PROTOCOL: CTAP101-CL-3007

Study Title:	A Multi-Center Study to Evaluate the Efficacy, Safety and Pharmacokinetics of CTAP101 Extended-release Capsules to Treat Secondary Hyperparathyroidism in Pediatric Subjects of Ages 8 to <18 Years with Stage 3 or 4 Chronic Kidney Disease and Vitamin D Insufficiency
Study Number:	CTAP101-CL-3007
Study Phase:	3
Product Name:	CTAP101 Extended-release Capsules
Investigators:	Multi-Center

Sponsor:

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This study will be conducted in compliance with the protocol, United States (US) Code of Federal Regulations applicable to clinical studies, principles of International Council for Harmonisation (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, and all applicable regulatory requirements.

	Date
Version 3.0	January 11, 2022

SYNOPSIS

Sponsor:

EirGen Pharma Ltd. (EirGen)

OPKO Pharmaceuticals, LLC, is an affiliate of the IND sponsor (EirGen) and performs clinical trial services on its behalf with respect to this study.

Name of Finished Product:

CTAP101 Extended-release Capsules (30 mcg)

Name of Active Ingredient:

Calcifediol, calcidiol, 25-hydroxyvitamin D_3

Test Products, Dose, and Mode of Administration:

CTAP101 Extended-release (ER) Capsules (30 or 60 mcg/day) or matching placebo by the oral route, referred to as "CTAP101 Capsules" in this document.

Study Title:

A Multi-Center Study to Evaluate the Efficacy, Safety and Pharmacokinetics of CTAP101 Extended-release Capsules to Treat Secondary Hyperparathyroidism in Pediatric Subjects of Ages 8 to <18 Years with Stage 3 or 4 Chronic Kidney Disease and Vitamin D Insufficiency

Study Number:

CTAP101-CL-3007

Study Phase: 3

Primary Objectives:

The primary objectives of this study are:

1. To evaluate the efficacy of repeated dosing with CTAP101 ER Capsules versus placebo in reducing plasma intact parathyroid hormone (iPTH) by ≥30% from pre-treatment baseline;
2. To investigate the safety and tolerability of repeated dosing with CTAP101 Capsules; and,
3. To assess the pharmacokinetic (PK) profile of 25-hydroxyvitamin D_3 after repeated doses of CTAP101 Capsules in pediatric subjects of ages 8 to <18 years with secondary hyperparathyroidism (SHPT), stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency (VDI).

Secondary Objectives:

The secondary objectives of this study are:

1. To evaluate the efficacy of repeated dosing with CTAP101 Capsules versus placebo in raising serum total 25-hydroxyvitamin D to ≥30 ng/mL;
2. To determine the time courses of mean absolute changes from pre-treatment baseline in serum total 25-hydroxyvitamin D and plasma iPTH during administration of repeated doses of CTAP101 Capsules;

3. To assess the pharmacodynamic (PD) effects of repeated doses of CTAP101 Capsules versus placebo on mean serum calcium (corrected for albumin), serum phosphorus and serum calcium-times-phosphorus (CaxP) product, and the change in mean urine calcium:creatinine ratio; and,
4. To evaluate the safety of CTAP101 Capsules versus placebo with regard to the incidence of hypercalcemia and hyperphosphatemia.

[redacted]

Study Design:

This is a phase 3, multi-center, randomized, double-blind, placebo-controlled study which will be conducted primarily or entirely within the United States (US). The study will involve approximately 108 eligible subjects, balanced for gender and CKD stage, having ages of 8 to <18 years, SHPT, stage 3 or 4 CKD and VDI. Approximately 72 subjects having ages of 12 to <18 years will be enrolled initially (Cohort 1) and, after prior approval from the US Food and Drug Administration (FDA), another approximately 36 subjects having ages of 8 to <12 years will be enrolled (Cohort 2). Subjects in both cohorts will be randomized in a 2:1 ratio into two treatment groups to receive a daily bedtime dosage of (a) CTAP101 Capsules, or (b) matching placebo for 26-weeks. Subjects in Cohort 1 who are assigned to treatment with CTAP101 Capsules will start dosing at 30 mcg/day (1 CTAP101 Capsule) and, at the end of 12-weeks of treatment, will undergo upward dose titration to 60 mcg per day (two CTAP101 Capsules) provided that (a) plasma iPTH has not decreased by at least 30% from pretreatment baseline, (b) serum calcium (corrected for albumin) is <9.8 mg/dL, (c) serum phosphorus is ≤5.5 mg/dL and (d) serum total 25-hydroxyvitamin D is ≤65 ng/mL. The initial dosage in Cohort 2 will be determined based on an interim analysis of data obtained from Cohort 1, as described below. The efficacy of CTAP101 Capsules (compared to placebo) in treating SHPT will be assessed from multiple plasma iPTH and serum 25-hydroxyvitamin D levels obtained in the efficacy assessment period (EAP), defined as the last 6 weeks of the 26-week treatment period.

An Interactive Response System (IRS) will provide study treatment group assignments (using a computer-generated randomization code provided by the IRS vendor) and dosing adjustments. An independent, unblinded Data Safety Monitoring Board (DSMB) will be established to oversee the IRS and verify the appropriateness of all dosing adjustments, and to monitor subject safety and the effectiveness of CTAP101 Capsules at regular intervals. Members of the DSMB will also conduct periodic reviews of study conduct to verify that all

required data are captured to a sufficiently high degree (>95%) and within specified time frames (usually within 5 days), and to promptly recommend appropriate corrective actions to address any noted deficiencies, in an effort to minimize missing data. Specific responsibilities and activities of the DSMB will be defined in the charter ratified at the pre-study organizational meeting. These responsibilities will include the completion of an interim analysis of the data obtained from Cohort 1 to justify a starting dose for Cohort 2, and an interim analysis of the data obtained from Cohort 2 to justify a starting dose for a separate phase 2 study in subjects having ages of 1 month to <8 years.

Subjects receiving treatment prior to study enrollment with calcitriol or another 1α-hydroxylated vitamin D analog, or calcimimetics prior to study enrollment will forgo further dosing with these agents for the duration of the study and complete an 8-week washout period prior to baseline assessments.

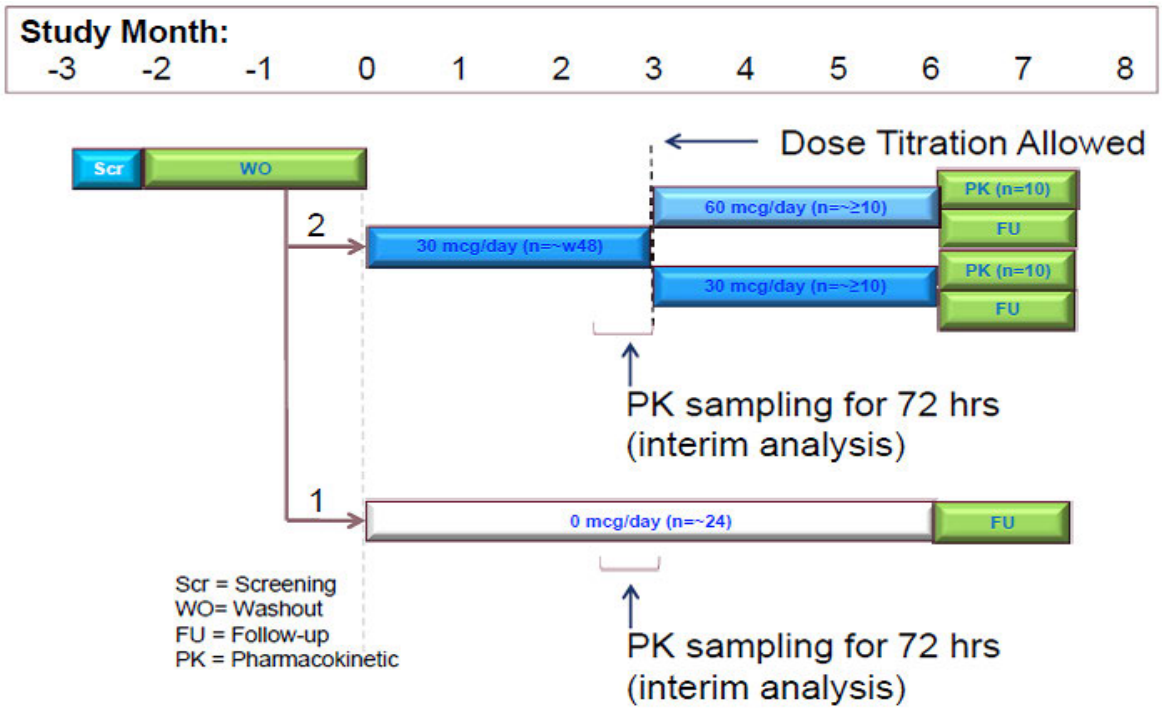
Subjects receiving vitamin D supplementation at a rate above 1,700 IU/day or 50,000 IU (1,250 mcg) per month prior to study enrollment must reduce the dose to ≤1,700 IU/day for the duration of the study and undergo an 8-week washout period prior to baseline assessments if serum total 25-hydroxyvitamin D is ≥30 ng/mL. The washout period is unnecessary if serum total 25-hydroxyvitamin D is <30 ng/mL. Subjects will complete a 6-week follow-up (FU) period after completing the 26-week treatment period or after early termination (ET).

Blood samples will be collected at weekly, biweekly or monthly intervals during the 10-week pre-treatment screening/baseline period, the 26-week treatment period and the 6-week post-treatment FU period. Sparse PK samples will be collected from all subjects on Day 83 at 0 (pre-dose), 6, 12, 24 hours (Day 84 pre-dose) and 48 hours (Day 85 pre-dose). Additional PK blood samples will be collected in both Cohort 1 and Cohort 2 in subsets of 10 subjects treated with CTAP101 Capsules and 5 subjects treated with placebo during the last 3 days of the 12th week of treatment (prior to dose titration). The additional PK samples will be collected as follows: Day 83: -2, 2, 4 and 8 hours. End of study PK blood samples will be collected in other subsets of approximately 20 subjects (20 subjects from each cohort) during the post-treatment FU period. In each cohort, an attempt will be made to collect PK samples from 10 subjects on each ending daily dose level (30 or 60 mcg) of CTAP101 Capsules, in order to establish the terminal elimination half-lives ($t_{1/2}$) of 25-hydroxyvitamin D_3 at each of these dose levels.

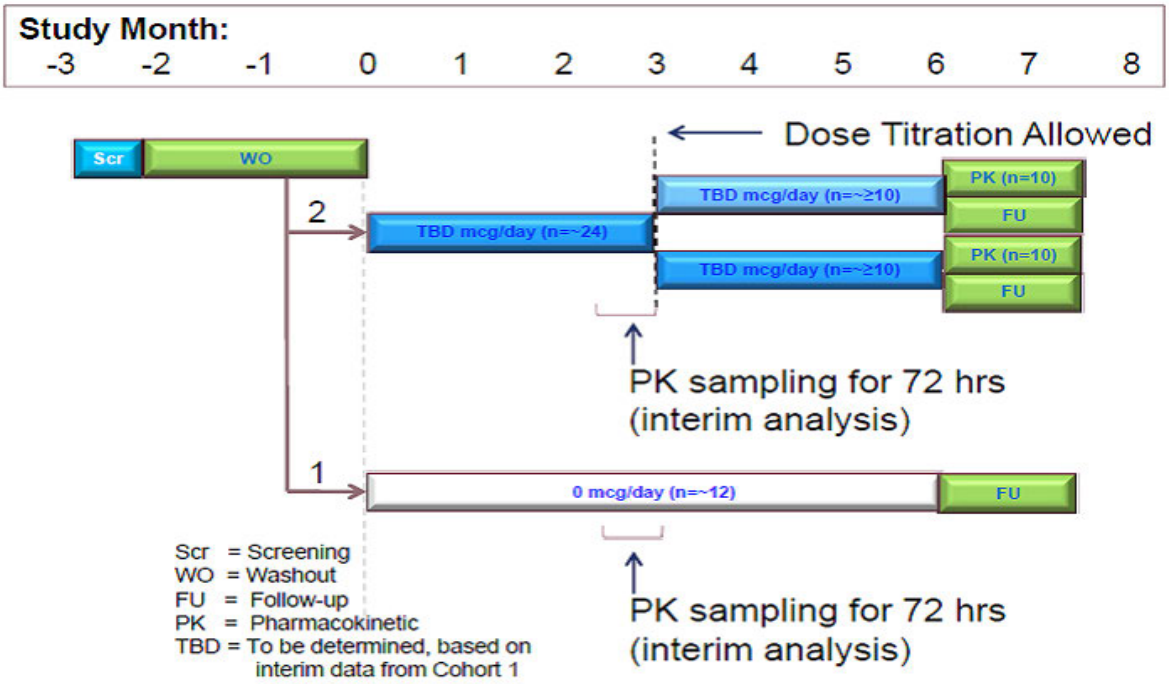
All subjects, study personnel and the sponsor will be blinded to the administered treatments and to plasma iPTH, serum total 25-hydroxyvitamin D and serum 25-hydroxyvitamin D_3 data until the last subject completes 26 weeks of treatment. Unblinded data will be provided to all study sites when the final clinical study report becomes available.

An interim analysis of data obtained from the 15 subjects in Cohort 1 who provide intensive PK samples during the last three days of treatment week 12 will be undertaken by the DSMB to determine the appropriate starting dose for Cohort 2. A second interim analysis of data obtained from 15 subjects in Cohort 2 who provide intensive PK samples during the last three days of treatment week 12 will be undertaken by the DSMB to determine the appropriate starting dose for a separate phase 2 study in subjects of ages 1 month to <8 years.

A diagram of the study design for Cohort 1 (n=~72) is shown below:



A diagram of the study design for Cohort 2 (n=~36) is shown below:



Duration of Study:

Each subject will participate in the study for up to approximately 42 weeks (2-weeks screening/baseline, 8-weeks washout, if required, 26-weeks of treatment with CTAP101 Capsules or matching placebo, and 6-weeks of FU evaluation).

Study Parameters:

Key parameters to be monitored at regular intervals during the study include: plasma iPTH, serum calcium (corrected for serum albumin), serum phosphorus, serum CaxP product, serum total 25-hydroxyvitamin D, serum 25-hydroxyvitamin D_3, and urine calcium:creatinine ratio. Vital signs (VS) and adverse events (AEs) will be monitored at each study visit. Other parameters to be monitored less frequently include brief physical examinations (PEs), clinical laboratory tests (hematology and clinical and urine chemistries) and patient-reported palatability and acceptability. Twelve-lead electrocardiograms (ECGs) will be obtained at baseline and at the end of treatment or ET. [redacted]

Dosing Plan:

Subjects in Cohort 1 will receive two capsules (CTAP101 Capsules and/or matching placebo capsules) every day at bedtime to achieve the targeted initial daily dose of 30 mcg of calcifediol (one CTAP101 capsule plus one placebo capsule) or 0 mcg of calcifediol (two placebo capsules). Any food intake within 60 minutes of medication administration will also be recorded. At the end of 12 weeks of treatment, subjects assigned to active treatment will undergo upward dose titration to 60 mcg per day (two CTAP101 Capsules) provided that (a) plasma iPTH has not decreased by at least 30% from pretreatment baseline, (b) corrected serum calcium is <9.8 mg/dL, (c) serum phosphorus is ≤5.5 mg/dL and (d) serum total 25-hydroxyvitamin D is ≤65 ng/mL. Subjects in Cohort 2 will receive a starting daily bedtime dose which will be determined on the basis of the interim analysis of data obtained in Cohort 1 (see above), and will undergo upward dose titration to a new daily dose that is two times higher than the starting dose at the end of 12 weeks of treatment, provided that (a) plasma iPTH has not decreased by at least 30% from pretreatment baseline, (b) corrected serum calcium is <9.8 mg/dL, (c) serum phosphorus is >6.0 mg/dL and (d) serum total 25-hydroxyvitamin D is ≤65 ng/mL.

Subjects in both cohorts will reduce the dose by one capsule per week, as necessary, and no more frequently than at biweekly intervals, in the event that any one of the following four criteria are met: plasma iPTH is confirmed to be <35 pg/mL (for subjects with stage 3 CKD) or <70 pg/mL (for subjects with stage 4 CKD), serum calcium (corrected) is confirmed to be >10.3 mg/dL, serum total 25-hydroxyvitamin D is confirmed to be >100 ng/mL, or serum phosphorus is confirmed to be >5.5 mg/dL (ages 12 to <18 years) or >6.0 mg/dL (ages 8 to <12 years), provided that the investigator has deemed the elevated serum phosphorus to be related to study drug administration and has taken appropriate and persistent actions to control serum phosphorus by initiating or adjusting any phosphate binder therapy.

Dose reductions will be accomplished by consistently omitting doses on a specific day of the week, as follows:

- First dose reduction: Dosing will be omitted on all Mondays (M).
- Second dose reduction: Dosing will be omitted on all M and Wednesdays (W)
- Third dose reduction: Dosing will be omitted on all M, W and Fridays (F)
- Fourth dose reduction: Dosing will be omitted on all M, W, F and Sundays (S)

Any subject who requires a further dose reduction will terminate dosing with study drugs and immediately commence the 6-week FU period.

Subjects on dose reduction will be allowed an unscheduled safety visit if deemed appropriate by the investigator to have FU blood sampling within 48 hours of any dose reduction.

A summary of the initial and reduced weekly dose levels, in mcg units, after each of the four possible dose reductions appears in the table below:

	Weekly Dose (mcg)				
Daily (mcg)	Weekly (mcg)	1st Reduction	2nd Reduction	3rd Reduction	4th Reduction
60	420	360	300	240	180
30	210	180	150	120	90
0	0	0	0	0	0

Subjects will suspend dosing if plasma iPTH is persistently <30 pg/mL (three consecutive visits) or serum calcium (corrected) is confirmed to be >11.0 mg/dL, and resume when iPTH is ≥35 pg/mL and serum calcium is <9.8 mg/dL at the next lower dose level.

