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STATISTICAL ANALYSIS PLAN

A Multi-Center, Randomized, Two-Cohort Phase 2 Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of CTAP101 (calcifediol) Extended-Release Capsules to Treat Secondary Hyperparathyroidism in Subjects with Vitamin D Insufficiency and Chronic Kidney Disease Requiring Regular Hemodialysis.

Sponsor: EirGen Pharma Ltd.
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4400 Biscayne Boulevard
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Protocol Number: CTAP101-CL-2010, Cohort 1

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A Multi-Center, Randomized, Two-Cohort Phase 2 Study to Evaluate the Safety, Efficacy, Pharmacokinetics and Pharmacodynamics of CTAP101 (calcifediol) Extended-Release Capsules to Treat Secondary Hyperparathyroidism in Subjects with Vitamin D Insufficiency and Chronic Kidney Disease Requiring Regular Hemodialysis.

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Date

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14-Sep-2022 | 09:04 EDT

Date

SVP, Clinical R&D and Medical Affairs
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[redacted]

List of Abbreviations

$1,25D_3$	1,25-dihydroxyvitamin D_3, calcitriol
1,25D	1,25-dihydroxyvitamin D
$24,25D_3$	24,25-dihydtoxyvitamin D_3
25D	25-hydroxyvitamin D
$25D_3$	25-hydroxyvitamin D_3
ADaM	Analysis Data Model
AE	Adverse Event
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical
AUC	Area under the (concentration) Curve
BL	Baseline
BLOQ	Below the Limit of Quantification
BMI	Body Mass Index
CI	Confidence Interval
CKD	Chronic Kidney Disease
CL/F	Clearance divided by the bioavailable fraction
C_{max}	Maximum Concentration
CS	Clinically Significant
C_{ss}	Steady-State Concentration
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
DBP	Vitamin D Binding Protein
EAP	Efficacy Assessment Period
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EOT	End of Treatment
ER	Extended-release
ET	Early Termination
FAP	Follow-up Assessment Period
FDA	Food and Drug Administration
FU	Follow-up
[redacted]	[redacted]
HD	Hemodialysis
HR	Heart Rate
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iPTH	Intact Parathyroid Hormone
IRT	Interactive Response Technology
ITT	Intent-to-Treat
[redacted]	[redacted]
k_{el}	Terminal Elimination Rate Constant

λ_z	Terminal Rate Constant
LSMeans	Least Squares Means
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intent-to-Treat
MMRM	Mixed Model Repeated Measures
NCS	Not Clinically Significant
PD	Pharmacodynamic(s)
PDF	Portable Document Format
PE	Physical Examinations
PK	Pharmacokinetic(s)
PP	Per Protocol
PT	Preferred Term
RTF	Rich Text Format
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
Scr	Screening
SD	Standard Deviation
[redacted]	[redacted]
SDTM	Study Data Tabulation Model
SHPT	Secondary Hyperparathyroidism
SOC	System Organ Class
[redacted]	[redacted]
$t_{1/2}$	Terminal Elimination Half-life
TEAE	Treatment-Emergent Adverse Event
tiw	Three Times per Week
t_{max}	Time to Maximum Concentration
t_{ss}	Time to Steady-State Concentration
US	United States of America
V_Z/F	Volume of Distribution based on the terminal phase divided by the bioavailable fraction
VDI	Vitamin D Insufficiency
WHO	World Health Organization
WO	Washout

1. Introduction

The purpose of this statistical analysis plan (SAP) is to describe the planned analyses and reporting for Cohort 1 within protocol CTAP101-CL-2010, version 11.0 dated 05 May 2020 Cohort 2 analyses and summaries will be detailed in a separate SAP.

This SAP is being written with due consideration of the recommendations outlined in the most recent International Conference on Harmonisation (ICH) E9 Guideline entitled Guidance for Industry: Statistical Principles for Clinical Trials and the most recent ICH E3 Guideline, entitled Guidance for Industry: Structure and Content of Clinical Study Reports.

