investigator's discretion) and any initial dose below the minimum will be rounded up to 0.25 mcg per dose. The maximum allowable dose of study drug will be 16 mcg per dose TIW.

Dose adjustments of study drug:

Subsequent dose adjustments of study drug are to be based on iPTH, calcium and phosphorus levels from the subject's most recent laboratory results.

Dose decreases of study drug can occur at any time, while dose increases can occur in approximately 2-week intervals beginning at Week 2 visit in Dosing Period 1 and at approximately 4-week intervals in Dosing Period 2. All doses of paricalcitol will be rounded down to the nearest 0.25 mcg for doses < 2 mcg or down to the nearest 1 mcg for doses > 2 mcg.

Subjects who require a dose reduction of study drug for any reason below 0.25 mcg per dose TIW, will hold dosing until corrected calcium or phosphorus levels are within the subject's age limit (Appendix D) and iPTH >150 pg/mL. They will then re-start study drug at 0.25 mcg per dose BIW or TIW, upon investigator's discretion, at the next scheduled visit and continue at the same dosing schedule as long as corrected calcium or phosphorus levels are within the subject's age limit (Appendix D) and iPTH between 150-300 pg/mL.

If the subject's iPTH level is >300 pg/mL and the subject is receiving 0.25 mcg per dose BIW, the study drug dose frequency will be increased to 0.25 mcg TIW. Subsequent study drug dose adjustments will continue as per protocol according to the study drug dosing decision algorithm unless the study drug is withheld longer than 2 weeks per Section 5.4.1, then subject will be permanently discontinued from the study drug per Section 5.4.1.

Subjects who require a dose increase of study drug for any reason above 16 mcg per dose TIW will discontinue study drug administration.

The following laboratory parameters are suggested when making study drug dosing adjustments decisions (Figure 3).

Serum Calcium

If at any time, the corrected calcium is above the subject's age-specific limit (Appendix D), the dose of study drug should be reduced by 50%.

Corrected calcium should be obtained at least every week until corrected calcium returns within the subject's age-specific limit. If corrected calcium is still above the subject's age-specific limit (Appendix D), then the dose reduction of study drug should be repeated at the investigator's discretion.

Serum Phosphorus

If at any time serum phosphorus is above the subject's age-specific limit, serum phosphorus values should be obtained weekly until phosphorus returns within the subject's age-specific limit (Appendix D).

- For the first occurrence of phosphorus above the subject's age-specific limit: subject and parent or legal guardian are to receive dietary counseling and medication adherence discussion, and the dose of study drug should be maintained.

- For the second consecutive occurrence of phosphorus above the subject's age-specific limit: the investigator should initiate, increase or modify phosphate binder therapy (per investigator discretion), and the dose of study drug should be maintained.
- For the third consecutive occurrence of phosphorus above the subject's age-specific limit, the dose of study drug should be reduced by 50%.

Serum phosphorus should be obtained every week until phosphorus returns within the subject's age-specific limit. If phosphorus is still above the subject's age-specific limit (Appendix D), then dose reduction of study drug should be repeated.

iPTH

If corrected calcium and phosphorus are within the subject's age-specific limits (Appendix D), and:

- If iPTH < 150 pg/mL (16.5 pmol/L), the dose of study drug should be reduced by 50% and iPTH levels should be obtained every 2 weeks until iPTH ≥ 150 pg/mL (16.5 pmol/L). If iPTH is still < 150 pg/mL (16.59 pmol/L), then dose reduction of study drug should be repeated.
- If iPTH ≥ 150 pg/mL (16.5 pmol/L) and ≤ 300 pg/mL (33.0 pmol/L), then maintain the current dose of study drug.
- If iPTH > 300 pg/mL (33.0 pmol/L), the dose of study drug should be increased by 50%.

Study drug dosing decisions as described above are summarized in Figure 3.

[redacted]

Study Drug Administration:

Study drug will be administered to study subject TIW, no more frequently than every other day, by a parent or legal guardian following the instructions for use (Appendix E), with verification and source documentation of the correct dose and supervision from either a study nurse or a home health nurse.