Primary Efficacy Endpoint:

The primary estimand is the reduction of mean plasma iPTH by at least 30% from pre-treatment baseline. The primary efficacy endpoint is the proportion of subjects in the intent-to-treat (ITT) population (age 8 to <18 years) attaining a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline compared to placebo during the EAP.

Primary Safety Endpoints:

Safety and tolerability will be evaluated in the safety population by AEs, PEs, VS, hematology and clinical chemistries, and ECGs.

Pharmacokinetic Endpoints:

For the interim analysis, repeated-dose (steady-state) PK determinations will be performed in subsets of subjects in both Cohort 1 and Cohort 2 by analyzing serum 25-hydroxyvitamin D_3 concentrations versus time recorded during dosing with CTAP101 Capsules (n=10) or placebo (n=5) in the last three days of the 12th week of treatment.

For the final analysis, repeated-dose (steady-state) PK determinations will be performed in both Cohort 1 and Cohort 2 by analyzing serum 25-hydroxyvitamin D_3 concentrations versus time recorded (a) during dosing with CTAP101 Capsules or placebo in the last three days of the 12th week of treatment and (b) after the last administered dose in each active treatment group.

The following PK parameters will be calculated using observed and baseline-adjusted 25-hydroxyvitamin D_3 concentrations: (a) area under the concentration curve (AUC), maximum concentration, (C_{max}), time to maximum concentration (t_{max}), and steady-state concentration (C_{ss}); and (b) $t_{½}$, clearance (CL/F) and volume of distribution (Vd/F), as feasible. Relative exposure and dose proportionality will be examined, if possible.

Secondary Endpoints:

Secondary efficacy endpoints include the proportion of subjects in the per-protocol (PP) population attaining a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline during the EAP and the proportions of subjects in the ITT and PP populations attaining a mean serum total 25-hydroxyvitamin D of at least 30 ng/mL, in aggregate and by mean weekly study dose in the EAP. Additional secondary endpoints include the time courses of mean absolute changes from pre-treatment baseline in serum total 25-hydroxyvitamin D and plasma iPTH; PD effects on mean serum calcium (corrected), serum phosphorus, serum CaxP product, and the urine calcium:creatinine ratio; the proportion of subjects in each treatment group with hypercalciuria (>200 mg calcium/g creatinine), hypercalcemia (2 consecutive visits with serum calcium >10.3 mg/dL) or hyperphosphatemia (2 consecutive visits with serum phosphorus >5.5 mg/dL (ages 12 to <18 years) or >6.0 mg/dL (ages 8 to <12 years), deemed to be study drug related); and the proportion of subjects who attain 2 consecutive plasma iPTH values ≤70 pg/mL.

[redacted]

Additional Assessments:

Patient reported outcomes on palatability and acceptability.

Sample Size Estimation:

Sample size has been calculated (using Fisher's exact test statistics) to provide power of 80% for a two-sided, alpha 0.05 level test of equal proportions comparing the percentages of subjects attaining mean decreases of at least 30% in plasma iPTH (averaged over the last 6 weeks of treatment) compared to baseline on daily dosages of CTAP101 Capsules versus placebo. Assuming response rates of at least 0.4 (CTAP101 Capsules) versus 0.1 (placebo), and using a 2:1 ratio of CTAP101 Capsules:placebo subjects with an estimated 20% dropout rate over the course of the study, a sample size of approximately 108 subjects is required in the study with two-thirds apportioned to the 12 to <18 year age group (Cohort 1) and one-third apportioned to the 8 to <12 year age group (Cohort 2), allocated as 72 subjects to CTAP101 Capsules and 36 subjects to placebo.

Statistical Analyses:

Efficacy analyses will be performed for the ITT and PP populations, as indicated. The ITT population will be defined as all subjects who have been randomized to receive study medication. The PP population will be defined as all subjects for whom at least two plasma

iPTH determinations are included in the calculated baseline value, defined as weeks -2 through -1, and in the EAP, and who do not have a major protocol deviation.

Primary efficacy will be assessed in the ITT population by comparing the proportions of subjects in each treatment group (CTAP101 Capsules versus placebo) attaining a mean decrease from baseline in plasma iPTH of ≥30% in the EAP using the Cochran-Mantel-Haenszel test statistic (alpha=0.05) for overall efficacy of the multicenter results. Subjects who do not have at least two plasma iPTH determinations in the EAP will be deemed non-responders.

Secondary efficacy will be assessed in the PP population by comparing the proportions of subjects in each active treatment group attaining mean decreases in plasma iPTH of ≥30% (from baseline) in the EAP to the corresponding proportion of subjects in the placebo group, and in the ITT and PP populations by comparing the proportions of subjects in each active treatment group attaining mean serum total 25-hydroxyvitamin D of ≥30 ng/mL in the EAP to the corresponding proportions of subjects in the placebo group, in aggregate and by mean weekly study dose in the EAP. Mean weekly dose in the EAP will be calculated for three groups of subjects: those receiving 0 mcg per day; those receiving >0 and ≤30 mcg per day; and, those receiving >30 mcg/day of calcifediol.

Primary safety analyses will be conducted in the ITT population, and the statistical summary will be descriptive and performed by treatment group. No inferential hypothesis testing will be performed on the safety parameters with the exception of serum calcium, serum phosphorus, serum CaxP product, and urine calcium:creatinine ratio.

Secondary safety analyses will compare the proportions of subjects with confirmed corrected serum calcium >10.3 mg/dL or confirmed serum phosphorus >5.5 mg/dL (ages 12 to <18 years) or >6.0 mg/dL (ages 8 to <12 years) (deemed to be study drug related) or serum confirmed CaxP product >55 (for Cohort 1) or >60 (for Cohort 2) between the CTAP101 Capsules and placebo treatment groups using the Cochran-Mantel-Haenszel test statistic (alpha=0.05) for overall safety in the multicenter results.

Descriptive statistics will be applied to evaluate patient reported palatability and acceptability.

Inclusion Criteria:

Each subject must meet the following criteria to be enrolled in this study:

1. Cohort 1: Be 12 to <18 years of age and have a body weight of ≥40 kg; Cohort 2: be 8 to <12 years of age and have a body weight of ≥20 kg.
2. Be diagnosed with stage 3 or 4 CKD at least six months prior to the screening visit, and have an estimated glomerular filtration rate (eGFR) of ≥15 to <60 mL/min/1.73m^2 at screening.
3. Be without any disease state or physical condition that might impair evaluation of safety or which, in the investigator's opinion, would interfere with study participation, including:
   a. Serum albumin ≤ 3.0 g/dL;
   b. Serum transaminase (alanine transaminase [ALT], glutamic pyruvic transaminase [SGPT], aspartate aminotransferase [AST] or glutamic oxaloacetic transaminase [SGOT]) > 2.5 times the upper limit of normal at screening, and,

c. Urinary albumin excretion of >3000 mcg/mg creatinine.

4. Exhibit during the initial or, if necessary, a screening visit after washout:
   a. Plasma iPTH >100 pg/mL (stage 3 CKD) or >160 pg/mL (stage 4 CKD)
   b. Serum calcium <9.8 mg/dL (corrected for albumin);
   c. Serum total 25-hydroxyvitamin D <30 ng/mL; and,
   d. Serum phosphorus >2.5 to ≤5.5 mg/dL (12 to <18 years) or ≤6.0 mg/dL (ages 8 to <12 years).
5. If taking calcitriol or other 1α-hydroxylated vitamin D analogs, or cinacalcet, be willing to forgo treatment with these agents for the duration of the study and complete an 8-week washout period prior to commencing treatment in the study.
6. If taking more than 1,000 mg/day of elemental calcium, discontinue or reduce calcium use and/or use non-calcium based therapies for the duration of the study.
7. If receiving ≤1,700 IU/day nutritional vitamin D (ergocalciferol or cholecalciferol) therapy, must agree to remain on a stable dose during the study.
8. If taking more than 1,700 IU/day of nutritional vitamin D, must discontinue or decrease the dose to ≤1,700 IU/day, maintain that dose for the duration of the study, and complete an 8-week washout period prior to commencing treatment in the study provided that serum total 25-hydroxyvitamin D is ≥30 ng/mL. The washout period is not necessary if serum total 25-hydroxyvitamin D is <30 ng/mL.
9. If taking any bone metabolism therapy that could interfere with study endpoints, must discontinue use of such agent(s) for the duration of the study.
10. Willing and able to comply with study instructions and commit to all clinic visits for the duration of the study.
11. Female subjects of childbearing potential must be neither pregnant nor lactating and must have a negative urine pregnancy test at the first screening visit.
12. All female subjects of childbearing potential and male subjects with female partners of childbearing potential must agree to use effective contraception (eg, implants, injectables, combined oral contraceptives, intrauterine device, sexual abstinence, vasectomy or vasectomized partner) for the duration of the study.
13. Each subject or their legal representative must be able to read, understand and sign the Informed Consent Form (ICF).

Exclusion Criteria:

Subjects who meet any of the following criteria will be excluded from the study:

1. History of or planned kidney transplant or parathyroidectomy.
2. History (prior three months) of serum calcium ≥9.8 mg/dL
3. Use of bisphosphonate therapy or other bone modifying treatment (eg, denosumab) within six months prior to enrollment.
4. Known previous or concomitant serious illness or medical condition, such as malignancy, human immunodeficiency virus, significant gastrointestinal or hepatic disease or

cardiovascular event or hepatitis, or physical condition that in the opinion of the investigator may worsen and/or interfere with participation in the study.

5. History of neurological/psychiatric disorder, including psychotic disorder, or any reason which, in the opinion of the investigator makes adherence to a treatment or FU schedule unlikely.
6. Known or suspected hypersensitivity to any of the constituents of either investigational product.
7. Currently participating in, or has participated in, an interventional/investigational study within 30 days prior to study screening.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

[redacted]	[redacted]
[redacted]	[redacted]
$25D_3$	25-hydroxyvitamin D_3, calcifediol, calcidiol
25D	25-hydroxyvitamin D
AE	adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	area under the curve
BA	bioavailability
[redacted]	[redacted]
BMI	body mass index
CaxP	calcium-times-phosphorus product
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CL/F	clearance
C_{max}	maximum concentration
CRF	case report form
C_{ss}	steady-state concentration
[redacted]	[redacted]
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
EAP	efficacy assessment period
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ER	extended-release
ET	early termination
EU	European Union
FDA	Food and Drug Administration
[redacted]	[redacted]
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HDPE	high-density polyethylene
IB	Investigator Brochure

ICF	Informed Consent Form
ICH	International Council for Harmonisation
iPTH	intact parathyroid hormone
IR	immediate-release
IRB	Institutional Review Board/Ethics Committee
IRS	interactive response system
ITT	intent-to-treat
IU	International Units
KDIGO	Kidney Disease Improving Global Outcomes
K/DOQI	Kidney/Disease Outcomes Quality Initiative
MedDRA	Medical Dictionary for Regulatory Activities
MBD	metabolic bone disease
[redacted]	[redacted]
PD	pharmacodynamic
PE	physical examinations
PK	pharmacokinetic
PP	per-protocol
PT	Preferred Terms
PTH	parathyroid hormone
RCT	randomized clinical trial
SAE	serious adverse event
SAS®	Statistical Analysis Software
SD	standard deviation
SE	standard error
SGOT	Serum glutamic-oxaloacetic transaminase
SGPT	Serum glutamic-pyruvic transaminase
SHPT	secondary hyperparathyroidism
SOC	system organ class
SOP	standard operating procedure
SUSAR	serious unexpected suspected adverse event
$t_{1/2}$	terminal elimination half-life
[redacted]	[redacted]
TEAE	treatment-emergent adverse events
t_{max}	time to maximum concentration
T_{ss}	time to steady-state concentration
US	United States
Vd/F	volume of distribution

VDI	vitamin D insufficiency
VDRA	vitamin D receptor agonist
VS	vital signs

1 INTRODUCTION

1.1 CTAP101 Capsules

CTAP101 Capsules is an extended-release (ER) oral formulation of calcifediol which was approved as Rayaldee® ER Capsules in June 2016 by the United States (US) Food and Drug Administration (FDA) for the treatment of secondary hyperparathyroidism (SHPT) in adult patients with stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency (VDI), defined as serum total 25-hydroxyvitamin D levels less than 30 ng/mL. EirGen is further developing CTAP101 Capsules for this same indication in pediatric patients.

Calcifediol is 25-hydroxyvitamin D_3, the physiological precursor to the vitamin D hormone, calcitriol (1,25-dihydroxyvitamin D_3). This prohormone is synthesized by the liver from cholecalciferol (vitamin D_3) generated endogenously in skin following exposure to sunlight or obtained from the diet or supplements. Another prohormone, 25-hydroxyvitamin D_2, is synthesized hepatically from ergocalciferol (vitamin D_2), which cannot be produced endogenously, but is obtained from diet or supplements. These two prohormones are collectively referred to as "25-hydroxyvitamin D". Unless an individual is receiving significant ergocalciferol supplementation, essentially all of the 25-hydroxyvitamin D in blood consists of calcifediol.

1.2 Chronic Kidney Disease

CKD is a worldwide public health problem with steadily increasing incidence, prevalence, and cost [Coresh 2007]. Key factors driving growth of CKD in developed countries include aging populations, the increasing incidence of obesity and its associated complications of hypertension and adult-onset diabetes. CKD is categorized into five successive stages on the basis of estimated glomerular filtration rate (eGFR), with each successive stage representing more advanced disease. Stage 3 CKD is defined by an eGFR in the range of 30 to <60 mL/min/1.73m^2, and stage 4 CKD is defined by an eGFR in the range of 15 to <30 mL/min/1.73m^2. CKD afflicts approximately 6-13% of the global population. Despite treatment, CKD continues to be associated with poor outcomes, reflecting the inadequacies of the current standard of care [Nicola 2016, Levey 2005].

1.3 Secondary Hyperparathyroidism

SHPT is a common condition that occurs with advancing CKD and is characterized by excessive production of parathyroid hormone (PTH), hypocalcemia and hypertrophy of the parathyroid glands. SHPT affects 40% to 82% of patients with stage 3 or 4 CKD [Levin 2007]. SHPT requires prompt and effective treatment, as prolonged elevation of PTH causes calcium and phosphorus release from bone, leading to metabolic bone disease and extra-skeletal calcification. In the absence of effective treatment, SHPT becomes progressively more severe and unresponsive to medical treatment as the parathyroid gland becomes hyperplastic and less sensitive to calcium and vitamin D hormone signaling [Nigwekar 2014].

1.4 Pathogenesis of Secondary Hyperparathyroidism

CKD-associated SHPT develops as the result of phosphorus retention, mild hypocalcemia and VDI [Levin 2007]. VDI plays a central role in the pathogenesis of SHPT in CKD [Cunningham 2011]. It limits the normal activation of 25-hydroxyvitamin D to vitamin D hormone (1,25-

dihydroxyvitamin D) in the kidney and in other tissues which contain cytochrome P450 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) by reducing the amount of available substrate for conversion. Declining hormone concentrations increase PTH secretion by the parathyroid glands and decrease calcium absorption in the small intestine, leading to hypocalcemia.

1.5 Treatment of Vitamin D Insufficiency

Vitamin D supplementation is recommended by both the K/DOQI and KDIGO Clinical Practice Guidelines, although there is no consensus in regarding how vitamin D supplements should best be administered. Published studies have reported the use of daily doses of vitamin D (either cholecalciferol or ergocalciferol) of 700 to 4,000 International Units (IU), weekly doses of 5,000 to 50,000 IU, and monthly doses of 50,000 to 300,000 IU. Irrespective of the treatment regimen used, no or inadequate reductions in PTH levels have been observed in randomized clinical trials (RCTs) and nutritional vitamin D remains unproven as an effective treatment for SHPT in patients with stage 3-4 CKD [Agarwal 2016, Kalantar-Zadeh 2009]. Immediate-release (IR) formulations of calcifediol, used occasionally in the European Union (EU), have also shown no or inadequate reductions in PTH in clinical trials focused on stage 3-4 CKD.

1.6 Vitamin D Insufficiency

VDI affects an estimated 71% to 83% of patients with stage 3 or 4 CKD [La Clair 2005, Wolf 2007]. It is defined by the National Kidney Foundation as serum total 25-hydroxyvitamin D of ≥15 to <30 ng/mL, and vitamin D deficiency as <15 ng/mL in its Kidney Disease Outcomes Quality Initiative (K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease, [K/DOQI 2003]. The more recent Kidney Disease: Improving Global Outcomes (KDIGO) Guideline for Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) [KDIGO 2009] points out that most published studies define VDI as serum 25-hydroxyvitamin D levels down to 10 ng/mL and vitamin D deficiency as levels below 10 ng/mL. The Endocrine Society's Guideline for the Treatment and Prevention of Vitamin D Deficiency [Holick 2011] defines vitamin D sufficiency as serum 25-hydroxyvitamin D concentrations between 30 and 100 ng/mL (inclusive). The US Institute of Medicine expert committee noted in their 2011 report [Ross 2011] that the general population is at risk of vitamin D deficiency at serum 25-hydroxyvitamin D concentrations <12 ng/mL and some individuals are potentially at risk for inadequacy at levels ranging from 12 to 20 ng/mL. Multiple factors contribute to VDI in CKD including nutritional inadequacy, decreased sunlight exposure, proteinuric loss and decreased hepatic synthesis of 25-hydroxyvitamin D, and increased expression of fibroblast growth factor (FGF23) and CYP24A1, the cytochrome P450 enzyme that specifically catabolizes vitamin D and its metabolites [Helvig 2010, Sprague 2014]. VDI is associated with increased morbidity and mortality [Fernandez-Juarez 2013, Ravani 2009].