This SAP describes the data that will be analyzed, the subject characteristics, and the efficacy and safety assessments that will be evaluated. This SAP provides details of the specific statistical methods that will be used for each analysis respectively. The statistical analysis methods presented in this document will extend and, where necessary, supersede the statistical analysis methods described in the clinical protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they may be completed and will be identified in the clinical study report.

2. Study Objectives and Endpoints

2.1 Primary Objectives

The primary objectives of Cohort 1 in this study are:

1. To evaluate the efficacy of repeated dosing with 900 mcg per week of CTAP101 extended-release (ER) Capsules versus placebo in raising mean serum total 25-hydroxyvitamin D (25D) to ≥50 ng/mL and in reducing mean plasma intact parathyroid hormone (iPTH) by at least 30% from pre-treatment baseline;
2. To investigate the safety and tolerability of repeated dosing with 900 mcg per week of CTAP101 Capsules; and
3. To assess the pharmacokinetic (PK) profiles of serum calcifediol after a single dose of 900 mcg (6 capsules) at the start of CTAP101 study drug treatment (at the Single Dose PK Period), and after a single dose of subject's current dose (2 capsules) at the end of CTAP101 study drug treatment (at the Repeat Dose PK Period) in subjects with secondary hyperparathyroidism (SHPT), vitamin D insufficiency (VDI) and chronic kidney disease (CKD) who are undergoing hemodialysis (HD) three times per week (tiw).

2.2 Secondary Objectives

The secondary objectives of Cohort 1 in this study are:

1. To evaluate the efficacy of repeated dosing (tiw) with 300 mcg of CTAP101 ER Capsules versus placebo in raising mean serum total 25D to ≥50 ng/mL and in reducing mean plasma iPTH by at least 10 or 20% from pre-treatment baseline;
2. To determine the time courses of mean absolute changes from pre-treatment baseline in serum total 25D and plasma iPTH during administration of repeated doses of CTAP101 Capsules;
3. To assess the effects of body weight, age, gender, race, dose, severity of SHPT and VDI, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics on the safety and efficacy of repeated (tiw) doses of 300 mcg of CTAP101 Capsules versus placebo in raising serum total 25D to ≥50 ng/mL and in reducing plasma iPTH by at least 10, 20 and 30% from pre-treatment baseline;
4. To assess the pharmacodynamic (PD) effects of repeated doses (tiw) of 300 mcg of CTAP101 Capsules versus placebo on mean serum calcium (corrected for albumin), phosphorus, vitamin D binding protein (DBP), total free 25D, total 1,25-dihydroxyvitamin D (1,25D), 1,25-dihydroxyvitamin D_3 ($1,25D_3$), and 24,25-dihydroxyvitamin D_3 ($24,25D_3$);
5. To characterize the population PK of serum calcifediol relative to body weight, age, gender, race, dose, severity of SHPT and VDI, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics; and,
6. To evaluate the safety of CTAP101 Capsules versus placebo with regard to the incidence of hypercalcemia and hyperphosphatemia.

[redacted]

2.4 Primary Endpoints

There is no primary efficacy endpoint for Cohort 1, as efficacy in this part of the study is merely observational.

The primary safety and tolerability endpoints for Cohort 1 in the Safety population (defined as all subjects who have received at least one dose of study drug) include the following:

- Adverse events (AEs)
- Physical examinations (PEs)
- Vital signs
- Hematology
- Clinical chemistries
- 12-lead electrocardiograms (ECGs).

2.5 Secondary Endpoints

The key secondary efficacy endpoint for Cohort 1 is the proportion of subjects in the modified intent-to-treat (mITT) population attaining both a mean serum total 25D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline during the efficacy assessment period (EAP) (refer to Section 8.2 of the SAP for definitions), calculated for each treatment group and for each final dose group.