Study drug must be administered by mouth only. Administration of study drug via feeding tubes, nasogastric tubes or gastric tubes is not allowed.

Once the study drug is transferred into the oral dispenser, it must be administered within 1 hour. It is recommended study drug be taken at approximately the same time each day (TIW) under non-fasting conditions within approximately 30 minutes after a meal. The meal consumed prior to study drug administration should be similar, contain well balanced calories from protein, fat and carbohydrate and be consistent with the nutritional recommendations for the subjects individual nutritional plan.[19]

It is not appropriate to dilute the paricalcitol oral solution with liquids including milk as the solution is not miscible and could lead to a reduced delivered dose. Citrus containing products, including but not limited to those containing orange or grapefruit juices or extracts, should not be consumed following study drug administration.

If a dose of study drug is not taken at the regularly scheduled dose time, the dose should be taken as soon as possible on that dosing day. If the dose of study drug is missed completely for that day, the subject should not take another dose until the next scheduled dosing day. If the dose of study drug is partially or fully expectorated within one hour of administration, the full dose of study drug should be re-administered.

As soon as lab results are available after each visit where limited chemistry labs are collected, the site should contact the subject's parents/legal guardian, and home health nurse if applicable, to do one of the following actions: continue the same dose (no changes), increase dose, reduce dose, interrupt dose, or restart dose (per Section 5.5.4). The date of any dose adjustment of study drug and the dose administration change (including replacement of an expectorated dose) must be recorded in the source documents and on the appropriate eCRF.

5.5.5 Blinding

This is an open-label, single treatment arm study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

All doses of study drug will be administered by the parent or legal guardian with supervision by either a study nurse or home health nurse. The nurse will verify and document each dose administered in the source document.

For all subjects who receive doses at home, the parents or legal guardian will be instructed to return all bottles (even if empty) for each treatment visit at the study site.

5.5.7 Drug Accountability

The Investigator or designee will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing the Proof of Receipt or equivalent or via direct recoding in the IRT. An accurate (running) inventory of study drug will be kept by the site, and will include the lot number, Proof of Receipt number(s), the number of bottles of study drug dispensed, subject number, initials of person who dispensed the drug and the date study drug was dispensed for each subject. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the study and at the site close-out visit. All bottles of study drug must be inventoried, accounted for, and returned to AbbVie or destroyed per instructions from AbbVie and according to local regulations. A copy of the Drug Accountability Form, in accordance with instructions provided by the AbbVie monitor, will also be included in the shipment.

The investigator and/or the designee agree not to supply study drug to any persons not enrolled in the study.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

This is a 24-week, open label, single arm study designed to evaluate the safety, efficacy and pharmacokinetics of paricalcitol oral solution in pediatric subjects, 0 to 9 years of age with SHPT associated with stage 5 CKD, receiving PD or HD. Dosing Period 1 (first 12 weeks) will be used to determine the primary efficacy endpoint and safety. Secondary efficacy endpoints will be analyzed in Dosing Period 1, in Dosing Period 2, and in the Dosing Periods 1 and 2 combined (24 weeks), and the overall safety including the incidence of hypercalcemia will be assessed for Dosing Period 1, for Dosing Period 2 and for Dosing Period 1 and 2 combined (24 weeks).

5.6.2 Appropriateness of Measurements

All clinical and laboratory procedures in this study are standard and generally accepted.

5.6.3 Suitability of Subject Population

The purpose of this study is to evaluate paricalcitol oral solution in pediatric subjects with SHPT associated with CKD stage 5 receiving PD or HD. Therefore, subjects 0 to 9 years of age currently diagnosed or being treated for SHPT have been selected as the target population. Subjects who have underlying diseases/conditions and/or on medications affecting bone metabolism, history of allergic reactions to paricalcitol or VDRAs will be excluded to avoid confounding factors.

5.6.4 Selection of Doses in the Study

[redacted]

6.0 Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 6.2.2). For adverse events, please refer to Section 6.1 through Section 6.1.5. For product complaints, please refer to Section 6.2.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause for the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (e.g., COVID-19 infection) temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse

events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).

Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will use the following definitions to rate the severity of each adverse event:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **sufficient** evidence (information) to suggest a causal relationship.
No Reasonable Possibility	After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is **insufficient** evidence (information) to suggest a causal relationship

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

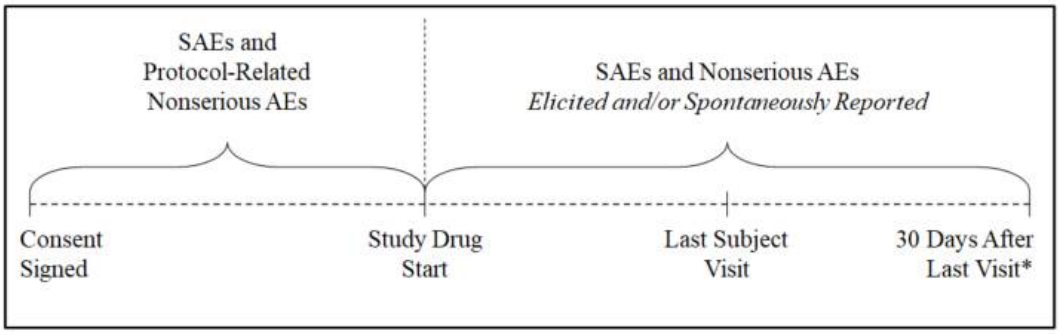
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All adverse events reported from the time of study drug administration until 30 days following discontinuation of study drug administration have elapsed will be collected, whether solicited or spontaneously reported by the subject. In addition, serious adverse events and protocol-related non-serious adverse events will be collected from the time the subject signed the study-specific informed consent/assent. For subjects who discontinue study drug but do not withdraw consent, the Investigator will monitor each subject for SAEs and non-serious AEs at all scheduled visits, as indicated in Section 5.4.1.

Adverse event information will be collected as shown in Figure 4.

Figure 4. Adverse Event Collection Period



* Subjects who discontinue from study drug will continue with visits as described in Section 5.4.1.

6.1.5 Adverse Event Reporting

In the event of a serious adverse event, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event by entering the serious adverse event data into the electronic data capture (EDC) system. Serious adverse events that occur prior to the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE Non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the serious adverse event.

Email: PPDINDPharmacovigilance@abbvie.com

FAX to: +1 (847) 938-0660

For safety concerns, contact Clinical Trial Patient Safety at:

Clinical Trial Patient Safety
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064

Office: +1 847-935-7577
Email: GPRD_SafetyManagement_Hormones@abbvie.com

For subject safety concerns, please contact the physician listed below:

[redacted] MD
[redacted]
AbbVie Inc.
[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Cell: [redacted]
Email: [redacted]

In emergency situations involving study subjects when the primary TA MD is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie TA MD:

Phone: +1 (973) 784-6402

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Global and Local Regulation and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI).

6.1.6 Pregnancy

Only subjects who have not reached puberty will be enrolled. If a subject has reached puberty during the study, they will be discontinued from the study.

6.2 Product Complaint

6.2.1 Definition

A Product Complaint is any Complaint (see Section 6.0 for the definition) related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

6.2.2 Reporting

Product Complaints concerning the investigational product and/or device must be reported to the Sponsor within 1 business day of the study site's knowledge of the event via the Product Complaint form. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product Complaints may require return of the product with the alleged complaint condition (oral dispenser). In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol unless when necessary to eliminate an immediate hazard to study subjects. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Review Board (IRB), regulatory authorities (as applicable), and the following AbbVie Clinical Monitor(s)/study staff:

Primary Contact:

[redacted]
AbbVie Inc.

1 N. Waukegan Rd.
North Chicago, IL 60064

Cell: [redacted]

Alternate Contact:

[redacted]
AbbVie Inc.

1 N. Waukegan Rd.
North Chicago, IL 60064

Cell: [redacted]

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the Statistical Analysis Plan (SAP). The analyses will be performed using SAS® (SAS Institute Inc., Cary, NC, USA).