1.7 Treatment of Secondary Hyperparathyroidism

In current clinical practice, therapy with a vitamin D receptor activator (VDRA) is typically initiated when vitamin D supplementation is found ineffective in controlling PTH in patients with stage 3 or 4 CKD. Three VDRAs are available in the US for oral administration: calcitriol, paricalcitol and doxercalciferol. Another oral VDRA, alfacalcidol, is widely available outside of the US. Although VDRAs can control elevated PTH, they leave serum total 25-hydroxyvitamin D uncorrected (and potentially lower), depriving tissues of adequate substrate for local hormone production [de Boer 2013]. Bolus oral administration of VDRAs produce supraphysiological

surges in blood vitamin D hormone levels, causing unwanted elevation of FGF23 and CYP24A1-mediated vitamin D catabolism, both of which are implicated in the observed development of resistance to vitamin D therapy [de Boer 2013]. VDRAs also stimulate intestinal absorption of calcium and phosphorus, leading to elevation of serum calcium and phosphorus which increase the risk of vascular calcification, the primary cause of morbidity and mortality in CKD [Paloian 2014]. Both the original K/DOQI and KDIGO Clinical Practice Guidelines (Guideline 8A and Chapter 4.2, respectively) recommend the use of VDRAs in CKD, but the recently updated KDIGO Clinical Practice Guideline for CKD-MBD [KDIGO 2017] recommends against the routine use of VDRAs in patients with stage 3 or 4 CKD due to the increased risk of hypercalcemia and hyperphosphatemia (Chapter 4.2)

1.8 The Unmet Medical Need

Prior to FDA approval of CTAP101 Capsules, healthcare professionals were limited to two therapeutic options for SHPT in patients with stage 3-4 CKD: vitamin D supplements and VDRAs (calcitriol and its 1α-hydroxylated analogs). Nutritional vitamin D supplements are safe and inexpensive, but published RCTs have shown that they are ineffective for reducing elevated PTH and often delay the initiation of effective therapy [Agarwal 2016]. In contrast, VDRA's are effective for controlling PTH, but increase the risk of hypercalcemia, hyperphosphatemia and adynamic bone disease, and associated vascular calcification [KDIGO 2017]. Calcimimetic therapies (cinacalcet and etalcalcetide) are approved only for use in dialysis-dependent stage 5 CKD and cause hypocalcemia and hyperphosphatemia in patients with stage 3-4 CKD [Chonchol 2009]. CTAP101 Capsules address a pressing need for a new, improved treatment for SHPT in patients with stage 3-4 CKD. This product needs to be developed for pediatric patients.

1.9 Nonclinical Experience with Calcifediol

Toxicity associated with calcifediol is consistent with that observed due to vitamin D overdose and is similar to that seen with calcitriol. Generally, such toxicity is subsequent to hypercalcemia. Hypercalcemia and increased calcium loading can cause calcium deposits in kidneys and vasculature, and can cause parathyroid atrophy and generalized tissue deposition of calcium. Vitamin D-related toxicity is generally characterized by increases in both urine and serum calcium levels, mineralization of soft tissues (believed to develop subsequent to hypercalcemia) and increases in bone formation with a resulting reduction in bone marrow space.

An early (pre-commercial) formulation of CTAP101 Capsules was administered to dogs for three months (CTAP101-TX-0100) and resulted in typical vitamin D-induced toxicities including hypercalcemia, hypercalciuria, soft tissue mineralization (eg, kidney, stomach, aorta and heart) and death. Severe adverse reactions to CTAP101 Capsules were observed in dogs treated with 500 or 1000 µg/day and were associated with 25-hydroxyvitamin D_3 levels >450 ng/mL following one month of treatment.

The current (commercially available) formulation of CTAP101 Capsules was administered daily to dogs for three months (CTAP101-TX-0102) at doses of up to 45 µg (~4.5 µg/kg/day). No signs of toxicity were observed at the highest dose tested which was associated with 25-hydroxyvitamin D_3 levels >150 ng/mL.

Calcifediol administration (orally through addition to the diet) to rats for six months (Calderol NDA 018312) has been reported to produce signs of toxicity at daily doses >40 µg/kg.

Toxicities included an increased incidence of nephrocalcinosis and uroliths. Oral administration of calcifediol to dogs at ≤2 µg/kg/day resulted in no compound-related findings.

Results from in vitro drug release and nonclinical PK studies in male Yucatan swine (CTAP101-PK-0012) demonstrated that CTAP101 Capsules have an ER profile. In swine, the bioavailability (BA) of calcifediol following the administration of CTAP101 Capsules was approximately 30% lower than that from an IR capsule preparation. Further, a delay in the release of the active ingredient (time to maximum concentration or t_{max} >7 hours) was observed as compared to the IR formulation (t_{max} ~4 hours).

1.10 Metabolism of Calcifediol

The metabolism of calcifediol has been extensively reviewed in the literature [Bikle 2014, DeLuca 2004]. Calcifediol is metabolized by the following three routes: conversion to calcitriol by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1), located in the kidney, parathyroid gland, and other tissues; hepatic catabolism to water-soluble forms excreted in bile, a significant fraction of which have been identified as glucuronide conjugates; and, conversion to 24,25-dihydroxyvitamin D_3, which is biologically inactive, and subsequently calcitroic acid by CYP24A1. Excretion of calcifediol occurs primarily through the biliary fecal route [Ledger 1986] which can be inhibited by uremic toxins, causing the terminal elimination half-life ($t_{1/2}$) to increase as CKD progresses [Dreisbach 2008].

1.11 Pharmacodynamics of CTAP101 Capsules

CTAP101 Capsules gradually release calcifediol and thereby prevent the abrupt increases in serum 25-hydroxyvitamin D_3 and calcitriol seen with IR formulations. The gradual rise in systemic calcifediol is characterized by a lower maximum concentration (C_{max}) and a longer t_{max} compared to IR formulations.

The single-dose pharmacodynamic (PD) profile of CTAP101 Capsules was compared in a randomized, open-label study to IR calcifediol in adult patients with SHPT, stage 3 or 4 CKD and VDI [Petkovich 2015]. Patients were randomly assigned to receive a single oral dose of 450 mcg or 900 mcg of CTAP101 (5 or 10 capsules each containing 90 µg) or a single IR (intravenous) dose of 448 mcg calcifediol. All patients were followed for six weeks postdose. Blood samples were collected predose and postdose for the analysis of serum 25-hydroxyvitamin D_3, 1,25-dihydroxyvitamin D and 24,25-dihydroxyvitamin D_3. Serum levels of 24,25-dihydroxyvitamin D_3 were used to monitor the degree of CYP24A1 upregulation, since human tissue biopsy analysis was impractical. A total of 28 subjects were enrolled in this study; nine received 450 mcg oral CTAP101, nine received 900 mcg oral CTAP101, and 10 received 448 µg intravenous calcifediol. Administration of 900 µg of CTAP101 resulted in gradual increases in serum 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D without significantly elevating serum 24,25-dihydroxyvitamin D_3, and produced meaningful, sustained PTH suppression. Conversely, administration of IR calcifediol produced rapidly rising and higher drug exposures due to a substantially faster delivery and higher bioavailability. IR dosing also caused abrupt, large increases in serum 25-hydroxyvitamin D_3, 1,25-dihydroxyvitamin D and 24,25-dihydroxyvitamin D_3, consistent with greater CYP24A1 activity, and negligible PTH suppression.

A parallel nonclinical study [Petkovich 2015] showed that renal production of calcitriol is driven by the supply of calcifediol until CYP27B1 is suppressed. The faster calcifediol is supplied, the

more calcitriol is produced. However, the abrupt increase in serum 25-hydroxyvitamin D after bolus IR (intravenous) dosing produced a corresponding surge in serum 1,25-dihydroxyvitamin D, which in turn triggered massive upregulation of CYP24A1 in both kidney and parathyroid gland. Increased expression of CYP24A1 in CKD patients attenuated the further rise of serum 1,25-dihydroxyvitamin D, boosted serum levels of 24,25-dihydroxyvitamin D_3, and blocked clinically meaningful reductions in plasma PTH. In contrast, CTAP101 Capsules gradually increased both serum 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D, avoided excessive increases in 24,25-dihydroxyvitamin D_3 and yielded serum 1,25-dihydroxyvitamin D concentrations that were similar despite much lower calcifediol exposures. CTAP101 produced much greater and more prolonged suppression of plasma PTH in CKD patients. These data showed that the rate at which exogenous calcifediol is supplied to a patient with SHPT, stage 3 or 4 CKD and VDI has a significant effect on treatment outcome, with CTAP101 being more effective in reducing elevated plasma PTH than IR calcifediol.

1.12 Pharmacokinetics of CTAP101 Capsules

Bioequivalence between CTAP101 Capsules and any IR preparation of calcifediol was not expected since the rate of absorption of calcifediol from CTAP101 Capsules is more gradual. The BA of calcifediol from an IR preparation was reported in the literature to be between approximately 62 to 77% of the administered dose [Haddad 1976]. The BA of CTAP101 Capsules is lower (approximately 25%), consistent with a lower C_{max}.

Healthy adult volunteers treated in the fasted state (CTAP101-CL-1011) with a single oral dose of 900 µg of CTAP101 exhibited serum 25-hydroxyvitamin D_3 concentrations that rose gradually to a mean baseline-corrected C_{max} of 35.9 ng/mL at a median t_{max} of 21.0 hours. Serum 25-hydroxyvitamin D_3 concentrations in similar subjects given a single dose of 448 µg of intravenous calcifediol increased to a mean baseline-corrected C_{max} of 133.7 ng/mL at a median t_{max} of 0.17 hours. The post-dose PK profiles for these two treatment groups demonstrated single-order characteristics with a mean $t_{1/2}$ of approximately 11 days and a mean clearance (CL/F) of 0.027 to 0.028 L/h. The mean apparent volume of distribution (Vd/F) was 8.8 L after CTAP101 and 9.7 L after intravenous calcifediol.

In a food effect study (CTAP101-CL-1016), a single oral dose of 450 µg of CTAP101 was given to healthy adult volunteers in the fed and fasting states. The median t_{max} was 11 hours in the fed group compared to 32 hours in the fasted group. Mean C_{max} and area under the curve (AUC) were 5- and 3.5-fold higher, respectively, in fed versus fasted subjects.

Another study conducted in adults with SHPT, stage 3 or stage 4 CKD and VDI provided multiple-dose data on serum 25-hydroxyvitamin D_3, total 25-hydroxyvitamin D and total 1,25-dihydroxyvitamin D for population PK analysis [Sprague 2014]. In this study, subjects received daily bedtime doses of 30, 60 or 90 µg of CTAP101 or placebo for six weeks and were monitored for six weeks after the last dose. Mean serum 25-hydroxyvitamin D_3 increased gradually in a dose-proportional manner. The t_{max} after the last dose was 38–43 hours with a tendency toward higher values with increasing dose. Mean C_{max}, after adjustment for baseline values, was 28, 60 and 86 ng/mL for the 30, 60 and 90 µg groups, respectively. Calcifediol exposures, calculated as mean background-adjusted AUC, were dose proportional and the mean $t_{1/2}$ was between 25 and 50 days. Steady-state serum 25-hydroxyvitamin D_3 levels were not reached after six weeks of dosing.

The effect of alcohol on the release of calcifediol from CTAP101 Capsules was evaluated in an in vitro dissolution study. Concentrations of ethanol up to 40% by volume had no effect on the release of calcifediol.

1.13 Clinical Efficacy and Safety

In CTAP101-CL-2008, a double-blind, placebo-controlled, randomized repeat-dose study, daily administration of CTAP101 Capsules increased serum total 25-hydroxyvitamin D levels to ≥30 ng/mL in nearly all subjects and decreased mean plasma intact PTH (iPTH) from baseline and compared to placebo during six weeks of treatment. The mean % decrease in iPTH from baseline was related to the administered dose: 20.2±20.8 (standard deviation [SD]), 32.0±22.3, 37.9±15.9 for the 30, 60 and 90 µg groups, respectively.

The efficacy was confirmed in the phase 3 program with nearly all CTAP101 Capsules subjects (97%), who completed the study without a deviation, achieving a normal serum total 25-hydroxyvitamin D level and with 60% of subjects achieving a mean reduction in iPTH from baseline of at least 30%. Fewer than 9% of placebo subjects achieved a 30% reduction in iPTH or achieved a normal 25-hydroxyvitamin D level.

CTAP101 Capsules did not cause significant adverse effects on serum calcium or phosphorus. Treatment-emergent adverse events (TEAEs), including those related to the investigational study drug, were comparable across treatment groups, except for hyperphosphatemia, which was observed in four subjects, none of which was considered by the investigator to be related to the study drug.

For all clinical studies, the AE profiles did not identify any events specific to CTAP101 Capsules. After both single and repeat-dose administration, CTAP101 Capsules was generally well-tolerated. The overall TEAE profile in the phase 3 program was comparable between CTAP101 Capsules and placebo groups. Subjects receiving CTAP101 Capsules had a greater mean (standard error [SE]) increase in serum calcium ($P<0.001$) than placebo patients (ie, 0.2 [0.02] versus 0.1 [0.03] mg/dL); for serum phosphorus, subjects receiving CTAP101 Capsules had a greater mean (SE) increase ($P<0.05$) than placebo patients ([ie, 0.2 [(0.03]) versus 0.1 [(0.04]) mg/dL)].

CTAP101 Capsules have not been previously studied in pediatric patients.

This protocol may be amended in due course to include subjects having ages less than 8 years.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives of this study are:

1. To evaluate the efficacy of repeated dosing with CTAP101 ER Capsules versus placebo in reducing plasma iPTH by ≥30% from pre-treatment baseline;
2. To investigate the safety and tolerability of repeated dosing with CTAP101 Capsules; and,
3. To assess the pharmacokinetic (PK) profile of serum 25-hydroxyvitamin D_3 after repeated doses of CTAP101 Capsules in pediatric subjects of ages 8 to <18 years with SHPT, stage 3 or 4 CKD and VDI.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

1. To evaluate the efficacy of repeated dosing with CTAP101 Capsules versus placebo in raising serum total 25-hydroxyvitamin D to ≥30 ng/mL;
2. To determine the time courses of mean absolute changes from pre-treatment baseline in serum total 25-hydroxyvitamin D and plasma iPTH during administration of repeated doses of CTAP101 Capsules;
3. To assess the PD effects of repeated doses of CTAP101 Capsules versus placebo on mean serum calcium (corrected for albumin), serum phosphorus and serum calcium-times-phosphorus (CaxP) product, and the change in mean urine calcium:creatinine ratio; and,
4. To evaluate the safety of CTAP101 Capsules versus placebo with regard to the incidence of hypercalcemia and hyperphosphatemia.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a phase 3, multi-center, randomized, double-blind, placebo-controlled study which will be conducted primarily or entirely within the US. The study will involve approximately 108 eligible subjects, balanced for gender and CKD stage, having ages of 8 to <18 years, SHPT, stage 3 or 4 CKD and VDI. Approximately 72 subjects having ages of 12 to <18 years will be enrolled initially (Cohort 1) and, after prior approval from the US FDA, another 36 subjects having ages of 8 to <12 years will be enrolled (Cohort 2). Subjects in both cohorts will be randomized in a 2:1 ratio into two treatment groups to receive a daily bedtime dosage of (a) CTAP101 Capsules, or (b) matching placebo for 26-weeks. Subjects in Cohort 1 who are assigned to treatment with CTAP101 Capsules will start dosing at 30 mcg/day (1 CTAP101 Capsule) and, at the end of 12-weeks of treatment, will undergo upward dose titration to 60 mcg per day (two CTAP101 Capsules) provided that (a) plasma iPTH has not decreased by at least 30% from pretreatment baseline, (b) serum calcium (corrected for albumin) is <9.8 mg/dL, (c) serum phosphorus is ≤5.5 mg/dL, and (d) serum total 25-hydroxyvitamin D is ≤65 ng/mL. The initial dosage in Cohort 2 will be determined based on an interim analysis of data obtained from Cohort 1, as described below. The efficacy of CTAP101 Capsules (compared to placebo) in treating SHPT will be assessed from multiple plasma iPTH and serum 25-hydroxyvitamin D levels obtained in the efficacy assessment period (EAP), defined as the last 6 weeks of the 26-week treatment period.

An Interactive Response System (IRS) will provide study treatment group assignments (using a computer-generated randomization code provided by the IRS vendor) and dosing adjustments. An independent, unblinded Data Safety Monitoring Board (DSMB) will oversee the IRS and verify the appropriateness of all dosing adjustments, and monitor subject safety and the effectiveness of CTAP101 Capsules at regular intervals. Members of the DSMB will also conduct periodic reviews of study conduct to verify that all required data are captured to a sufficiently high degree (>95%) and within specified time frames (usually within 5 days), and to promptly recommend appropriate corrective actions to address any noted deficiencies, in an effort to minimize missing data. Specific responsibilities and activities of the DSMB will be defined in the charter ratified at the pre-study organizational meeting. These responsibilities will include the completion of an interim analysis of the data obtained in Cohort 1 to justify a starting dose for Cohort 2, and an interim analysis of the data obtained from Cohort 2 to justify a starting dose for a separate phase 2 study in subjects having ages of 1 month to <8 years.