Additional secondary efficacy endpoints for Cohort 1 include:

- The proportion of subjects in the per-protocol (PP) population attaining both a mean serum total 25D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline during the EAP;
- The proportion of subjects in the PP population attaining both a mean serum total 25D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 10 or 20% from pre-treatment baseline during the EAP;
- The time courses of mean absolute changes from pre-treatment baseline in serum total 25D and plasma iPTH;
- Categorical comparisons of safety and efficacy based on body weight, age, gender, race, dose, severity of SHPT and VDI, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics;
- PD effects on mean serum calcium (corrected), phosphorus, vitamin D binding protein (DBP), total free 25D, total 1,25D, $1,25D_3$, and $24,25D_3$; and,
- Population PK of serum calcifediol relative to body weight, age, gender, race, dose, severity of SHPT and VDI, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics.

- The average of concentration of 25D at steady state and the time to reach steady state,

2.6 Pharmacokinetic Endpoints

Single-dose and repeated-dose (steady-state) PK determinations will be performed by analyzing serum calcifediol concentrations versus time recorded in Cohort 1 after (a) a single, initial dose of 900 mcg of CTAP101 Capsules, and (b) after the last administered dose in the 26 weeks of treatment in a subset of approximately 21 (Cohort 1) subjects in the active treatment group. The following PK parameters will be calculated using observed and baseline-adjusted serum calcifediol concentrations, if possible:

- Area under the serum concentration time curve from time zero to the timepoint with the last measurable concentration ($AUC_{0\text{-}t}$),
- Maximum serum concentration (C_{max}),
- Time to maximum concentration (t_{max}),
- Terminal elimination half-life ($t_{½}$),
- Clearance divided by the bioavailable fraction (CL/F),
- Volume of distribution based on the terminal phase divided by the bioavailable fraction (V_z/F), and,
- Terminal rate constant (λ_z).

2.7 Pharmacodynamic Endpoints

In an effort to characterize the dose-concentration-response relationships and to determine the impact of intrinsic and extrinsic factors on these relationships, population PD models will be developed from serum calcifediol data collected from subjects in Cohort 1. PD markers to be considered in the population PD analysis include:

- Plasma iPTH,
- Serum calcium (corrected for albumin),
- Serum phosphorus, and,
- Serum 1,25D or $1,25D_3$.

2.9 Subgroup Analyses

The safety and efficacy of CTAP101 will be compared based on categories of body weight, age, gender, race, dose, severity of SHPT and VDI, dialysis vintage, etiology of CKD, and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics.

2.10 Statistical Hypotheses

No formal hypothesis testing will be concluded; all inferential testing will be considered exploratory and hypothesis-generating.

3. Study Design and Procedures

3.1 General Study Design

This is a phase 2, multi-center, randomized, two-cohort study to evaluate the safety, efficacy, PK, and PD of CTAP101 Capsules to treat SHPT in male and female subjects aged at least 18 years with VDI and CKD requiring thrice weekly in-center HD. The study will be conducted in two successive cohorts at multiple sites within the United States (US). Subjects in Cohort 1 will participate in a randomized, single-blinded (subjects only), placebo-controlled, repeated-dose exploratory safety and efficacy study of CTAP101 Capsules administered at one, high dose level (900 mcg per week). Subjects in Cohort 2 will not be enrolled until sufficient data have been obtained from Cohort 1 and reviewed with the US Food and Drug Administration (FDA) to make a reasonable decision to proceed with the second cohort, potentially under a further amendment to the study protocol. This SAP only focuses on analysis of data from Cohort 1 of the study.