Continuous variables will be summarized by sample size (N), mean, standard deviation, median, minimum and maximum. Frequency and percentages will be provided for the categorical variables and 95% confidence intervals will be generated for parameter estimates of interest.

Unless otherwise specified, the baseline measurement is defined as the last non-missing measurement collected prior to the first dose of study drug (i.e., at or before the Day 1 Visit). The baseline iPTH for the efficacy endpoint analysis is defined as the average of the last measurement in the screening or washout period and Day 1, if both are non-missing, otherwise the last non-missing measurement collected prior to the first dose of study drug. The final measurement is defined as the last non-missing measurement collected between the first dose and no more than 3 days after the last dose of study drug.

Exploratory analyses of the data will be conducted as deemed appropriate.

8.1.1 Analysis of Dataset and Windows for Scheduled Visits

The All Treated Dataset is defined as the set of all subjects who take at least 1 dose of study drug including those who prematurely discontinued study treatment. All efficacy and safety analyses will be conducted on the All Treated Dataset, unless otherwise specified.

To perform visit wise data summaries, the measurements at the scheduled and/or optional visits (Week 2, 4, 6, 8, 10, 12, 16, 20, and 24) are determined by comparing the days of the measurement relative to the first dose of study drug with the pre-specified visit

windows corresponding to the nominal days of the scheduled visits. For the assessments taken at each scheduled visit the corresponding windows and nominal days are given in Table 3 below.

Table 3. Analysis Visit Window

Scheduled Visits	Nominal Days	Visit Window (Days)
2	15	[2, 21]
4	29	[22, 35]
6	43	[36, 49]
8	57	[50, 63]
10	71	[64, 77]
12	85	[78, 98]
16	113	[99, 126]
20	141	[127, 154]
24	169	[155, 182]

When there is more than one measurement taken within a specific window, the one taken on a day closest to the nominal day will be chosen for the analysis. If 2 values are equidistant from the nominal day, one being before and one being after the nominal day, then the later measurement will be considered the measurement for that visit. For any given variable, if more than one measurement exists for a subject on the same day, the average of the measurements will be considered to be that subject's measurement for that day.

8.1.2 Demographics, Baseline Characteristics, Subject Disposition, and Concomitant Medications

Demographic and Baseline Characteristics Analyses

Demographic and baseline characteristics will be summarized including age, gender, race, ethnicity, dialysis modality and length of time on dialysis.

Baseline laboratory assessments for hematology, complete chemistry variables and iPTH will be summarized using descriptive statistics.

Medical history will be summarized using descriptive statistics.

Subject Accountability and Disposition

Subject Accountability will summarize the number of subjects who entered Screening/Washout Periods and the number of subjects who received at least 1 dose of study drug over all subjects and by Investigator. Subject Disposition will summarize the final status of the subjects through completion of the study or premature discontinuation of study and drug, respectively. Descriptive summary statistics will be generated for both of these measures.

Prior and Concomitant Medications

Concomitant medications will be summarized by generic name assigned by the World Health Organization (WHO) dictionary and will include the number and percentage of subjects that take the medications. Concomitant medications are those medications, other than study drug, taken after the first dose of study drug and collected on the case report forms. In addition, for each concomitant medication, a table displaying subject numbers for those subjects that took the medication will be provided. Subjects reporting the same medication generic name 2 or more times will be counted only once for that generic name. Subjects reporting more than one medication will be counted only once in the total number of subjects taking a concomitant medication. A similar summarization will be performed for prior medications. Prior medications are those medications taken within 4 weeks of the initial screening visit and prior to the first dose of study drug and collected on the case report forms.

8.1.3 Efficacy Analyses

Primary efficacy endpoint is the proportion of subjects who achieve a positive response, defined as having either two consecutive ≥ 30% reductions from baseline in iPTH or

two consecutive iPTH values in the target range between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L)[13] (defined as positive response) during the 12-weeks of Dosing Period 1. The point estimate of the positive response rate and its 95% exact confidence interval (CI) will be provided.