Subjects receiving treatment prior to study enrollment with calcitriol or another 1α-hydroxylated vitamin D analog, or calcimimetics prior to study enrollment will forgo further dosing with these agents for the duration of the study and complete an 8-week washout period prior to baseline assessments. Subjects receiving vitamin D supplementation at a rate above 1,700 IU/day or 50,000 IU (1,250 mcg) per month prior to study enrollment must reduce the dose to ≤1,700 IU/day for the duration of the study and undergo an 8-week washout period prior to baseline assessments if serum total 25-hydroxyvitamin D is ≥30 ng/mL. The washout period is unnecessary if serum total 25-hydroxyvitamin D is <30 ng/mL. Subjects will complete a 6-week follow-up (FU) period after completing the 26-week treatment period or after early termination (ET).

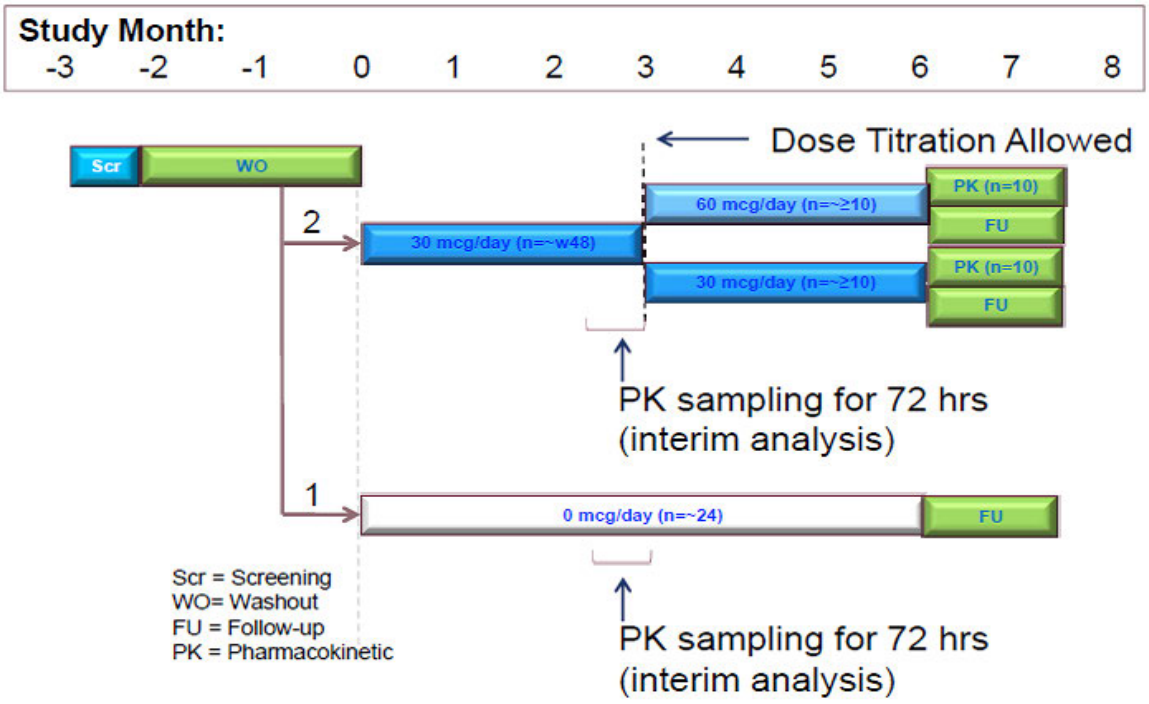
Key parameters to be monitored at regular intervals during the study include: plasma iPTH, serum calcium (corrected for serum albumin), serum phosphorus, serum CaxP product, serum total 25-hydroxyvitamin D, serum 25-hydroxyvitamin D_3, and urine calcium:creatinine ratio. Vital signs (VS) and adverse events (AEs) will be monitored at each study visit. Other parameters to be monitored less frequently include brief physical examinations (PEs), clinical laboratory tests (hematology and clinical and urine chemistries) and patient-reported palatability and acceptability. Twelve-lead electrocardiograms (ECGs) will be obtained at baseline and at the end of treatment or ET. [redacted] All subjects, study personnel and the sponsor will be blinded to the administered treatments and to plasma iPTH, serum total 25-hydroxyvitamin D and serum 25-hydroxyvitamin D_3 data until the last subject completes 26 weeks of treatment. Unblinded data will be provided to all study sites when the final clinical study report becomes available.

Blood samples will be collected at weekly, biweekly or monthly intervals during the 10-week pre-treatment screening/baseline period, the 26-week treatment period and the 6-week post-treatment FU period. Sparse PK samples will be collected from all subjects on Day 83 at 0 (pre-dose), 6, 12, 24 hours (Day 84 pre-dose) and 48 hours (Day 85 pre-dose). Additional PK blood samples will be collected in both Cohort 1 and Cohort 2 in subsets of 10 subjects treated with CTAP101 Capsules and 5 subjects treated with placebo during the last 3 days of the 12th week of treatment (prior to dose titration). The additional PK samples will be collected as follows: Day 83: -2, 2, 4 and 8 hours. End of study PK blood samples will be collected in other subsets of 20 subjects (20 subjects from each cohort) during the post-treatment FU period, 10 subjects on each ending daily dose level (30 or 60 mcg) of CTAP101 Capsules, in order to establish the $t_{1/2}$ of serum 25-hydroxyvitamin D_3 at each of these dose levels.

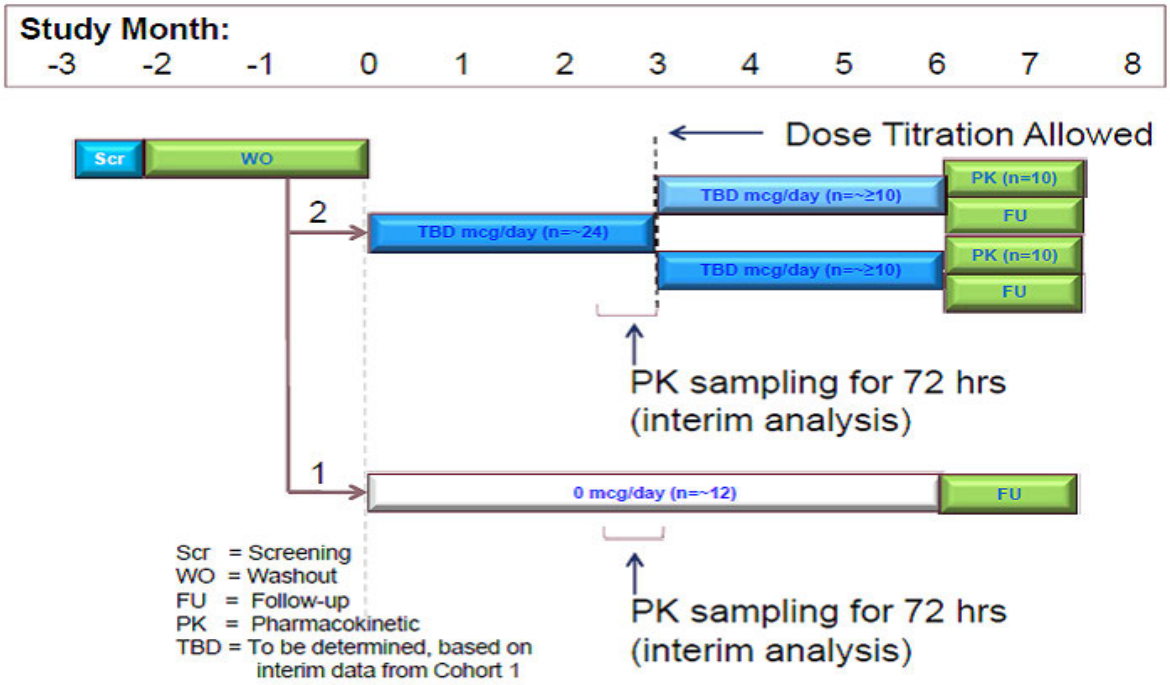
All subjects, study personnel and the sponsor will be blinded to the administered treatments and to plasma iPTH, serum total 25-hydroxyvitamin D and serum 25-hydroxyvitamin D_3 data until the last subject completes 26 weeks of treatment.

An interim analysis of data obtained from the 15 subjects in Cohort 1 who provide intensive PK samples during the last three days of treatment week 12 will be undertaken by the DSMB to determine the appropriate starting dose for Cohort 2. A second interim analysis of data obtained from 15 subjects in Cohort 2 who provide intensive PK samples during the last three days of treatment week 12 will be undertaken by the DSMB to determine the appropriate starting dose for a separate phase 2 study in subjects of ages 1 month to <8 years.

A diagram of the study design for Cohort 1 (n=~72) is shown below:



A diagram of the study design for Cohort 2 (n=~36) is shown below:



3.2 Rationale for Study Design and Control Group

EirGen is developing CTAP101 Capsules for the treatment of SHPT in pediatric patients with stages 3 or 4 CKD and VDI. The active ingredient in CTAP101 Capsules is calcifediol, which is formulated as ER capsules for oral administration.

The present study is designed to compare the efficacy of CTAP101 Capsules to matching placebo with regard to reducing mean plasma iPTH levels by at least 30% from pre-treatment baseline in pediatric patients with stage 3 or 4 CKD and VDI. The study will also examine the safety and tolerability of CTAP101 Capsules compared to placebo. This adequate and well-controlled, randomized and double-blind study provides the best means to evaluate efficacy, safety and tolerability of CTAP101 Capsules because no therapy has yet been approved by the FDA to treat elevated iPTH levels associated with low serum total 25-hydroxyvitamin D levels in pediatric CKD patients. In other studies conducted in adult subjects with stage 3 or 4 CKD and SHPT, administration of placebo therapy for 26-weeks has not been shown to result in untoward effects [Coyne 2006; Coburn 2004]. However, since iPTH values >900 pg/mL have been associated with increased risk of fracture in hemodialysis patients [Jadoul 2006], subjects will be terminated from this study for confirmed iPTH levels >900 pg/mL.

The starting dose of 30 mcg per day is based on the results from two phase 3 studies (CTAP101-CL-3001 and CTAP101-CL-3002) conducted in adults with SHPT, stage 3 or 4 CKD and VDI. Data from these studies demonstrated that steady-state serum 25-hydroxyvitamin D_3 levels were reached after 12 weeks of treatment at daily doses of 30 or 60 mcg of CTAP101 Capsules. Accordingly, upward dose titration is not allowed in the present study until after 12 weeks, when subjects receiving the initial dose of CTAP101 Capsules have attained steady-state blood levels of serum total 25-hydroxyvitamin D. A 26-week treatment period was selected for this study to ensure that steady-state will be attained in subjects who undergo upward dose titration at the beginning of treatment week 13.

Previous PK analyses in adult CKD patients have determined that the $t_{1/2}$ of serum 25-hydroxyvitamin D_3 is approximately 30 days (CTAP101-CL-2008). Consequently, the post-dosing FU period of 6-weeks should be sufficient for determining the $t_{1/2}$ in pediatric patients.

Study drug will be reduced or suspended for confirmed excessive elevations in serum calcium, phosphorus or serum total 25-hydroxyvitamin D or for confirmed over suppression of plasma iPTH.

[redacted]

3.3 Study Duration

Each subject will participate in the study for up to approximately 42-weeks (2-weeks screening/baseline, 8-weeks washout, if required, 26-weeks of treatment with CTAP101 Capsules, and 6-weeks of FU evaluation).

Subjects who participate in Cohort 1 will not be eligible for participation in Cohort 2.

4 STUDY POPULATION SELECTION

4.1 Study Population

The target population for this study is subjects having ages of 8 to <18 years who have been diagnosed with stage 3 or 4 CKD (as demonstrated by medical history and by an eGFR of ≥15 and <60 mL/min/1.73m^2 at screening) who do not require regular hemodialysis, and present with both VDI (serum total 25-hydroxyvitamin D <30 ng/mL) and SHPT (plasma iPTH >100 pg/mL for stage 3 CKD and >160 pg/mL for stage 4 CKD).

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled in this study:

1. Cohort 1: Be 12 to <18 years of age and have a body weight of ≥40 kg; Cohort 2: be 8 to <12 years of age and have a body weight of ≥20 kg.
2. Be diagnosed with stage 3 to 4 CKD at least six months prior to the screening visit, and have an eGFR of ≥15 to <60 mL/min/1.73m^2 at screening.
3. Be without any disease state or physical condition that might impair evaluation of safety or which, in the investigator's opinion, would interfere with study participation, including:
   a. Serum albumin ≤ 3.0 g/dL;
   b. Serum transaminase (ALT or SGPT, AST or SGOT) > 2.5 times the upper limit of normal at screening; and,
   c. Urinary albumin excretion of >3000 mcg/mg creatinine.
4. Exhibit during the initial or, if necessary, a screening visit after washout:
   a. Plasma iPTH >100 pg/mL (stage 3 CKD) or >160 pg/mL (stage 4 CKD)
   b. Serum calcium <9.8 mg/dL (corrected for albumin);
   c. Serum total 25-hydroxyvitamin D <30 ng/mL; and,
   d. Serum phosphorus >2.5 to ≤5.5 mg/dL (12 to <18 years) or ≤6.0 mg/dL (ages 8 to <12 years);
5. If taking calcitriol or other 1α-hydroxylated vitamin D analogs, or cinacalcet, be willing to forgo treatment with these agents for the duration of the study and complete an 8-week washout period prior to commencing treatment in the study.
6. If taking >1,000 mg/day of elemental calcium, discontinue or reduce calcium use and/or use non-calcium based therapies for the duration of the study.
7. If receiving ≤1,700 IU/day nutritional vitamin D (ergocalciferol or cholecalciferol) therapy, must agree to remain on a stable dose during the study.
8. If taking >1,700 IU/day of nutritional vitamin D, must discontinue or decrease the dose to ≤1,700 IU/day, maintain that dose for the duration of the study, and complete an 8-week washout period prior to commencing treatment in the study provided that serum total 25-hydroxyvitamin D is ≥30 ng/mL. The washout period is not necessary if serum total 25-hydroxyvitami D is <30 ng/mL.
9. If taking any bone modifying treatment that could interfere with study endpoints, must discontinue use of such agent(s) for the duration of the study.

10. Willing and able to comply with study instructions and commit to all clinic visits for the duration of the study.
11. Female subjects of childbearing potential must be neither pregnant nor lactating and must have a negative urine pregnancy test at the first screening visit.
12. All female subjects of childbearing potential and male subjects with female partners of childbearing potential must agree to use effective contraception (eg, implants, injectables, combined oral contraceptives, intrauterine device, sexual abstinence, vasectomy or vasectomized partner) for the duration of the study.
13. Each subject or their legal representative must be able to read, understand and sign the informed consent form (ICF).

4.3 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

1. History of or planned kidney transplant or parathyroidectomy.
2. History (prior three months) of serum calcium ≥9.8 mg/dL
3. Use of bisphosphonate therapy or other bone modifying treatment (eg, denosumab) within six months prior to enrollment.
4. Known previous or concomitant serious illness or medical condition, such as malignancy, human immunodeficiency virus, significant gastrointestinal or hepatic disease or cardiovascular event or hepatitis, or physical condition that in the opinion of the investigator may worsen and/or interfere with participation in the study.
5. History of neurological/psychiatric disorder, including psychotic disorder, or any reason which, in the opinion of the investigator makes adherence to a treatment or FU schedule unlikely.
6. Known or suspected hypersensitivity to any of the constituents of either investigational product.
7. Currently participating in, or has participated in, an interventional/investigational study within 30 days prior to study screening.

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 CTAP101 Capsules Description

Dosage form: Soft capsule

Dose strength: 30 mcg capsule

Product description: Blue oval soft capsules containing white to off-white to slightly blue waxy material; 30 capsules per bottle

Active component: Calcifediol, calcidiol, 25-hydroxyvitamin D_3

Non-active components: Paraffin wax, mineral oil, mono- and diglycerides, dehydrated alcohol, lauroyl polyoxylglycerides, butylated hydroxytoluene, hypromellose, modified starch, carageenan, sodium phosphate dibasic, sorbitol and sorbitan solution, FD&C Blue #1, titanium dioxide, medium chain triglycerides (coconut oil)

Storage conditions: 15°C to 30°C (59°F to 86°F); protect from light and heat

5.1.2 Placebo Capsules Description

Dosage form: Soft capsule

Dose strength: 0 mcg capsule

Product description: Blue oval soft capsules containing white to off-white to slightly blue waxy material; 30 capsules per bottle

Active component: None

Non-active components: Paraffin wax, mineral oil, mono- and diglycerides, dehydrated alcohol, lauroyl polyoxylglycerides, butylated hydroxytoluene, hypromellose, modified starch, carrageenan, sodium phosphate dibasic, sorbitol and sorbitan solution, FD&C Blue #1, titanium dioxide, medium chain triglycerides (coconut oil)

Storage conditions: 15°C to 30°C (59°F to 86°F); protect from light and heat

5.2 Treatments Administered

Study drug should **NOT** be administered to individuals known to be allergic to any component of the drug. All subjects should be observed for allergic reaction following study drug administration. All allergic reactions will be documented as AEs in the source documents and the electronic case report forms (eCRF).

Study drug will be provided in white, round, wide-mouth, high-density polyethylene (HDPE) bottles with 28-mm white, polypropylene, child-resistant (push down and turn) caps with aluminum heat induction seal liners and contain 30 capsules per bottle. Each bottle will contain either active drug or a matching placebo.

Drug accountability will be performed throughout the treatment period (Section 5.12 Storage and Accountability). All procedures being performed during the course of this clinical study are

listed sequentially by visit in Section 7 Study Activities and may be found as a table in Appendix 1 Schedule of Events.