In Cohort 1, approximately 100 subjects will be screened to randomize approximately 44 eligible subjects in a 3:1 ratio into two groups receiving the following treatments in a single-blinded fashion (subjects only) for 26 weeks: (a) CTAP101 Capsules at 900 mcg per week or (b) matching placebo. Cohort 1 consists of two subgroups (PK subgroup and non-PK subgroup). The schedule of events differs between the subgroups of Cohort 1. Randomization will be accomplished in blocks of four subjects using two computer-generated codes, one for the PK subgroup (n=~28) and one for the non-PK subgroup (n=~16). Cohort 1 consists of a single 26-week treatment period followed by a 6-week FU period in which cinacalcet dosing occurred for some subjects.

In Cohort 1, subjects who have been consented and did not meet eligibility criteria at the conclusion of the Screening Visit (Visit 1, Days -83 to -69) are considered a Screen Failure. Subjects who are eligible after Visit 1 but do not meet eligibility criteria at either Visit 2 (Days -13 to -7) or Visit 3 (Day 1; pre-randomized) are considered a Pre-Treatment Failure. Only subjects who are randomized to a treatment at Visit 3 (Day 1) who are then withdrawn during the study will complete early termination (ET) study procedures.

An Interactive Response Technology (IRT) system will provide study treatment group assignments using computer-generated randomization codes and dispense study drug according to randomized, dosing assignments and dosing adjustments as required.

All subjects will undergo regular HD during the study. Subjects receiving treatment with calcitriol or other 1α-hydroxylated vitamin D analog, vitamin D supplements, or calcimimetic prior to study enrollment will forgo further dosing with these agents after confirmed eligible at Visit 1 and for the duration of the study and complete an 8-week washout (WO) period prior to baseline assessments. Subjects will undergo a 6-week FU observation period after completing treatment.