Secondary:

- Proportion of subjects who achieve a positive response (as defined for the primary endpoint) during Dosing Period 2.
- Proportion of subjects who achieve a positive response (as defined for the primary endpoint) during the Dosing Periods 1 and 2 combined (24 weeks).
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during Dosing Period 1.
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during Dosing Period 2.
- Proportion of subjects who achieve two consecutive ≥ 30% reductions in iPTH from baseline during the Dosing Periods 1 and 2 combined (24 weeks).
- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 1.
- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during Dosing Period 2.
- Proportion of subjects who achieve two consecutive iPTH values between 150 pg/mL to 300 pg/mL (16.5 – 33.0 pmol/L) during the Dosing Periods 1 and 2 combined (24 weeks).

The study is targeted to achieve a ≥ 50% positive response rate. If the observed response rate in Dosing Period 1 is 50% or higher (i.e., at least 8 out of the 16 subjects), the study is considered to meet the efficacy endpoint. With a sample size of 16 subjects and an assumed true underlying positive response rate of 65%, the study has an approximately 93% probability to meet the efficacy endpoint.

8.1.4 Safety Analyses

8.1.4.1 Study Drug Exposure

Study drug exposure for each subject will be calculated using the last dose date minus the first dose date plus 1. The distribution of subjects within the following categories will be displayed: ≤ 4 weeks, > 4 to 8 weeks, > 8 to 12 weeks, > 12 to 16 weeks, > 16 to 20 weeks, > 20 weeks of study drug exposure. Study drug compliance will be summarized by total planned dose and total dose taken for each subject. Compliance (%) is defined as total dose taken relative to total planned dose. Compliance data will be listed, and simple summary statistics for overall compliance will be presented.

8.1.4.2 Adverse Events

The summary of adverse events will include "treatment-emergent" events (i.e., those that first occur or worsen after the first dose of study drug and with an onset date no more than 30 days after the last dose of study drug) and "observational" events (i.e., those that first occur or worsen after the first dose of study drug up to the last day in the study). Each adverse event will be mapped to a primary system organ class (SOC) and MedDRA preferred term according to the MedDRA adverse event-coding dictionary. Treatment-emergent and observational adverse events will be summarized as described below:

- An overview of the number and percentage of subjects with adverse events.
- A summary of the number and percentage of subjects with adverse events by MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with serious adverse events by MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with nonserious adverse events by MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with adverse events leading to discontinuation of study drug by MedDRA system organ class and preferred term.

- A summary of the number and percentage of subjects with drug-related (i.e., with reasonable possibility) adverse events by MedDRA system organ class and preferred term.
- A summary of the number and percentage of subjects with adverse events by MedDRA system organ class, preferred term and maximum severity (i.e., highest severity rating of severe, moderate or mild).
- A listing of subject numbers associated with adverse events by MedDRA system organ class and preferred term.

8.1.4.3 Laboratory Parameters

For all the laboratory parameters, change (and percentage change for iPTH) from baseline to final measurements, to minimum and to maximum values, will be summarized.

Where it is applicable to categorize a laboratory assessment by Normal, High, or Low according to the normal range provided by the central laboratory, shift tables will be provided for each laboratory parameter.

Longitudinal Data Analyses

The change from baseline on laboratory variables will be summarized at each scheduled visit using descriptive summary statistics.

As a descriptive tool, graphs will be produced for mean change (and percentage change for iPTH) from baseline on limited chemistry variables across post-baseline visits. In addition, graphs will be produced, by subject, for change from baseline on limited chemistry variables across post-baseline visits.

Moreover, number of subjects with single episodes of corrected calcium levels above the upper limit of normal (ULN) by age group, mean changes in serum calcium, number of subjects who have a dose reduction of study drug for either hyperphosphatemia [defined as having 3 consecutive occurrence, post baseline, phosphorus measurements above the subject's age-specific limit (Appendix D)], or for hypercalcemia [defined as having

2 consecutive post baseline corrected calcium measurements above the subject's age-specific limit (Appendix D)], or for low serum iPTH levels (defined as iPTH < 150 pg/mL) and number of subjects who interrupted study drug due to abnormal calcium, phosphorus and iPTH levels will be summarized.