5.3 Selection and Timing of Dose for Each Subject

Subjects in Cohort 1 will receive two capsules (CTAP101 Capsules and/or matching placebo capsules) every day at bedtime to achieve the targeted initial daily dose of 30 mcg of calcifediol (one CTAP101 Capsule plus one placebo capsule) or 0 mcg of calcifediol (two placebo capsules). Any food intake within 60 minutes of medication administration will also be recorded. At the end of 12 weeks of treatment, subjects assigned to active treatment will undergo upward dose titration to 60 mcg per day (two CTAP101 Capsules) provided that (a) plasma iPTH has not decreased by at least 30% from pretreatment baseline, (b) corrected serum calcium is <9.8 mg/dL, (c) serum phosphorus is ≤5.5 mg/dL, and (d) serum total 25-hydroxyvitamin D is ≤65 ng/mL. Subjects in Cohort 2 will receive a starting daily bedtime dose which will be determined on the basis of the interim analysis of data obtained in Cohort 1, and will undergo upward dose titration at the end of 12 weeks of treatment to a new daily dose that is two times higher than the starting dose, provided that (a) plasma iPTH has not decreased by at least 30% from pretreatment baseline, (b) corrected serum calcium is <9.8 mg/dL, (c) serum phosphorus is ≤6.0 mg/dL and (d) serum total 25-hydroxyvitamin D is ≤65 ng/mL.

In order to maintain blinding, subjects will receive periodic supplies of study drug in bottles of identical appearance, some labeled “Bottle 1” and some labeled “Bottle 2,” along with the same dosing instructions regardless of randomization group directing the subject to take one capsule from one bottle labeled “Bottle 1” and one bottle labeled “Bottle 2” every day at bedtime.

An unblinded medical monitor who will be part of the independent, unblinded DSMB will oversee study drug assignments and dose adjustments (see below) by IRS.

5.4 Dose Reduction Criteria

Subjects will reduce the dose through the IRS by one capsule per week, as necessary, and no more frequently than at biweekly intervals, in the event that any one of the following four criteria are met: :

1. Two consecutive visits with plasma iPTH <35 pg/mL (for subjects with stage 3 CKD) or <70 pg/mL (for subjects with stage 4 CKD),
2. Two consecutive visits with serum calcium (corrected) >10.3 mg/dL,
3. Two consecutive visits with serum total 25-hydroxyvitamin D >100 ng/mL, or
4. Two consecutive visits with serum phosphorus >5.5 mg/dL (ages 12 to <18 years), or >6.0 mg/dL (ages 8 to <12 years) provided that the investigator has deemed the elevated serum phosphorus to be related to study drug administration and has taken appropriate and persistent actions to control serum phosphorus by initiating or adjusting any phosphate binder therapy.

Dose reductions will be accomplished by consistently omitting doses on a specific day of the week, as follows:

- First dose reduction: Dosing will be omitted on all M.
- Second dose reduction: Dosing will be omitted on all M and W
- Third dose reduction: Dosing will be omitted on all M, W and F

- Fourth dose reduction: Dosing will be omitted on all M, W, F and S

Any subject who requires a further dose reduction will terminate dosing with study drugs and commence the 6-week FU period.

Subjects on dose reduction will be allowed a safety visit if deemed appropriate by the investigator to have FU blood sampling within 48 hours of dose reduction.

A summary of the initial and reduced weekly dose levels, in mcg units, after each of the four possible dose reductions appears in the table below:

	Weekly Dose (mcg)				
Daily (mcg)	Weekly (mcg)	1st Reduction	2nd Reduction	3rd Reduction	4th Reduction
60	420	360	300	240	180
30	210	180	150	120	90
0	0	0	0	0	0

Subjects will suspend dosing if plasma iPTH is persistently <30 pg/mL (three consecutive visits) or serum calcium (corrected) is confirmed to be >11.0 mg/dL, and resume when iPTH is ≥35 pg/mL (for subjects with stage 3 CKD) or ≥70 pg/mL (for subjects with stage 4 CKD) and serum calcium is ≤9.8 mg/dL at the next lower dose level.

5.5 Overdose and Toxicity

CTAP101 Capsules contain calcifediol, which is a vitamin D metabolite. An increased serum calcium has been shown to be one of the first indicators of toxicity associated with vitamin D overdose and is frequently used as a surrogate marker of toxicity in patients treated with vitamin D therapy. Progressive hypercalcemia may require emergency attention. Acute hypercalcemia may exacerbate tendencies for cardiac arrhythmia and seizure, and may potentiate the action of digitalis. Chronic or repeated hypercalcemia can lead to generalized vascular and soft tissue calcification.

No specific antidote to CTAP101 Capsules exists. If overdose is suspected, the subject should be monitored closely and kept under observation by a physician. The $t_{½}$ of calcifediol is approximately 30 days in adult patients with stage 3 or 4 CKD. Possible clinical and laboratory events include hypercalcemia and hypercalciuria.

5.6 Method of Assigning Subjects to Treatment Groups

After signing the ICF, prior to any study-related activities, subjects will be assigned a site-generated, ascending subject identification number and will retain that number throughout the study. Should a subject be withdrawn from the study, the subject identification number will not be reassigned. Approximately 350 subjects will be screened to enroll approximately 108 subjects who meet the enrollment criteria.

An IRS will provide study treatment group assignments for these 108 subjects using the computer-generated randomization code provided by the IRS vendor. The randomization code will be stratified age group (8 to <12 years and 12 to <18 years) and balanced within each age group for gender and CKD stage (stages 3 and 4).

In Cohort 1 (ages 12 to <18 years), approximately 72 subjects, balanced for gender and CKD stage, will be randomized in a 2:1 ratio to active or placebo treatment, respectively. Ten (10) subjects will be randomly selected from the active group and five (5) subjects will be randomly selected from the placebo group for intensive PK evaluation during the last 3 days of the 12th week of treatment (prior to dose escalation). Twenty other subjects will be randomly selected for end of study PK evaluations from the active group, ten of which will be receiving an end of study dose of 30 mcg/day and the other ten will receiving an end of study dose of 60 mcg/day.

In Cohort 2 (ages 8 to <12 years), approximately 36 subjects, balanced for gender and CKD stage, will be randomized in a 2:1 ratio to active or placebo treatment, respectively. Ten (10) subjects will be randomly selected from the active group and five (5) subjects will be randomly selected from the placebo group for intensive PK evaluation during the last 3 days of the 12th week of treatment (prior to dose escalation). End of study PK evaluations will be made after 26 weeks of treatment. Twenty other subjects will be randomly selected for end of study PK evaluations from the active group, ten of which will be receiving an end of study dose of 30 mcg/day and the other ten will receiving an end of study dose of 60 mcg/day.

For both cohorts, an IRS will provide study treatment group assignments using the computer-generated randomization code.

5.7 Blinding

An IRS will provide study treatment group assignments (using a computer-generated randomization code provided by the IRS vendor) and dosing adjustments. An independent, unblinded DSMB will oversee the IRS and verify the appropriateness of all dosing adjustments, and monitor subject safety and the effectiveness of CTAP101 Capsules at regular intervals. Members of the DSMB will also conduct periodic reviews of study conduct to verify that all required data are captured to a sufficiently high degree (>95%) and within specified time frames (usually within 5 days), and to promptly recommend appropriate corrective actions to address any noted deficiencies, in an effort to minimize missing data. Specific responsibilities and activities of the DSMB will be defined in the charter ratified at the pre-study organizational meeting. These responsibilities will include the completion of an interim analysis of the repeated-dose PK data obtained during treatment week 12 in Cohort 1 to justify a starting dose for Cohort 2.

All subjects, site research staff and sponsor will be blinded as to whether a given subject is in the CTAP101 Capsules or placebo treatment group until after database lock or until the decision to break the blind is determined (eg, as a result of an emergent event, SUSAR). When the primary investigator determines that knowledge of treatment group assignment is required for medical management of an individual subject, the sponsor will be contacted immediately. The blind for the subject will be broken using the IRS system.

Further, all subjects, site research staff and sponsor will be blinded to the administered treatments and plasma iPTH, serum total 25-hydroxyvitamin D, and serum 25-hydroxyvitamin D_3 laboratory data until the last subject completes 26 weeks of treatment. Unblinded data will be provided to all study sites when the final clinical study report becomes available.

5.8 Prior and Concomitant Therapy

Subjects receiving ergocalciferol or cholecalciferol must be taking ≤1,700 IU/day and must remain on that same dose during the study.

Subjects receiving prior therapy with pharmacological doses (>1,700 IU/day) of ergocalciferol or cholecalciferol must be willing to discontinue or reduce the dose to ≤1,700 IU/day and agree to remain on a stable dose during the study.

Subjects receiving other vitamin D analogs and/or bone metabolism therapy that could interfere with study endpoints must be willing and able to discontinue such therapy for the duration of the study. This includes doses of vitamin D analogs (eg, Rocaltrol®, Zemplar®, Hectorol®, calcitriol), calcimimetics (Sensipar®, Pasabiv®), teriparatide (Forteo®), calcitonin, bisphosphonates, denosumab (Prolia®, Xgeva®) and other drugs that may affect calcium metabolism.

All concomitant medication usage from the 28 days prior to visit 1 until completion of the study will be recorded.

5.8.1 Phosphate Binder and Elemental Calcium Therapy

Use of calcium-based phosphate binder or antacid therapy such as calcium carbonate or calcium acetate (PhosLo®), are allowed up to 1000 mg/day of elemental calcium. Calcium-based phosphate binder or antacid therapy in excess of 1000 mg/day of elemental calcium should be discontinued or reduced for the duration of the study. Non-calcium based phosphate binder therapy such as sevelamer HCL (Renagel®) or lanthanum carbonate (Fosrenol®), and non-calcium based antacids can be used at the discretion of the investigator during the treatment and FU periods. Phosphate binder and calcium therapy should remain constant throughout the study. Any changes should be captured in the eCRF on the Phosphate Binder/Calcium Therapy page.

5.9 Restrictions

5.9.1 Dietary Restrictions

There are no study specific dietary restrictions. Subjects should follow their dietary plan if one has been prescribed. Any changes in prescribed dietary phosphorus or calcium therapy during the study should be captured in the eCRF.

5.9.2 Subject Activity Restrictions

Subjects should maintain their usual pattern of sun exposures (including use of tanning beds) and activities.

5.10 Treatment Compliance

During certain study visits, the study coordinator or designee will perform drug accountability and dosing compliance calculations (number of capsules that should have been taken versus actual number taken as evidenced by number of returned capsules). Dosing compliance at less than 80% should be reported as a protocol deviation.

5.11 Packaging and Labeling

Study drug will be provided in white, round, wide-mouth, HDPE bottles with 28-mm white, polypropylene, child-resistant (push down and turn) caps with aluminum heat induction seal liners and contain 30 capsules per bottle. Each bottle will contain either active drug or a matching placebo.

Study drug labels will include protocol number, name and address of the sponsor, investigational statement, storage conditions and instructions for use. Bottles will be assigned numbers that are linked to the randomization schedule through IRS to provide each subject with the appropriate dose per the schedule and the instructions of the IRS.

Do **NOT** dispense the bottle of capsules if the seal of the primary package appears compromised.

The subject will be instructed as follows:

NOT to take the drug if the product appears discolored or damaged upon visual inspection and to **NOTIFY** the site immediately of the condition of the study drug and the need to obtain replacement.

5.12 Storage and Accountability

CTAP101 Capsules will be shipped to sites following standardized shipment and temperature monitoring procedures.

While at the study site, CTAP101 Capsules will be stored at room temperature, 15-30°C (59-86°F) in the supplied packaging, with access granted to authorized personnel only.

All sites must ensure that study drug has been kept under required conditions prior to dispensing. A temperature log recording the daily storage temperatures will be maintained at each site for study drug. Accountability for study drug, from receipt until final reconciliation and return of drug by the monitor or designee, will be the responsibility of the investigator or the assigned designee(s).

In the case of temperature excursions, products should not be dispensed and the investigator or the assigned designee(s) should contact the clinical monitor or the sponsor representative as soon as possible to receive further instructions.

The investigator or assigned designee(s), will maintain study drug accountability records for study drug throughout the course of the study. Specifically, the investigator or assigned designee will confirm that all study drug supplies are received intact and in the correct amounts per the shipping forms. This will be documented by signing and dating the shipping forms and providing a copy to the sponsor or designee. A study drug accountability and dispensing log will record the study drug disposition, including dates, quantity of drug received, to whom dispensed (participant-by-participant accounting), and accounts of any drug accidentally destroyed. The site's running inventory of study drug supplies will be verified routinely throughout the course of the study. All opened and unopened containers of CTAP101 Capsules bottles are to be retained at the site until the sponsor or designee has performed a complete verification of the dispensation, following which study drug will be returned to the sponsor or designee.

5.13 Investigational Product Retention at Study Site

At the conclusion of the study, a final inventory will be performed by the investigator (or designee) and verified by the study monitor. Any discrepancies identified will be indicated, with a specific explanation of each discrepancy. The investigator (or designee) must return all unused medication in accordance with the sponsor's instructions, and a copy of the clinical supplies return documentation will be returned to the sponsor or designee. Drug accountability records, clinical drug supply receipts, and returns must be maintained by the investigator.

6 STUDY PROCEDURES

6.1 Informed Consent

A signed informed consent will be obtained from the subject's parent or legally appointed guardian prior to any study related procedures. The subject or their legally acceptable representative will be permitted time and opportunity to inquire about details of the study and to decide whether or not to participate. The subject or their legally acceptable representative will receive a copy of the signed and dated consent form and any written information provided to the study subjects. If any material change occurs that affects the conduct of the study, the subject will be required to sign an updated consent form.

The investigator or his/her designee will explain the nature of all aspects of the study to the subject, answer all questions regarding this study, and emphasize that missing data and premature termination of study participation will diminish the scientific value of the data obtained, prior to obtaining informed consent.

The process for obtaining subject informed consent will be in accordance with all applicable regulatory requirements. The subject or legally acceptable representative and the investigator or his/her designee must both sign and date the ICF before the subject can participate in the study. The original ICF will be retained in the site study records. The investigator or his/her designee will ensure documentation of the consent discussion in the subject's medical record/source document. The decision by the subject to participate in the study is entirely voluntary. The investigator or designee must emphasize to the subject that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the Institutional Review Board (IRB) and use of the amended form (including for ongoing subjects).

6.2 Medical History

A detailed medical history will be recorded at visit 1. The PE which is outlined in the following Table 1 Evaluations will be performed by a licensed physician or by another suitably-qualified person where permitted by local regulations.

6.3 Physical Examination, Vital Signs, Body Mass Index, Body Weight and Height, 12-Lead Electrocardiogram, and Patient-Reported Palatability and Acceptability Assessments

Table 1. Evaluations

Physical Examination (PE):	• Organized by body system (excluding a urogenital examination) at visits 1, 3 and 28/ET
Vital Signs (VS) Measurements:	• Scheduled pulse, respirations and blood pressure will be measured prior to any scheduled blood draws and after the subject has been sitting for at least two minutes • Body temperature (oral) in degrees Celsius • VS are measured at all visits
Body Weight and Height:	• Height will be recorded to the nearest 1 cm at visits 1, 3 and 28/ET. • Body weight will be recorded to the nearest 0.1 kg at visits 1, 3 and 28/ET
Body Mass Index (BMI):	• Defined as the subject's weight in kilograms divided by the square of the subject's height in meters (kg/m^2). This is a derived variable and recorded at PE visits 1, 3 and 28/ET.
eGFR	• This is a derived variable based in the Modification of Diet in Renal Disease equation. Visit 1 creatinine value to be used for eGFR calculation.
12-Lead Electrocardiogram (ECG):	• Each 12-lead ECG will be started after the subject has been in the supine position for at least five minutes • The original ECG tracings, with global interpretation and signature of qualified medical personnel will be retained in the subject's records at the study site. Global interpretation categories are: Normal ECG, Abnormal ECG – not clinically significant, Abnormal ECG – clinically significant • 12-lead ECG will be performed once during visits 3 and 28/ET • For consistency of ECG data, every effort will be made to utilize the same facility and reader for all ECGs at each site
Patient-Reported Palatability and Acceptability Assessments	• Patient-reported palatability and acceptability assessments will be performed at Visits 13 and 22 in accordance with the Schedule of Events (see APPENDIX 1). Age-appropriate assessments will be used based on already-established and standardized versions of the combined hedonic facial and 10 cm visual analog scale. Site staff will be trained to give standardized, age-appropriate, brief and clear instructions to the subjects or, where appropriate, to the parents/guardians.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

Blood will be drawn and analyzed as specified in Table 2 List of Laboratory Tests. [redacted]. All serum calcium values will be adjusted based on serum albumin level of <4.0 g/dL. Urine samples will be collected and analyzed as specified in Table 2 List of Laboratory Tests.

Please refer to Appendix 1 Schedule of Events for specific visits when each laboratory parameter will be determined.

All clinically significant laboratory values will be recorded as AEs and the investigator will FU according to Section 6.6.7 Clinical Significance.

Subjects will be in a seated position during blood collection.

Table 2. List of Laboratory Tests

Hematology:
- Hematocrit
- Hemoglobin
- Mean corpuscular hemoglobin
- Mean corpuscular hemoglobin concentration
- Mean corpuscular volume
- Platelet count
- Red blood cell count
- White blood cell count

Urine Chemistry and Urinalysis:
- Albumin
- Albumin/Creatinine ratio
- Appearance
- Bilirubin
- Calcium
- Calcium/Creatinine ratio
- Color
- Creatinine
- Glucose
- Ketones
- Nitrite
- Occult blood
- pH
- Phosphorus
- Protein
- Specific gravity
- Urobilinogen

Urine pregnancy test (only for females of childbearing potential)

[redacted]

Serum Full Chemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT) / Serum glutamic-pyruvic transaminase (SGPT)
- Aspartate aminotransferase (AST) / Serum glutamic-oxaloacetic transaminase (SGOT)
- Blood urea nitrogen
- Calcium (corrected for serum albumin)
- Carbon dioxide
- Chloride
- Creatinine*
- Gamma-glutamyl transferase
- Globulin
- Glucose
- Lactate dehydrogenase
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

Serum Partial Chemistry:
- Calcium (corrected for serum albumin)
- Phosphorus
- Albumin

- Plasma iPTH (blinded)
- Serum total 25-hydroxyvitamin D (blinded)
- Serum 25-hydroxyvitamin D_3 (blinded)

*Note: Visit 1 creatinine value to be used for eGFR calculation.