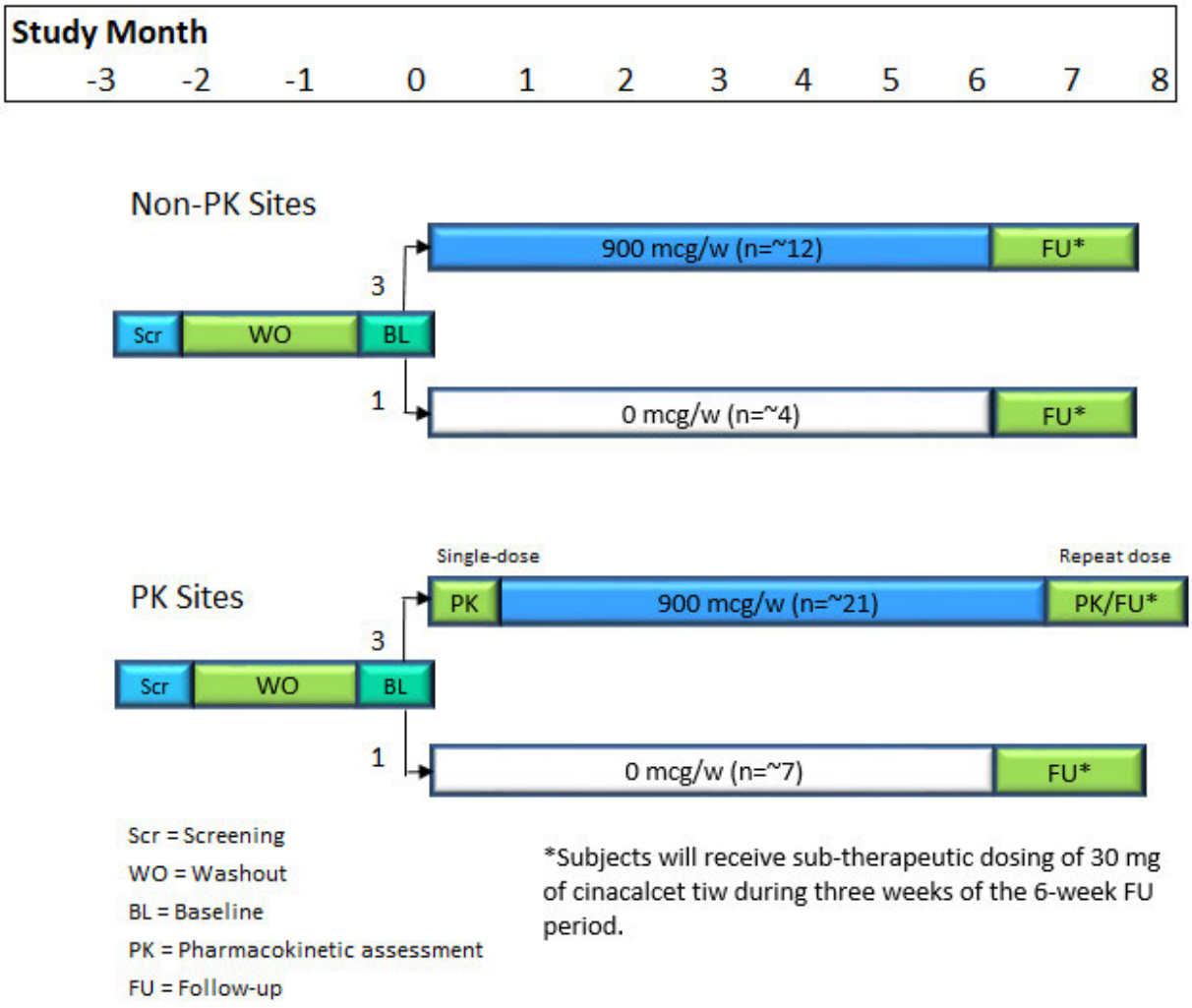
On two occasions which bracket the 26-week treatment period, a subset of subjects (n=~21) from Cohort 1 who are assigned to treatment with CTAP101 Capsules will be housed after the end-of-week HD (on Friday or Saturday) in a nearby phase 1 unit for 3 days in order to provide blood samples for determination of single-dose and repeated-dose PK profiles of serum calcifediol and associated PD profiles for serum calcium (corrected), phosphorus, [redacted] DBP, total free 25D, total 1,25D, $1,25D_3$, and $24,25D_3$. The remaining subjects from each treatment group will forgo all PK assessments and complete 26 weeks of treatment and undergo a 6-week FU observation period after completing treatment. Subjects who have completed 6 months of treatment with either CTAP101 Capsules or placebo will receive, at their election, sub-therapeutic doses of cinacalcet (30 mg tiw at the end of HD) during 3 weeks of the 6-week FU observation period in order to observe its effects on plasma iPTH when serum total 25-hydroxyvitamin D is still elevated relative to pre-treatment baseline values.

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

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

[redacted]

Figure 1. Cohort 1 (randomized, single-blinded design)



3.2 Schedule of Visits and Assessments

Study visits will be referred to in all tables and listings as the Visit number (Day number) to enable reviewers to understand the assessment timing without referring to the protocol visit schedule. Table 1 shows the scheduled study visits, their planned study day, and the acceptable visit window for each study visit:

Table 1a. Cohort 1: Non-PK Sites

Scheduled Visit	Planned Study Day	Visit Window
Visit 1 (Screening)	Days -83 to -69	N/A
Washout Period	Days -68 to -14	N/A
Visit 2	Days -13 to -7	± 3 days
Visit 3 (Baseline)	Day 1	± 3 days
Visit 4	All subjects skip Visit 4	N/A
Visits 5 and 6	Days 4 and 6	No study procedures
Visits 7-9	All subjects skip Visits 7-9	N/A
Visits 10-16	Days 8-71	± 3 days
Visit 17	Day 85	± 3 days
Visits 18-23	Days 99-169	± 3 days
Visit 24	Day 183 or Early Termination (ET)	± 3 days
Visit 25	All subjects skip Visit 25	N/A
Visits 26-29	Days 186-193	No study procedures
Visits 30-31	Days 197-211	± 3 days
Visit 32	Day 225	± 3 days