8.1.4.4 Summary of the Proportion of Subjects Experiencing Hypercalcemia

The number and proportion of subjects experiencing hypercalcemia, defined as having 2 consecutive, post baseline, corrected calcium measurements above the subject's age-specific limit (Appendix D), during the 12-week Dosing Period 1 will be summarized using descriptive summary statistics. An exact 95% confidence interval will be generated for the proportion of subjects who experience hypercalcemia. The incidence of hypercalcemia during Dosing Period 2 and during the Dosing Periods 1 and 2 combined (24 weeks) will be provided as well.

8.1.4.5 Vital Signs

Change from baseline to final measurements on vital sign variables will be summarized using descriptive summary statistics. In addition, change from baseline on vital signs visits will be summarized at each visit using descriptive summary statistics.

8.2 Determination of Sample Size

The study is targeted to achieve a ≥ 50% positive response rate. If the observed response rate in Dosing Period 1 is 50% or higher (i.e., at least 8 out of the 16 subjects), the study is considered to meet the efficacy endpoint. With a sample size of 16 subjects and an assumed true underlying positive response rate of 65%, the study has an approximately 93% probability to meet the efficacy endpoint.

Sixteen subjects will initially be enrolled in Dosing Period 1, and subjects that withdraw or discontinue will be replaced to ensure that 16 subjects complete Dosing Period 1. Subjects that complete Dosing Period 1 will continue into the 12-week Dosing Period 2.

8.3 Pharmacokinetic and Exposure-Response Analysis

Individual paricalcitol plasma concentrations will be tabulated for each subject and summarized with appropriate statistical methods.

Data from this study may be combined with data from other studies conducted in adults and older subjects with CKD for the population pharmacokinetic and exposure-response analyses to evaluate potential differences in populations or CKD stage.

Pharmacokinetic models will be built using a non-linear mixed-effects modeling approach with non-linear mixed effects modeling software with the structure of the starting model based on the PK analysis of data from previous studies conducted in adult and adolescent subjects.

Once an appropriate base pharmacokinetic model (including inter-and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using non-linear mixed effects modeling. The relationship between these conditional estimates CL/F and V/F values with only potentially physiologically relevant or clinically meaningful covariates (such as subject age, sex, race, body weight, disease state such as CKD stage, baseline values of albumin, baseline value of creatinine, baseline value of iPTH, baseline value of calcium, and baseline value of phosphorus, will be explored using stepwise forward selection method, or another suitable regression/smoothing method.

Linear or non-linear relationships of primary PK parameters with various covariates will be explored and parameters from the final pharmacokinetic model and subject-specific covariates found to significantly contribute to the final model will be used to explain the relationships between paricalcitol exposure and serum iPTH, calcium and phosphorus levels.

For the same subjects from whom the PK samples will be collected, relationships between paricalcitol exposure and clinical observations (primary efficacy variable) will be explored. For exposure response analysis, the indirect response structural model

previously developed in adult and adolescent subjects will be utilized as the base model to describe the time courses of serum iPTH, calcium and phosphorus.

Exposure-response relationships for secondary efficacy variables and/or some safety measures of interest may also be explored, and additional analyses will be performed if useful and appropriate.

9.0 Ethics

9.1 Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IRB. The IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IRB approval of the protocol, informed consent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP and all other applicable regulatory requirements.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and any additional reports required by local regulations) to the IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments and alternative locations for data collection. In response to the COVID-19 pandemic, AbbVie has included several revisions in the protocol such as alternate procedures including phone contacts or virtual site visits for assessments and shipping investigational product and/or supplies direct to subjects to ensure continuity of treatment. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject and parent or legal guardian, and answer all questions regarding this study. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject and/or parent or legal guardian, the person who administered the informed consent, and any other signatories according to local requirements. When deemed necessary by the IRB, the documented assent for subjects who are minor children must be obtained. A copy of the informed consent form and assent (if applicable) will be given to the subject and parent or legal guardian and the original will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent

was obtained prior to any study-related procedures and that the subject received a signed copy.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded to the appropriate source document. The Investigator Awareness Date (SAE CRF) may serve as the source for this data point. This adverse event data point required for eCRF completion can be entered directly in the eCRF.