6.4.2 Sample Collection, Storage, and Shipping

Redraws for missing samples or samples resulting in values outside entrance criteria ranges should be performed during screening only. Any other missed samples at any other visits should not be redrawn and noted as not done in source documentation along with a reason. Laboratory samples not done should be noted as a protocol deviation.

A central laboratory experienced in clinical research studies will be utilized. Collection, processing, storage and shipping procedures will be performed in accordance with the instructions provided by the central laboratory. Detailed instructions will be provided separately from this protocol in the laboratory manual. Blood samples will be collected and analyzed for clinical laboratory [redacted] tests. Approximately 357 mL of blood will be collected over the entire duration of the study from each of the 15 subjects who provide intensive PK samples during the last three days of treatment week 12. Approximately 373 mL of blood will be collected over the entire duration of the study from each of the 20 subjects who provide PK samples during the post-treatment FU period. Approximately 323 mL of blood will be collected over the entire duration of the study from all other subjects.

Additional blood draws may be needed for unscheduled or repeat visits. Given the nature of this pediatric patient population, care should be taken with the amount of blood drawn at any one study visit or cumulative over a four week period.

[redacted]

Samples are to be shipped to the central laboratory for each subject as visits are completed. The investigator will provide a limited access, and a -20°C or lower freezer space for respective serum and plasma aliquots.

6.4.3 Clinical Supplies

The sponsor or assigned designee will supply vacutainers, blood collection tubes, labels, boxes with labels for storage of serum and plasma samples and all necessary shipping supplies/containers. The investigator will supply all phlebotomy and centrifugation equipment including biohazard and/or safety supplies. The investigator will ensure that all biohazard wastes are disposed of in accordance with investigator site standard operating procedures (SOPs) and local regulations.

6.5 Dispensing Study Drug

As described in Section 5.6 Method of Assigning Subjects to Treatment Groups, the IRS will assign the study drug bottle(s) to the subject at the time of randomization (Visit 3) and at Visit 13. The study coordinator (or designated site personnel) will obtain the study drug assignment from the IRS for each subject and dispense the appropriate drug.

Subjects and their appointed guardians are to be instructed NOT to take study drug if it appears discolored or damaged. Subjects are to be advised that the study drug is to be stored at room temperature, 15-30°C (59-86°F). Protect from light and heat.

Subjects will receive a sufficient number of bottles of study drug at visits 3 and 13. Some bottles will contain CTAP101 Capsules and others may contain a matching placebo, dependent on

individual subject dose assignment. Throughout the treatment period the number of capsules remaining in the bottle will be counted by the investigator or designee and recorded on the drug accountability log at Visits 13 and 22. The bottles will then be returned to the subject. Prior to dispensing new bottle(s) of study drug, the coordinator will collect the previous bottle(s) of study drug. See Section 5.3 Selection and Timing of Dose for Each Subject for further details of drug dispensation.

6.6 Adverse Events Assessments

6.6.1 Definition

An AE is defined as any untoward medical occurrence in a subject regardless of its causal relationship to study treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or symptom) or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

6.6.2 Performing Adverse Events Assessments

The investigator or designee will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. The investigator or designee will assess and record any AE in detail in the source document and on the appropriate eCRF including the date of onset, description, severity, duration, relationship of the AE to study drug(s), action(s) taken and outcome. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be reported on the appropriate eCRF.

6.6.3 AE Collection Period

All AEs that occur after the ICF has been signed must be reported in detail in the AE section of the eCRFs, documented in the source document and followed to a satisfactory resolution, until the investigator deems the event to be chronic or the subject to be stable, or until the subject's participation in the study ends.

Information to be collected includes type of event, date of onset, date of resolution, investigator-specified assessment of severity and relationship to study drugs, seriousness, as well as any required treatment or evaluations and outcome.

AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must be documented as AEs. Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs, but must be documented in the Medical History section of the eCRF and in the source document. However, if the subject experiences a clinically significant worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition.

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory values or ECG parameters are only considered to be AEs if they are judged to be clinically significant (ie, if some action or intervention is required or if the

investigator judges the change to be beyond the range of normal physiological fluctuation). If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (eg, increased liver enzymes in hepatitis), the diagnosis only should be reported as an AE.

Pre-planned procedures (surgeries or therapies) that were scheduled prior to the start of AE collection are not considered AEs. However, if a pre-planned procedure is performed early (eg, as an emergency) due to a worsening of the preexisting condition, the worsening of the condition should be captured as an AE. Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source document and captured in the eCRF as procedures.

Any report of pregnancy identified for any female subject or for a female partner of a male subject should be reported immediately (within 24 hours of being informed) to the medical monitor. Pregnancies will be considered 'events of special interest' and will not be captured as serious adverse events (SAEs). The Pregnancy Reporting form will be utilized to obtain baseline and FU information. Pregnancies will be followed to termination or six weeks post-delivery for determination of resolution to the event. Subjects who become pregnant during treatment must immediately be withdrawn from the study.

The Medical Dictionary for Regulatory Activities (MedDRA), Version 20.0 or later, will be used to code all AEs.

6.6.4 Severity

The intensity of the AE will be rated by the investigator as mild, moderate or severe using the following criteria:

- Mild: Symptoms causing no or minimal interference with usual social and functional activities
- Moderate: Symptoms causing greater than minimal interference with usual social and functional activities
- Severe: Symptoms causing inability to perform usual social and functional activities

It should be noted that the clinical severity and seriousness of an AE are not synonymous, eg, a severe headache is not classified as serious until it meets the required elements as an SAE.

The maximum severity attained for each AE reported will be recorded in the eCRFs.

6.6.5 Relationship

The investigator's assessment of an AE's relationship to study drug is not a factor in determining whether the AE is reported in the AE section of the eCRF. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

The relationship or association of the study drugs in causing or contributing to the AE will be characterized by the investigator using the following classifications and criteria:

Definite – The AE:

- Follows a reasonable temporal sequence from drug administration;

- Abates upon discontinuation of the drug (dechallenge); and/or
- Is confirmed by reappearance of the reaction on repeat exposure (rechallenge).

Probable – The AE:

- Follows a reasonable temporal sequence from drug administration;
- Abates upon discontinuation of the drug; and/or
- Cannot be reasonably explained by the known characteristics of the subject's clinical state.

Possible – The AE:

- Follows a reasonable temporal sequence from drug administration;
- Could have been produced by the subject's clinical state or by other modes of therapy administered to the subject.

Unrelated – The AE:

- Is definitely produced by the subject's clinical state or by other modes of therapy administered to the subject.

6.6.6 Expectedness

AEs must be assessed as to whether they were expected to occur or unexpected, meaning not anticipated based on current knowledge about the investigational compound found in the protocol, Investigator Brochure (IB), product insert, or label. Categories are:

- Unexpected - nature or severity of the event is not consistent with information about the condition under study or intervention in the protocol, consent form, product brochure, or IB.
- Expected - event is known to be associated with the intervention or condition under study.

6.6.7 Clinical Significance

Changes in laboratory values, ECG parameters or other diagnostic procedures are only considered to be AEs if they are judged to be clinically significant (ie, if some intervention or therapy is required or if the investigator judges the change to be beyond the expected variation). Any changes or abnormalities will be assessed by the investigator, indicating whether the value is clinically significant or not clinically significant directly on the laboratory report or ECG tracing.

6.6.8 Serious Adverse Events

6.6.8.1 Definition

An SAE is defined by the investigator or sponsor as any AE occurring during an investigational study that results in any of the following outcomes:

- Death
- Life-threatening AE

- Hospitalization or prolongation of existing hospitalization
- A persistent or significant disability (substantial disruption of the ability to conduct normal life functions)/incapacity
- A congenital anomaly/birth defect
- Important medical event requiring medical or surgical intervention

The report of an SAE may require information about the study procedures or about the study drug that will result in the need to unblind the treatment. Codes linking randomization number for each subject to actual treatment will be secured in a sealed, opaque envelope and maintained in a locked drawer in the research center and/or the research pharmacy.

Research subjects will be instructed to notify the research center for any emergent condition and will be given the emergency contact number for the study during the consenting process.

Important medical events that may not be life threatening, result in death, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse. Hospitalizations to conduct diagnostic procedures will be captured in the eCRF on the PROCEDURES AND DIAGNOSTICS page.

6.6.8.2 Reporting Serious Adverse Events

Any AE considered serious (see Section 6.6.8 Serious Adverse Events) by the investigator that meets the previously mentioned criteria must be reported to the following numbers within 24 hours from the time when site personnel first learn about the event.

SAE Fax line: [redacted]
SAE email: [redacted]

A written report will follow as soon as possible and should consist of the SAE report and other documents, including the following pages from the eCRF: the demographics page(s), the medical history page(s), the AE page(s), and the concomitant medications page(s). If the subject is hospitalized because of or during the course of an SAE, then the investigator should attempt to obtain a copy of the hospital discharge summary and any pertinent laboratory or diagnostic reports, and provide them to the sponsor or designee as soon as possible.

For any information not available at the time of the first report that becomes available later, the investigator should add this information to the initial SAE section of the eCRFs and provide any additional written documentation to the above number immediately or within 24 hours of receipt.

The sponsor or designee will notify the appropriate regulatory agencies of any serious and unexpected SAEs associated with the use of the study drugs according to regulations. Copies of any reports to regulatory agencies regarding serious and unexpected suspected adverse reactions (SUSAR) will be provided to the investigators by the sponsor or designee for review and submission to the IRB. A report received for a serious, unexpected, suspected adverse reactions (SUSAR) will be unblinded for regulatory reporting.

The investigator is responsible for informing his or her IRB of any SAEs at that site. Copies of SAE correspondence with the IRB, ethics committees, regulatory authorities, and other physicians must be submitted to the sponsor's Clinical Services Department.

A subject experiencing one or more SAEs will receive treatment and FU evaluations by the investigator, or they will be referred to another appropriate physician for treatment and FU. Withdrawal from the study and all therapeutic measures will be at the discretion of the investigator at the site.

All SAEs will be followed until resolution or should the event become indistinguishable from the chronic disease condition, the subject will be followed for a minimum of 30 days after study drug administration and subsequently all events will be closed. Pregnancies will be followed until six weeks following delivery to determine the outcome.

6.6.9 Treatment-Emergent Adverse Events

A TEAE is defined as any adverse event with onset or worsening reported by a subject from the time that the first dose of study drug is taken until 30 days following discontinuation of study drug administration.

6.7 Concomitant Medication Assessments

The study coordinator or designee will record concomitant medication history in the source document and eCRF. Changes in phosphate binder and calcium supplement therapy will be collected in the eCRFs.

6.8 Removal of Subjects from the Study or Study Drug

The investigator may withdraw a subject from the study for any of the following reasons:

- A major protocol deviation occurs;
- A serious or intolerable AE occurs;
- A clinically significant change in a laboratory parameter occurs;
- The sponsor or investigator terminates the study;
- The subject requires more than four dose reductions;
- The subject requests to be discontinued from the study;
- If the investigator believes it is no longer in the best interests of the subject to continue
- A subject experiences more than a 100% increase in plasma iPTH after 26 weeks of treatment from pre-treatment baseline; or
- A subject exhibits plasma iPTH above 600 pg/mL on consecutive visits (if at least 2 weeks apart) after 12-weeks of treatment.

6.9 Appropriateness of Measurements

Reduction in plasma iPTH is an accepted marker for improvement of SHPT in the CKD population. The efficacy of CTAP101 Capsules will be determined by comparing the effect of CTAP101 Capsules to that observed with placebo to lower elevated iPTH levels and to

normalize vitamin D levels. Pre- and postdose averages will be used to minimize the effect of any intrasubject and interassay variability. The post-dose average will be obtained over the last six-weeks of treatment (visits 19-22) to allow subjects to achieve steady state serum 25-hydroxyvitamin D levels.

AEs, serum calcium and phosphorus have been used to assess safety of vitamin D compounds and will be monitored in this study. The safety and tolerability of CTAP101 Capsules will be determined by comparing each active group to placebo.

7 STUDY ACTIVITIES

7.1 Screening Period

7.1.1 Visit 1 (Day -70 to -63)

- AE Assessment
- A signed ICF will be obtained from the subject prior to any study related procedures
- Review of inclusion/exclusion criteria, including eGFR measurement
- Medical history and demographics: date of birth, gender, race, ethnicity, cause and date of CKD. A complete medical history, including alcohol, tobacco and nicotine-containing product use histories and method of contraception, as appropriate, will be recorded
- Medication History: All prescription and over the counter medication usage for the 28 days prior to visit 1 will be recorded
- General PE (including weight, height and BMI)
- VS measurements
- Urine chemistry
- Blood samples to be drawn prior to dosing and washout (if required):
  - Chemistry (full panel) and hematology
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D
- Urine pregnancy test (only for females of childbearing potential)
- Washout assessment: Subjects who are taking any vitamin D and/or bone metabolism therapy, including vitamin D supplements (>1,700 IU/day of ergocalciferol or cholecalciferol), will discontinue or reduce therapy to ≤1700 IU/day for the duration of the study. Subjects taking more than 1000 mg/day of elemental calcium will discontinue or reduce therapy for the duration of the study.
  - If washout is not required proceed to visit 3.
  - If washout is required, proceed to visit 2 after completion of at least 8 weeks of washout.

If the screening values do not meet study entry criteria after visit 1, subject may receive supportive care per the investigator's discretion and be retested once. If values do not fall within study entry criteria on retest, the subject will be considered a screen failure and be withdrawn from the study. Only the screening test(s) that did not meet entry criteria at visit 1 are required to be re-drawn and meet entry criteria at the time of the visit 1 retest.

7.1.2 Visit 2 (Day -7 to -1)

This visit is only applicable for subjects requiring washout. Subjects requiring washout will need to undergo visit 2 to confirm study entry laboratory values meet or continue to meet study entrance criteria.

- Review of inclusion/exclusion criteria

- Concomitant medications
- AE assessment
- VS measurements
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D

7.1.3 Visit 3 (Day 1)

Subjects will need to confirm study entry laboratory values continue to meet study entrance criteria for serum calcium, phosphorus, total 25-hydroxyvitamin D, and plasma iPTH. This visit should occur after screening values from visit 1 (visit 2 for subjects requiring washout) meet study entry criteria.

- Review of inclusion/exclusion criteria
- Concomitant medications
- AE assessment
- General PE (including weight, height and BMI)
- VS measurements
- 12-lead ECG
- Urine chemistry and urinalysis
- Blood samples will be drawn for the following:
  - Chemistry (partial panel)
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D
  - Serum 25-hydroxyvitamin D_3, [redacted]
  - [redacted]
- Urine pregnancy (only for females of childbearing potential)
- Randomization of subject
- Dispense assigned bottles of study drug with dosing instructions

7.2 Treatment Period (Weeks 1-26)

7.2.1 Visits 4-10 (Days 8-71)

- May occur ±3 days of scheduled day
- AE assessment
- Concomitant medications

- VS measurements
- Blood samples drawn for:
  - Chemistry (partial panel)
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D

7.2.2 Visits 11-12 (Days 83-84)

- Must occur on the scheduled days
- AE Assessment
- Concomitant medications
- VS measurements
- Blood samples drawn for all subjects at 0 (pre-dose), 6 and 12 hours and additionally, only for subjects assigned to intensive PK evaluation, at -2, 2, 4 and 8 hours after dosing on Day 83 for:
  - Chemistry (partial panel)
  - Serum 25-hydroxyvitamin D_3, [redacted]
- Blood samples drawn at 24 hours ±4 hours before dosing on Day 84 for:
  - Chemistry (partial panel)
  - Serum 25-hydroxyvitamin D_3, [redacted]

7.2.3 Visit 13 (Day 85):

- Must occur on the scheduled day
- Urine pregnancy (for females of childbearing potential)
- AE assessment
- Concomitant medications
- Urine pregnancy (only for females of childbearing potential)
- VS measurement
- Urine chemistry and urinalysis
- Blood samples drawn at 48 hours ±4 hours before dosing for:
  - Chemistry (full panel) and hematology
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D
  - Serum 25-hydroxyvitamin D_3, [redacted]
  - [redacted]
- Drug accountability
- Patient reported palatability and acceptability

- Dispense assigned bottles of study drug

7.2.4 Visits 14-21 (Days 92-169)

- May occur ±3 days of scheduled day
- Visits 14 and 16 are required only for subjects who underwent upward dose titration at visit 13
- AE assessment
- Concomitant medications
- VS measurements
- Blood samples drawn for:
  - Chemistry (partial panel)
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D

7.2.5 Visit 22 (Day 183):

- Must occur on the scheduled day
- Urine pregnancy (only for females of childbearing potential)
- AE assessment
- Concomitant medications
- VS measurements
- Urine chemistry and urinalysis
- Blood samples drawn for:
  - Chemistry (full panel) and hematology
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D
  - Serum 25-hydroxyvitamin D_3, [redacted]
  - [redacted]
- Patient reported palatability and acceptability
- Drug accountability

7.3 Follow-up Period or Second PK Assessment

7.3.1 Visit 23 (Day 190)

- Must occur on the scheduled day
- Required only for subjects participating in the second PK assessment
- AE Assessment

- Concomitant medications
- VS measurements
- Blood samples drawn for:
  - Chemistry (partial panel)
  - Serum 25-hyroxyvitamin D_3, [redacted]

7.3.2 Visit 24 (Day 197)

- May occur ±3 day of scheduled day
- Required only for subjects participating in the second PK assessment
- Concomitant medications
- AE assessment
- VS measurements
- Blood samples drawn for:
  - Chemistry (full panel) and hematology
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D
  - Serum 25-hydroxyvitamin D_3, [redacted]

7.3.3 Visits 25-27 (Days 204-218)

- Must occur on the scheduled days
- Required only for subjects participating in the second PK assessment
- AE Assessment
- Concomitant medications
- VS measurements
- Blood samples drawn for:
  - Chemistry (partial panel)
  - Serum 25-hyroxyvitamin D_3, [redacted]

7.3.4 Visit 28/ET (Day 225)

- May occur ±3 day of scheduled day
- Concomitant medications
- AE assessment
- PE (including weight, height and BMI)
- VS measurements
- 12-lead ECG

- Urine chemistry and urinalysis
- Urine pregnancy (only for females of childbearing potential)
- Blood samples drawn for:
  - Chemistry (full panel) and hematology
  - Plasma iPTH
  - Serum total 25-hydroxyvitamin D
  - Serum 25-hydroxyvitamin D_3, [redacted]
  - [redacted]

8 QUALITY CONTROL AND ASSURANCE

A quality assurance audit may be performed by the sponsor and/or its designee at selected site(s) to verify that the study was conducted in accordance with the protocol, ICH/GCP, and applicable SOP and regulations, to ensure that the safety and welfare of subjects are addressed, and to confirm that problems reported by study monitors have been resolved. Verification of study documents and study activities (if applicable) will be conducted to confirm accuracy of recorded data and its' analysis. Audit observations and findings will be documented and communicated to appropriate study personnel and management. An inspection may be conducted by regulatory authorities. The investigator must allow direct access to study documents during these inspections and audits.