Table 1b. Cohort 1: PK Sites

Scheduled Visit	Planned Study Day	Visit Window
Visit 1 (Screening)	Days -83 to -69	N/A
Washout Period	Days -68 to -14	N/A
Visit 2	Days -13 to -7	± 3 days
Visit 3 (Baseline)	Day 1	0 days
Visit 4	Days 2-3, Placebo subjects skip this visit	0 days
Visit 5	Days 4	0 days

Scheduled Visit	Planned Study Day	Visit Window
Visits 6-8	Days 6-11 Placebo Subjects skip Visits 7-8	0 days
Visit 9	Day 15	0 days
Visits 10-16	Days 8-71 for subjects randomized to placebo; Days 22-85 for subjects randomized to active	± 3 days
Visit 17	Day 85 for subjects randomized to placebo; Day 99 for subjects randomized to active	± 3 days
Visits 18-23	Days 99-169 for subjects randomized to placebo; Days 113-183 for subjects randomized to active	± 3 days
Visit 24	Day 183 for subjects randomized to placebo; Day 197 for subjects randomized to active; or Early Termination (ET)	± 3 days
Visit 25	Days 184-185 for subjects randomized to placebo; Days 198-199 for subjects randomized to active; Placebo subjects have no procedures	0 days
Visits 26	Day 186 for subjects randomized to placebo; Day 200 for subjects randomized to active; Placebo subjects have no procedures	0 days
Visits 27-29	Days 188-193 for subjects randomized to placebo; Days 202-207 for subjects randomized to active; Placebo subjects have no procedures	0 days
Visits 30-31	Days 197-211 for subjects randomized to placebo; Days 211-225 for subjects randomized to active	± 3 days
Visit 32	Day 225 for subjects randomized to placebo; Day 239 for subjects randomized to active	± 3 days

The schedule of visits and assessments is provided in Appendix 1.

4. Study Treatments

Subjects will receive two capsules (one or two CTAP101 Capsules, 150 mcg strength, and/or matching placebo) tiw in the dialysis center at approximately one hour (±30 minutes) into the regularly scheduled HD session to achieve the total cumulative weekly dose. The time between dosing and any food intake

during or immediately after HD will be monitored and recorded for all subjects. Subjects will be requested to abstain from eating within one hour of starting dialysis, and a small snack will be allowed (if requested) during dialysis.

Subjects who have completed 6 months of treatment with either CTAP101 Capsules or placebo will receive, at their election, sub-therapeutic doses of cinacalcet (30 mg tiw at the end of HD) during 3 weeks of the 6-week FU observation period in order to observe its effects on plasma iPTH when serum total 25D is still elevated relative to pre-treatment baseline values. Subjects who will begin treatment with cinacalcet must have a serum calcium of ≥8.6 mg/dL and a plasma iPTH ≥300 pg/mL. Dosing with cinacalcet will be suspended if plasma iPTH is <150 pg/mL or serum calcium is <7.5 mg/dL.

4.1 Dose Reduction Criteria

Subjects will have their dose reduced in increments of 300 mcg (two CTAP101 Capsules) per week in the event that plasma iPTH is confirmed (by a second determination obtained at the earliest opportunity) to be <150 pg/mL, corrected serum calcium is confirmed to be >10.4 mg/dL, or serum phosphorus is confirmed to be >6.5 mg/dL as shown in Table 2. More details can be found in the Protocol.

Table 2. Weekly Dosing Schedule for Study Drugs

Treatment Day:	M or T	W or Th	F or S	Total/Week
# of Administered Capsules:				
Dose reduced or suspended to 0 mcg dose/week or Placebo				
Active (150 mcg/capsule)	0	0	0	0
Placebo	2	2	2	6
Dose reduced to 300 mcg dose/week				
Active (150 mcg/capsule)	1	0	1	2
Placebo	1	2	1	4
Dose reduced to 600 mcg dose/week				
Active (150 mcg/capsule)	1	1	2	4
Placebo	1	1	0	2
900 mcg dose/week treatment group				
Active (150 mcg/capsule)	2	2	2	6
Placebo	0	0	0	0