The investigator(s)/institution(s) will permit study-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source data documents.

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available

through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

During the COVID-19 pandemic, remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

11.0 Data Quality Assurance

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and

reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

12.0 Use of Information

All information concerning paricalcitol and AbbVie operations, such as AbbVie patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this clinical study is also considered confidential and will be used by AbbVie in connection with the development of paricalcitol. This information may be disclosed as deemed necessary by AbbVie to other clinical investigators, other pharmaceutical companies, to the US Food and Drug Administration (FDA) and to other governmental agencies. To allow for the use of the information derived from this clinical study and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with complete test results and all data developed in this study and to provide direct access to source data/documents for trial related monitoring, audits, IRB review and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie and shall not be used except in the performance of this study.

The Investigator will maintain a confidential subject identification code list of all subjects enrolled in the study (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by

both the investigator and AbbVie. The investigator will provide a final report to the IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must submit, maintain, and archive any records related to the study according to ICH GCP and all other applicable regulatory requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit or the last subject's actual date of follow-up contact, whichever is later.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Paricalcitol.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	A Phase 3, Prospective, Open-Label, Multicenter Study to Evaluate the Safety, Efficacy and Pharmacokinetics of Paricalcitol Oral Solution for the Treatment of Secondary Hyperparathyroidism in Pediatric Subjects Ages 0 to 9 Years with Stage 5 Chronic Kidney Disease Receiving Peritoneal Dialysis or Hemodialysis
Protocol Date:	13 July 2023

Signature of Principal Investigator | Date

Name of Principal Investigator (printed or typed)

15.0 Reference List

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Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Appendix C. Study Activities

Activity	Screening Period[a] (Up to 4 Weeks)	Washout Period[b,c] (Up to 12 Weeks)			Dosing Period 1[b,d] (12 Weeks)			Dosing Period 2[d] (12 Weeks)		Unscheduled Visit	Premature Discontinuation Visit[e]	Follow-Up Contact[f]
	Screening Visit	WO 1	WO 2	WO 3	Day 1	Wks 2, 4, 6, 8, 10	Wk 12	Wks 16, 20	Wk 24			
Informed Consent/Assent[g]	X											
Medical History[h]	X				X							
Physical Exam	X				X		X		X		X	
ECG[i]	X				X		X		X		X	
Vital Signs[j]	X				X	X	X	X	X		X	
Height/Length[k]	X				X		X		X		X	
Weight[l]	X				X	X	X	X	X		X	
Hematology[m]	X				X		X		X		X	
Complete Chemistry[m]	X				X		X		X		X	
Limited Chemistry[m,n]		X	X	X		X		X		X		
iPTH[m,o]	X	X	X	X	X	X	X	X	X	X	X	
PK blood draw[m]					X[p]	X[q,r]	X[q,r]				X[q,r]	
Prior/Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X

Activity	Screening Period[a] (Up to 4 Weeks)	Washout Period[b,c] (Up to 12 Weeks)			Dosing Period 1[b,d] (12 Weeks)			Dosing Period 2[d] (12 Weeks)		Unscheduled Visit	Premature Discontinuation Visit[e]	Follow-Up Contact[f]
	Screening Visit	WO 1	WO 2	WO 3	Day 1	Wks 2, 4, 6, 8, 10	Wk 12	Wks 16, 20	Wk 24			
Monitor Adverse Events[s]	X	X	X	X	X	X	X	X	X	X	X	X
IRT Call	X				X	X	X	X	X		X	
Dispense Study Drug					X	X	X	X				
Monitor Study Drug Compliance[t]					X	X	X	X	X	X	X	

a. Tests for eligibility may be repeated within the subject's 4-week Screening Period, at the discretion of the Investigator.