Monitoring visits will be performed to evaluate study conduct, data integrity, protocol, and GCP compliance and safety.

Each investigator is responsible for the accuracy, completeness, legibility, and timeliness of the data reported. All source documents are to be completed in a neat, legible manner to ensure accurate interpretation of data.

Source documents and laboratory reports will be reviewed to ensure that they are accurate and complete.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

All analyses will be performed using Statistical Analysis Software (SAS®) version 9.3 or higher (SAS® Institute, Cary, NC). All data collected on eCRFs and from clinical laboratory evaluations will be grouped and listed by treatment, subject, visit, date and time as feasible. Summary tables will be presented by treatment group where appropriate. Descriptive summaries of categorical outcomes will include the number and percent of subjects. Descriptive summaries of quantitative measures will include the number of subjects, mean, SD, median, minimum, and maximum or as appropriate. In descriptive summary tables, if needed, the geometric mean will be calculated as the n^{th} root of the resulting product of the values, and the coefficient of variation (in percent, %CV) will be calculated as 100* (SD/[arithmetic mean]).

Arithmetic means, SDs, medians, and geometric means will be reported with the same number of significant figures as the reported values. Minimum and maximum values will be reported with the same accuracy as the reported source data. The %CV will be rounded to one decimal place.

Denominators of percentage of subject calculations will be based on the number of subjects in the treatment group and selected population unless otherwise specified.

In the event there are multiple results at a given visit and/or time point, the following logic will be applied for purposes of summarization by visit or time point: for pre-dose measurements and selection of a baseline value (see Section 9.4 Definition of Baseline), the more recent non-missing result will be selected; for post-dose measurements, the earliest of the results will be selected. If multiple laboratory results are available for the same date and time and the discrepancy could not be resolved, then the arithmetic mean of the results could be used unless specified in the data management plan or data handling conventions finalized before breaking the study randomization blind. All subjects entered into the clinical database will be included in subject data listings.

For certain analyses, a one-sided familywise type 1 error rate of 2.5% may be appropriately applied. More details will be captured in the Statistical Analysis Plan.

9.2 Determination of Sample Size

Sample size has been calculated (using Fisher's exact test statistics) to provide power of 80% for a two-sided, alpha 0.05 level test of equal proportions comparing the percentages of subjects attaining a mean decrease of at least 30% in plasma iPTH (averaged over the last 6 weeks of treatment) compared to baseline on daily dosages of CTAP101 Capsules (active) versus placebo. Assuming response rates of at least 0.4 (CTAP101 Capsules) versus 0.1 (placebo), and using a 2:1 ratio of CTAP101 Capsules:placebo subjects with an estimated 20% dropout rate over the course of the study, a sample size of approximately 108 subjects is required in the study with two-thirds apportioned to the 12 to <18 year age group (Cohort 1) and one-third apportioned to the 8 to <12 year age group (Cohort 2), allocated as 72 subjects to CTAP101 Capsules and 36 subjects to placebo.

No subject replacement is planned.

9.3 Analysis Populations

9.3.1 Analysis Populations

Efficacy analyses will be conducted for the ITT and PP, as indicated. The ITT population will be defined as all subjects who have been randomized to receive study medication. The PP population will be defined as all subjects who have at least two plasma iPTH determinations included each in the calculated baseline value and in the EAP, defined as weeks 20 through 26 (visits 19-22). Safety analyses will be conducted in the safety population, defined as all randomized subjects who have received at least one dose of the study drug.

9.4 Definition of Baseline

Pretreatment "baseline" will be defined as the last (nearest) non-missing measurement obtained or performed prior to dosing with study drug, unless otherwise stated. Pre-dose measurements obtained or performed at visit 3 are considered as baseline, if available; otherwise measurements on prior visits constitute baseline. Any re-test values for screening visits will be used to calculate baseline in place of original test values obtained on that visit. Definitions of baseline for plasma iPTH and serum calcium, phosphorus, total 25-hydroxyvitamin D and [redacted] will be the average of measurements obtained at Visits 2 and 3.

9.5 Demographics Characteristics

Demographic and baseline characteristics will be summarized for the ITT and PP populations by treatment groups separately and combined. Baseline height, weight, BMI, age, sex, race, ethnicity, tobacco and nicotine history, and alcohol history will be tabulated for the safety population.

9.6 Subject Disposition and Withdrawal

Appropriate procedures will be followed, whenever possible, to prevent missing data and to collect the reason for missing data when it does occur, as delineated by [Fleming 2011]. The impact of missing data on the primary efficacy and safety endpoints will be evaluated by sensitivity analyses designed to show how different assumptions about the missing data influence the results. A tipping point analysis will be completed to evaluate the potential effect of further discontinuations and missing data on the study conclusions. These analyses will be detailed in the Statistical Analysis Plan.

Subject disposition will be tabulated and descriptively summarized for all randomized subjects by treatment groups separately and combined. Subject disposition will be summarized by presenting the number and percent of subjects randomized, ITT and PP subjects, subjects who completed study drug administration, subjects who completed the study, and subjects who discontinued prematurely from the study. The primary reason for premature study termination will be detailed together with the number and percent of subjects discontinuing for each reason. The primary reason for premature study termination will be collected from the ET eCRF page and will include the following:

- Occurrence of a SAE or AE
- Disease progression as assessed by clinical judgment and/or objective measurement
- Initiation of dialysis

- Violation of the protocol and/or subject non-compliance
- Lost to FU
- Pregnancy
- Withdrawal of consent at any time, for any reason, at the discretion of the enrolled subject
- Requirement for a 5th reduction in dose
- Other (specific reason)

Screen failure information will be collected regularly by the sponsor. Medical history will be collected on the eCRF at visit 1 and displayed in a data listing as well as summarized by treatment group. Date of diagnoses of CKD and SHPT, stage of CKD, underlying diagnosis of the CKD, and previous and concurrent diseases will be collected in the eCRF and documented on the history of CKD page or as medical history. Medical history events will be sorted alphabetically by System Organ Class (SOC). The coding of the data will be performed with MedDRA version 20.0 or higher, using Preferred Terms (PT).

9.7 Prior and Concomitant Medications

Prior medications are defined as any continuing or new medication used within 28 days before visit 1 and discontinued prior to the day of study drug administration. Concomitant medications are defined as any continuing or new medication taken from time of first dose of study drug (visit 3) or anytime thereafter until the end of the study. Type and dose of concomitant medications used for phosphate binder therapy will be collected on a separate eCRF page at each visit. Medication information will be collected through to the visit 28/ET visit. World Health Organization Drug Dictionary Enhanced version March 2018, Format C, or later will be used to code concomitant and prior medications. Prior and concomitant medications will be tabulated by treatment group using frequency counts and percents for each anatomical/therapeutic/chemical Class Level 2 and 4 and generic drug name. All medications recorded on the eCRF, including start and stop (or ongoing as of) dates, AE number (if applicable), indication, dose, unit, route, and frequency will be listed. For the purpose of inclusion in prior or concomitant medication tables, incomplete medication start and stop dates will be imputed and then categorized into prior or concomitant medication categories.

9.8 Analysis Endpoints

9.8.1 Primary Efficacy Endpoint

The primary estimand is the reduction of mean plasma iPTH by at least 30% from pre-treatment baseline. The primary efficacy endpoint is the proportion of subjects in the ITT population (age 8 to <18 years) attaining a mean decrease in plasma iPTH from pre-treatment baseline of ≥30% compared to placebo in the EAP.

9.8.2 Primary Safety Endpoints

The primary safety endpoints are:

- AEs
- Laboratory parameters (clinical chemistry, hematology, urine chemistry and urinalysis)

- PEs
- VS
- 12-lead ECGs

9.8.3 Pharmacokinetic Endpoints

For the interim analysis, repeated-dose (steady-state) PK determinations will be performed in subsets of subjects in both Cohort 1 and Cohort 2 by analyzing intensive serum 25-hydroxyvitamin D_3 concentrations versus time recorded during dosing with CTAP101 Capsules (n=10) or placebo (n=5) in the last three days of the 12th week of treatment.

For the final analysis, repeated-dose (steady-state) PK determinations will be performed in both Cohort 1 and Cohort 2 by analyzing serum 25-hydroxyvitamin D_3 concentrations versus time recorded (a) during dosing with CTAP101 Capsules or placebo in the last three days of the 12th week of treatment and (b) after the last administered dose in each active treatment group.

The following PK parameters will be calculated using observed and baseline-adjusted serum 25-hydroxyvitamin D_3 concentrations: (a) AUC, C_{max}, t_{max}, and C_{ss}; time to steady-state concentration (t_{ss}), and (b) $t_{½}$, CL/F, and Vd/F, as feasible. Relative exposure and dose proportionality will be examined, if possible.

9.8.4 Secondary Endpoints

The secondary endpoints of the study will be:

- Proportion of subjects in the PP population with a mean decrease of at least 30% in plasma iPTH from pre-treatment baseline in the EAP, in aggregate and by mean weekly study dose in the EAP
- Proportion of subjects in the ITT and PP populations attaining adequate serum total 25-hydroxyvitamin D (≥ 30 ng/mL) in the EAP, in aggregate and by mean weekly study dose in the EAP
- The time courses of mean absolute changes from pre-treatment baseline in serum total 25-hydroxyvitamin D and plasma iPTH
- Proportion of subjects who attain 2 consecutive plasma iPTH values ≤70 pg/mL
- PD effects on mean serum calcium (corrected), serum phosphorus, serum CaxP product, serum calcitriol, serum 24,25-dihydroxyvitamin D_3, and the urine calcium:creatinine ratio
- Proportion of subjects with hypercalciuria (>200 mg calcium/g creatinine)
- Proportion of subjects with hypercalcemia (2 consecutive visits with serum calcium >10.3 mg/dL)
- Proportion of subjects with hyperphosphatemia (2 consecutive visits with serum phosphorus >5.5 mg/dL deemed to be study drug related)

9.8.5 [redacted]

[redacted]

9.9 Additional Assessments

Patient reported outcomes on palatability and acceptability.

9.10 Efficacy Analysis

9.10.1 Primary Endpoint Analysis

Primary efficacy will be assessed in the ITT population by comparing the proportions of subjects in each treatment group (CTAP101 Capsules versus placebo) attaining a mean decrease from baseline in plasma iPTH of ≥30% in the EAP using the Cochran-Mantel-Haenszel test statistic (alpha=0.05) for overall efficacy of the multicenter results. Subjects who do not have at least two plasma iPTH determinations in the EAP will be deemed non-responders.

9.10.2 Secondary Endpoint Analyses

Secondary efficacy will be assessed in the PP population by comparing the proportions of subjects in each active treatment group attaining mean decreases in plasma iPTH of ≥30% from baseline in the EAP to the corresponding proportion of subjects in the placebo group, and in the ITT and PP populations by comparing the proportions of subjects in each active treatment group attaining mean serum total 25-hydroxyvitamin D of ≥30 ng/mL in the EAP to the corresponding proportions of subjects in the placebo group, in aggregate and by mean weekly study dose in the EAP. Mean weekly dose in the EAP will be calculated for two groups of subjects: those receiving ≤30 mcg per day; and those receiving >30 mcg/day. Secondary efficacy will also be assessed by the time courses of mean absolute changes from pre-treatment baseline in serum total 25-hydroxyvitamin D and plasma iPTH (i.e., continuous iPTH change); and pharmacodynamic (PD) effects on mean serum calcium (corrected), serum phosphorus, serum [redacted], and the urine calcium:creatinine ratio.

[redacted]

The number (n, %) of subjects attaining two consecutive reductions in plasma iPTH values ≥30% from baseline, as well as, the number (n, %) subjects with two consecutive plasma iPTH values ≤70 pg/mL will be compared between treatment groups.

9.11 Safety Analyses

All subjects who have received at least one dose of study drug (the "safety population") will be included in the safety analyses. Statistical summary analysis of safety data will be descriptive and performed by treatment group and by stratum (age and gender groups). No inferential hypothesis testing will be performed on the safety variables with the exception of serum calcium, serum phosphorus, serum CaxP product and urine calcium to creatinine ratio.

9.11.1 Primary Endpoints Analyses

9.11.1.1 Adverse Events

All AEs will be collected on the eCRF and coded via SOC and preferred term using MedDRA version 20.0 or higher. After randomization, AEs with missing onset date will be treated as TEAEs and missing onset date will be imputed as the date of study drug administration, unless the event end date indicates that the event resolved prior to administration of study drug, in which case it will be documented in medical history. AEs with partial onset date will be treated as TEAEs unless the partial onset date or end date of the event is complete enough to indicate that the event started or resolved prior to the administration of study drug, in which case it will be documented in medical history. Detailed information collected for each TEAE will include: AE number, a description of the event, start date, end date or ongoing as of date, outcome, therapy for event, whether the AE was serious, seriousness criteria (life-threatening, death, hospitalization/prolongation of hospitalization, congenital anomaly, persistent or significant disability/incapacity, required intervention to prevent permanent impairment/damage), severity, and relationship to study drug. The incidence of the AEs will be summarized by treatment group for all TEAEs, potentially drug-related TEAEs, serious TEAEs, discontinuation due to TEAEs, TEAEs by relationship to study drug (definite, probable, possible, unrelated) and TEAEs by severity (mild, moderate, severe). The number and percentages of subjects with a TEAE will be summarized by SOC and preferred term and presented overall and by treatment group. TEAEs will be sorted in descending order of total incidence of SOC and preferred term within each SOC. The percentages will be based on the number of ITT subjects in a particular treatment group. If a subject has more than one TEAE that code to the same preferred term, the subject will be counted only once for that preferred term. Similarly, if a subject has more than one TEAE within a SOC category, the subject will be counted only once in that SOC category. All AEs collected on the eCRF will be included in the listings. An additional listing of all subject deaths will also be provided.

9.11.1.2 Laboratory Evaluations

Clinical laboratory data will be listed and summarized using conventional units. All laboratory parameters will be listed and sorted by subject, collection date and laboratory test. Shift tables will capture change from baseline (see Section 9.4 Definition of Baseline) to visit 28/ET for each laboratory parameter, if feasible. Separate summary tables will be provided for mean absolute and percent change in plasma iPTH and serum total 25-hydroxyvitamin D, serum calcium, serum

CaxP product and phosphorus, and urine calcium:creatinine ratio. Proportions will be compared using a z-test or t-test, as appropriate.

9.11.1.3 Vital Signs

Observed VS values will be summarized descriptively at baseline and changes from baseline will be descriptively summarized by treatment group, CKD stage, age group and gender. Summaries will include n (%), mean, SD, median, minimum, and maximum. VS values will be listed.

9.11.1.4 Physical Examinations

Physical examination dates, whether a PE (including weight and height) is performed or not, abnormalities, if any, will be added to the medical history or reported as AEs as appropriate, and summarized by SOC and preferred term using MedDRA version 24.0 or higher.

9.11.1.5 ECG

12-lead ECG measurements will be assessed at the study sites at visit 3, 22 and visit 28/ET and results will be collected on the eCRF.

Observed ECG values for heart rate and the corrected QT interval will be descriptively summarized at baseline and changes from baseline will be summarized descriptively by treatment group at visit 28/ET. Summaries will include n, mean (%), SD, median, minimum, and maximum.

Shift in ECG categories (normal ECG, abnormal ECG – not clinically significant, abnormal ECG – clinically significant, missing) from baseline to visit 28/ET will be summarized descriptively in the form of frequencies and percentages.

The paired t-test will be used to perform within-subject comparisons between baseline and post-baseline values for heart rate and the corrected QT interval, if feasible.

Additionally, the two sample t-test will be used to perform pair-wise comparisons of change from baseline heart rate and corrected QT intervals between the treatment groups.

In the event of gross violations from the normality assumptions, the signed rank test will be used to perform the within-subject comparisons and a Wilcoxon rank sum test will be used to perform the pair-wise comparisons.

All ECG values will be listed.

9.11.2 Secondary Endpoint Analyses

The number (n, %) of subjects with hypercalciuria (>200 mg Ca/g creatinine), hypercalcemia (two consecutive visits with serum calcium >10.3 mg/dL) or hyperphosphatemia (two consecutive visits with serum phosphorus >5.5 mg/dL deemed to be study drug related) or serum confirmed CaxP product >55 (for Cohort 1) or >60 (for Cohort 2) will be compared between the treatment groups (active versus placebo) using the Cochran-Mantel-Haenszel test statistic (alpha=0.05) for overall efficacy of the multicenter results; the Chi-square test or Fisher's Exact test will be used for reporting the results in the separate strata.

9.12 Other Analysis

Descriptive statistics will be applied to evaluate patient reported palatability and acceptability. In addition, the proportion of subjects attaining the mean decrease from baseline in plasma iPTH of ≥30% in the subgroup of subjects with and without nutritional intake within 60 minutes of medication administration will be evaluated using the analysis methods described above.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Investigators and Study Administrative Structure

Investigators will be chosen based on their experience in treating SHPT in pediatric patients with stage 3 or 4 CKD with vitamin D therapies, their past successful and compliant conduct of clinical trials and their track records for subject recruitment, subject retention and high rates of data capture.

At screening, investigators will offer subjects notification of their primary care physician or nephrologist that he/she is participating in a clinical study. If the subject accepts, a brief letter outlining the study and identifying the study drug should be sent once the subject is enrolled.

10.2 Institutional Review Board Approval

GCP requires that the clinical protocol, any protocol amendments, the IB, the informed consent, and all other forms of subject information related to the study and any other necessary documents be reviewed by an IRB.

10.3 Ethical Conduct of the Study

In accordance with applicable country-specific regulations, the sponsor will obtain approval from the appropriate regulatory authority(ies) prior to initiating the study in that country.

10.4 Subject Information and Consent

The investigator or his/her qualified designee will explain the nature of the study to the subject and legal guardian, answer all questions regarding this study, and emphasize that missing data and premature termination of study participation will diminish the scientific value of the data obtained, prior to obtaining informed consent.

The investigator or his/her qualified designee will obtain informed consent from each subject or legal representative enrolled in the study, in accordance with the Declaration of Helsinki, the current version of the ICH guidelines and the local laws and applicable regulatory requirements.

It is the responsibility of the investigator to assure that the subject and legal guardian has signed the informed consent before any activity or treatment is undertaken which is not part of routine care. The subject will receive a signed copy of the ICF and the original will be retained in the site study records. The investigator or his/her designee will ensure documentation of the consent discussion in the subject's medical record/source documents. The decision by the subject and legal guardian to participate in the study is entirely voluntary. The investigator or designate must emphasize to the subject and legal guardian that consent regarding study participation may be withdrawn at any time without penalty or loss of benefits to which the subject is otherwise entitled.

If the ICF is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the IRB and use of the amended form (including for ongoing subjects).

10.5 Subject Confidentiality

Subject confidentiality will be strictly held in trust by the participating investigators, their staff, sponsor and their authorized representatives. This confidentiality is extended to cover testing of biological samples in addition to the clinical information relating to participating subjects.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party, without prior written approval of the sponsor.

Authorized representatives of the sponsor, the designated contract research organization (if applicable), the study monitor, employees of government authorities such as the US FDA or other government authorities, and members of the IRB may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

No information that would permit the identification of a specific individual will be provided for entry into the study database or study report. Study documentation submitted to the sponsor will identify study participants by study code and initials. The investigator will keep a separate confidential enrollment log that matches identifying study codes with the subjects' names and residencies.

10.6 Study Monitoring

The sponsor and/or its designee are responsible for monitoring the study in accordance with the requirements of the ICH/GCP, and in accordance with written SOPs and the Clinical Monitoring Plan.

The study will be monitored by the sponsor or designee at all stages of study conduct from inception to completion in accordance with current ICH/GCP protocol compliance. The investigator will allocate adequate time for such monitoring activities. This monitoring will be in the form of site visits and other communication and will include review of original source documents, CRFs, facilities and equipment, recruiting, record-keeping, protocol adherence, data collection, AE reporting, and other factors. The frequency of these visits will depend upon the progress of the study.

The investigator will ensure that the monitor or other compliance or quality assurance reviewers are given access to all the above noted study-related documents and study related facilities (eg, pharmacy, diagnostic laboratory, etc), and has adequate space to conduct the monitoring visit.

10.7 Case Report Forms and Study Records

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 on the appropriate source documents. All source documents should be completed using blue or black ink, in a neat, legible manner to ensure accurate interpretation of data.

Data capture and management will be consistent with applicable ICH/GCP guidelines.

All data collected during the study for subjects who are randomized will be recorded in an individual, subject-specific eCRF as part of an electronic data capture (EDC) system. The sponsor or designee will provide training to the investigative site on the EDC system and eCRFs. All eCRFs will be completed as soon as data are available in the source for each subject. As electronic data capture will be utilized, instructions, training records, and a log will be maintained to identify the designated site personnel who can enter data and/or sign off on an eCRF. Data for subjects who fail screening, including the reason for screen failure, will be recorded on a screening log which will be provided to the sponsor.

A subject eCRF must be completed for each subject (or legal representative) who signs a consent form and undergoes randomization. All data generated from external sources, (eg, central laboratory and PK/PD processing/analysis), will be integrated with the subject eCRF data through programming or other data integration techniques.

All eCRFs should be completed within five business days of the visit to enable the study monitor to review the subject's status throughout the course of the study in real time.

To ensure the quality of the clinical data across all subjects and sites, a Clinical Data Management review will be performed by the sponsor or designee on subject data entered or integrated into the EDC system. During the review, subject data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol, and ICH/GCP. Moreover, all data from external sources, eg, central laboratory and PD processing/analysis will be reconciled with subject eCRF data. To resolve any questions arising from the Data Management review process, data queries and/or data clarification notifications will be generated via the EDC system for completion and resolution.

The investigator will sign and date the indicated places on the eCRF via the EDC system's electronic signature. These signatures will indicate that the investigator reviewed the data on the eCRF, the data queries, and the data clarifications and agrees with the content.

10.8 Data Safety Monitoring Board

An independent, external unblinded Member of the DSMB will be responsible and will oversee the IRS and verify the appropriateness of all dosing adjustments, and to monitor subject safety and the effectiveness of CTAP101 Capsules at regular intervals. Members of the DSMB will also conduct periodic reviews of study conduct to verify that all required data are captured to a sufficiently high degree (>95%) and within specified time frames (usually within 5 days), and to promptly recommend appropriate corrective actions to address any noted deficiencies, in an effort to minimize missing data. Specific responsibilities and activities of the DSMB will be defined in the charter ratified at the organizational meeting of the DSMB. These responsibilities will include the completion of an interim analysis of the repeated-dose PK data obtained in Cohort 1 to justify a starting dose for Cohort 2.

10.9 Protocol Deviations

Protocol deviations are any intentional or unintentional change from an IRB approved protocol that was not approved by the IRB prior to initiation of the change.

Major protocol deviations are deviations that result in increased risk to subjects, affect the rights, safety, or welfare of the subjects or affect the integrity of the study.

Major protocol deviations may include but are not limited to deviations from the inclusion/exclusion criteria), informed consent deviations, concomitant medication restrictions, and any other protocol requirement that results in a significant added risk to the subject or has an impact on the quality of the data collected or the outcome of the study.

The sponsor requires that all major protocol deviations be reported to the IRB.

In addition, the investigator is responsible for adhering to his/her IRB's protocol deviation reporting requirements.

10.10 Source Documentation

Source data is all information, original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study.

Data collected during this study must be recorded on the appropriate source documents.

The investigator is responsible for the accuracy, completeness, legibility and timeliness of the data reported on the source documents. All source documents should be completed using blue or black ink, in a neat, legible manner to ensure accurate interpretation of data.

The subject screening log should list all consented subjects contacted by the investigator to participate in the study, regardless of the outcome.

10.11 Data Generation and Analysis

The investigators are responsible for the accuracy, completeness, and timeliness of the data reported on the eCRF. Study data management, monitoring, statistical analysis, and reporting will be performed by the sponsor using the sponsor's SOPs.

Completed eCRFs are required for each subject randomly assigned to study medication. Electronic data entry is accomplished through the 21CFR Part 11 compliant OmniComm eClinical System Solution for Life (Ft. Lauderdale, FL) remote data capture application, which allows for on-site data entry and data management. Furthermore, the investigators retain full responsibility for the accuracy and authenticity of all data entered into the EDC system. The completed dataset and their associated files are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized business representatives or appropriate governmental health or regulatory authorities, without written permission of the sponsor.

Data management, data analysis and programming the submission-ready tables, listings and figures will be responsibility of the sponsor and will be performed and managed per the sponsor's SOPs.

10.12 Retention of Data

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all CRFs and all source documents that support the data collected from each subject, and all study documents as specified in ICH/GCP Section 8, Essential Documents for the Conduct of a Clinical Trial and as specified by the applicable regulatory requirement. The investigator/institution will take measures to prevent accidental or premature destruction of these documents.

Essential documents must be retained until at least two years after the last approval of a marketing application in an ICH region or at least two have elapsed since the formal discontinuation of clinical development of the investigational product. These documents will be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

If the responsible investigator retires, relocates, or for other reasons withdraws from the study, the responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The sponsor must be notified in writing of the name and address of the new custodian. Under no circumstances shall the investigator relocate or dispose of any study documents before having obtained written approval from the sponsor.

10.13 Financial Disclosure

The principal investigator and all sub-investigators are required to provide certification (Financial Disclosure Form) that no financial arrangements with the sponsor have been made where study outcome could affect compensation; that the investigator has no proprietary interest in the tested product; that the investigator does not have a significant equity interest in the sponsor; and that the investigator has not received significant payments of other sorts. The investigator/sub-investigator is responsible for informing the sponsor if these circumstances change during the course of the study or within one year of the end of his/her participation in the study.

10.14 Publication and Disclosure Policy

Data derived from the study are the exclusive property of the sponsor. Any publication or presentation related to the study must be approved by the sponsor before submission of the manuscript. After publication of the results of the study, any participating center may publish or otherwise use its own data provided that any publication of data from the study gives recognition to the study group. In addition, the sponsor shall be associated with all such publications, it being understood that the sponsor is entitled to refuse the association.

The sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this study at least 60 days prior to submission for publication or presentation. Any information identified by the sponsor as confidential must be deleted prior to submission, it being understood that the results of this study are not to be considered confidential.

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APPENDIX 1 SCHEDULE OF EVENTS

Schedule of Events	Screening Period				Treatment Period						
	Visit 1		Visit 2[a]	Visit 3	Visit 4[b]	Visit 5[b]	Visit 6[b]	Visit 7[b]	Visit 8[b]	Visit 9[b]	Visit 10[b]
				Randomized							
	Days -70 to -63	Days -62 to -8	Days -7 to -1	Day 1	Day 8	Day 15	Day 22	Day 29	Day 43	Day 57	Day 71
Sign ICF	1	Washout (if applicable)									
Review or confirmation of inclusion/exclusion criteria	1		1	1							
Medical history and demographics	1										
Prior/concomitant medications	1		1	1	1	1	1	1	1	1	1
Adverse events	1		1	1	1	1	1	1	1	1	1
Physical exam (including weight, height and BMI)	1			1							
VS measurements	1		1	1	1	1	1	1	1	1	1
12-lead ECG				1							
Urine pregnancy test, as needed[c]	1			1							
Clinical chemistry (full panel)	1[d]		1								
Hematology	1		1								
Clinical chemistry (partial panel)				1	1	1	1	1	1	1	1
Urine chemistry	1			1							
Urinalysis				1							
Calculate eGFR	1										
Dispense study drug				1							
Drug accountability											
Plasma iPTH	1		1	1	1	1	1	1	1	1	1
Serum total 25D	1		1	1	1	1	1	1	1	1	1
Serum 25D3 [redacted]				1							
[redacted]				1							
Patient reported palatability and acceptability											

a. If washout of vitamin D, calcium and/or bone metabolism therapy is not required, Visit 2 is not required.
b. May occur ± 3 days of scheduled day
c. Only for females of childbearing potential
d. Visit 1 creatinine value will be used to calculate screening eGFR
e. Additional blood draws required at -2, 2, 4 and 8 hours only if subject is participating in the intensive PK assessment
f. Visit required only if subject underwent dose titration at Visit 13
g. Visit required only for subjects participating in the second PK assessment

Schedule of Events	Treatment Period								
	Visit 11[e]	Visit 12	Visit 13	Visit 14[b,f]	Visit 15[b]	Visit 16[b,f]	Visit 17[b]	Visit 18[b]	Visit 19[b]
	Day 83 (-2[e], 0, 2[e],4[e],6,8 [e], and 12 hours)	Day 84	Day 85	Day 92	Day 99	Day 106	Day 113	Day 127	Day 141
Sign ICF									
Review or confirmation of inclusion/exclusion criteria									
Medical history and demographics									
Prior/concomitant medications	1	1	1	1	1	1	1	1	1
Adverse events	1	1	1	1	1	1	1	1	1
Physical exam (including weight, height and BMI)									
VS measurements	1	1	1	1	1	1	1	1	1
12-lead ECG									
Urine pregnancy test, as needed[c]			1						
Clinical chemistry (full panel)			1						
Hematology			1						
Clinical chemistry (partial panel)	7	1		1	1	1	1	1	1
Urine chemistry			1						
Urinalysis			1						
Calculate eGFR									
Dispense study drug			1						
Drug accountability			1						
Plasma iPTH			1	1	1	1	1	1	1
Serum total 25D			1	1	1	1	1	1	1
Serum 25D3, [redacted]	7	1	1						
[redacted]			1						
Patient reported palatability and acceptability			1						

a. If washout of vitamin D, calcium and/or bone metabolism therapy is not required, Visit 2 is not required.
b. May occur ± 3 days of scheduled day
c. Only for females of childbearing potential
d. Visit 1 creatinine value will be used to calculate screening eGFR
e. Additional blood draws required at -2, 2, 4 and 8 hours only if subject is participating in the intensive PK assessment
f. Visit required only if subject underwent dose titration at Visit 13
g. Visit required only for subjects participating in the second PK assessment

Schedule of Events	Treatment Period			Follow-Up Period					
	Visit 20[b]	Visit 21[b]	Visit 22	Visits 23[g]	Visit 24[bg]	Visits 25[g]	Visits 26[g]	Visits 27[g]	Visit 28[b] / ET
	Day 155	Day 169	Day 183	Day 190	Day 197	Day 204	Day 211	Day 218	Day 225
Sign ICF									
Review or confirmation of inclusion/exclusion criteria									
Medical history and demographics									
Prior/concomitant medications	1	1	1	1	1	1	1	1	1
Adverse events	1	1	1	1	1	1	1	1	1
Physical exam (including weight, height and BMI)									1
VS measurements	1	1	1	1	1	1	1	1	1
12-lead ECG									1
Urine pregnancy test, as needed[c]			1						1
Clinical chemistry (full panel)			1		1				1
Hematology			1		1				1
Clinical chemistry (partial panel)	1	1		1		1	1	1	
Urine chemistry			1						1
Urinalysis			1						1
Calculated eGFR									
Dispense study drug									
Drug accountability			1						
Plasma iPTH	1	1	1		1				1
Serum total 25D	1	1	1		1				1
Serum 25D3 [redacted]			1	1	1	1	1	1	1
[redacted]			1						1
Patient reported palatability and acceptability			1						

a. If washout of vitamin D, calcium and/or bone metabolism therapy is not required, Visit 2 is not required.
b. May occur ± 3 days of scheduled day
c. Only for females of childbearing potential
d. Visit 1 creatinine value will be used to calculate screening eGFR
e. Additional blood draws required at -2, 2, 4 and 8 hours only if subject is participating in the intensive PK assessment
f. Visit required only if subject underwent dose titration at Visit 13
g. Visit required only for subjects participating in the second PK assessment

APPENDIX 2 INVESTIGATOR'S SIGNATURE

Study Title:	A Multi-Center Study to Evaluate the Efficacy, Safety and Pharmacokinetics of CTAP101 Extended-release Capsules to Treat Secondary Hyperparathyroidism in Pediatric Subjects of Ages 8 to <18 Years with Stage 3 or 4 Chronic Kidney Disease and Vitamin D Insufficiency
Study Number:	CTAP101-CL-3007
Final Date:	11 January 2022

I agree:

1. To assume responsibility for the proper conduct of the study at this site.
2. To conduct the study in compliance with this protocol, with any future amendments, and with any other written study conduct procedures provided and reviewed and approved by EirGen Pharma Ltd or its designee(s).
3. Not to implement any deviations from or changes to the protocol without agreement from the Sponsor and prior review and the written approval from IRB/IEC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).
4. That I am thoroughly familiar with the appropriate use of the investigational drug, as described in this protocol, and any other information provided by the Sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document provided by EirGen Pharma Ltd or its designee(s).
5. To ensure that all persons assisting me with the study are adequately informed about the investigational drug and of their study-related duties and functions as described in the protocol.
6. That I have been informed that certain regulatory authorities require the Sponsor to obtain and supply details about the investigator's ownership interest in the Sponsor or the study drug, and more generally about his/her financial ties with the Sponsor. EirGen Pharma Ltd will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply EirGen Pharma Ltd., with any information regarding ownership interest and financial ties (including those of my spouse and dependent children).
- Agree to update this information if any relevant changes occur during the course of the study and for one year following completion of the study.
- Agree that EirGen Pharma Ltd. may disclose this information about such ownership interests and financial ties to regulatory authorities.

Signed:_____ Date:_____

Printed Name: _____

Signature Page for Clinical Protocol CTAP101-CL-3007 v3.0

Signature Page for RIM-CLIN-000699 v3.0