b. Subjects should enter the next study period (Washout or Dosing, as applicable) within 4 weeks of the qualifying Screening or Washout visit.

c. Subjects will require Washout if the subject has current or previous exposure to a VDRA within 4 weeks of the Screening Visit. It is at the investigator's discretion to determine the timing of the WO visits, with a minimum of 2 weeks and a maximum of 4 weeks between visits.

d. Subjects are recommended to prospectively schedule their study visits from Week 2 through Week 12 to occur approximately 3 days following their last dose of study drug. Study visits should be conducted within ± 3 days of the expected visit date during Dosing Period 1 and ± 3 days during Dosing Period 2. All expected visit dates are calculated from Day 1.

e. Subjects that Prematurely Discontinue from the study and study drug should perform a premature discontinuation visit approximately 7 days (± 3 days) after their last dose of study drug. Subjects who discontinue study drug but remain in the study will continue with all visits and procedures as noted in Section 5.4.1.

f. A Follow-Up Phone Contact will be completed between 30 – 35 days after the last dose of study drug.

g. Signed informed consent and assent, if applicable, can be collected up to 30 days prior to the conduct of any Screening procedures or discontinuation of medications.

h. Complete medical history from birth will be obtained at the initial Screening visit and updated at Day 1 prior to study drug administration.

i. All 12-lead resting ECGs will be obtained after vital signs are measured and prior to blood collection; ECGs could be obtained at or within 1 week prior to the visit.

j. Vital signs measurements (blood pressure, heart rate, respiratory rate and body temperature) will be collected at Screening and each visit during the Dosing Periods and Premature Discontinuation visit, prior to dialysis and any scheduled blood draws or ECGs. Blood pressure and heart rate will be measured after the subject has been sitting or in the supine position for at least 5 minutes, if possible.

k. Length will be measured for infants < 2 years of age or incapable for standing independently and height without shoes will be measure for children ≥ 2 years of age and that are capable of standing independently at the initial Screening visit, Day 1, Week 12, Week 24, and premature discontinuation visit.

l. Weight with lightweight clothing and no shoes will be measured for all subjects at Screening and at each visit during the Dosing Periods and Premature Discontinuation visit, preferably after dialysis session.

m. Blood draws should be performed following completion of vital signs assessment and ECG (if applicable for visit) and prior to the start of dialysis.

n. A blood draw will be completed to measure limited chemistry (Serum Albumin, Calcium, and Phosphorus) every 2 weeks (± 3 days) during Dosing Period 1 and every 4 weeks (± 3 days) during Dosing Period 2.

o. A blood draw will be completed to measure iPTH every 2 weeks (± 3 days) during Dosing Period 1 and every 4 weeks (± 3 days) during Dosing Period 2.

p. Blood draw for PK on Study Day 1 should be collected immediately prior to (0 minutes) and 1 and 3 hours following the initial dose of study drug and before dialysis. Time of sample collection and time of initial dose of study drug will be recorded in the site source documentation.

q. Blood draw for PK on Dosing Period 1 (Study visits at Week 2, 4, 6, 8, 10 and 12) will be collected regardless of the study drug dosing time. Time of sample collection and time of two previous doses of study drug will be recorded in the site source documentation.

r. Blood draw for PK should only be performed at the premature discontinuation visit if the subject discontinues at any time during Dosing Period 1. Time of sample collection and time of two previous doses of study drug will be recorded in the site source documentation.

s. All adverse events reported from the time of the first dose of study drug administration (Day 1) until completion of the 30- day follow-up contact. In addition, serious adverse events and protocol-related non-serious adverse events will be collected from the time of the signature of the study-specific informed consent/assent.

t. Each dose of study drug will be administered to study subjects by a parent or legal guardian following the instructions for use (Appendix E), with supervision from either a study nurse or a home health nurse.

Appendix D. Age-Specific Limit for Phosphorus and Total Calcium

Age (yrs.)	Serum Phosphorus (mg/dL)	Serum Total Calcium (mg/dL)
< 1	7.4	11.0
1 – 5	6.5	10.8
6 – 9	6.5	10.3