4.2 Method of Assigning Subjects to Treatment Groups

After signing the informed consent form (ICF), prior to any study-related activities, each subject will be assigned a 5-digit identification number and will retain that number throughout the study. The 5-digit

identification number (C-SS-EE) will consist of a 1-digit cohort number (C), a 2-digit site number (SS), and a 2-digit consecutive enrollment number (EE) at the applicable clinical site. Should a subject be withdrawn from the study, that subject's 5-digit identification number will not be reassigned.

Study treatment arm assignments will be made via the IRT system using two computer-generated randomization codes for each subgroup in Cohort 1 (one for the PK subgroup and one for the non-PK subgroup). Randomization will be accomplished in blocks of 4 subjects, with 3 subjects being assigned to treatment with CTAP101 Capsules and 1 subject being assigned to treatment with placebo. If four qualified Japanese subjects are successfully enrolled into Cohort 1 they will be randomized within in the same block to treatment arms in the PK subgroup. Randomization will occur during Visit 3 provided that each subject is deemed eligible for enrollment based, in part, on laboratory assessments obtained at the preceding visit (Visit 2). Laboratory assessments obtained at Visit 3 will not be considered in the determination of enrollment eligibility.

4.3 Blinding and Unblinding

The IRT will provide study drug assignments and dosing adjustments. The study coordinator (or designated site personnel) at each site will obtain the study drug assignments from the IRT for each subject and administer the appropriate number of capsules at each HD, which will be recorded in the electronic case report form (eCRF).

All subjects in Cohort 1 will be blinded to CTAP101 Capsule and placebo treatment group assignments and to plasma iPTH, serum total 25D, and serum calcifediol data until the last subject completes 26 weeks of treatment, 6 weeks of FU and the data have been locked. However, subjects at PK sites will undergo differential assessments depending on treatment and may become unblinded. Site personnel and clinical study team members will not be blinded.

5. Sample Size and Power Considerations

Formal power calculations have not been undertaken for Cohort 1.

6. Data Preparation

6.1 Input Data

All reported study data will be recorded on the eCRFs supplied by Statistics & Data Corporation (SDC) using iMedNet™. Only the Principal Investigator and authorized study staff according to the Delegation of Responsibilities log are entitled to make entries in the eCRF.

After data are entered into the clinical study database, electronic edit checks and data review will be performed. All data validation specifications and procedures are detailed in the Data Validation Manual as a separate document. When the database has been declared to be complete and accurate, the database will be locked. Any changes to the database after data have been locked can only be made with the approval of the Sponsor in consultation with SDC.

External data (i.e., data not entered on the eCRF by the clinical sites but sent separately to SDC) will be reconciled with the clinical database by the Data Management team. External data will then be transferred to Biostatistics and incorporated into the Study Data Tabulation Model (SDTM) datasets. Refer to the study's Data Management Plan for information on external data sources and reconciliation and other data management considerations.

All analyses outlined in this document will be carried out after the following have occurred:

- All data management requirements are met according to SDC standard operating procedures, including data entry; edit and validation checks performance;, documentation and resolution of data queries, and database lock with written authorization provided by appropriate SDC and Sponsor personnel.
- Protocol deviations have been identified, categorized and classified for severity (i.e.,major/minor deviations, COVID-19 related).
- Analysis populations have been determined.

6.2 Output Data

Data from iMedNet™ and external data will be transferred to Biostatistics and incorporated into standard formats following the SDTM. Data will then be mapped to analysis datasets using the Analysis Data Model (ADaM). Both SDTM- and ADaM-formatted data will be used to create the subject listings, while all tables and figures will be based on the ADaM-formatted data.

Output data will implement the latest applicable SDTM and ADaM models and guidelines, and will be validated with the latest Pinnacle 21 version which will be identified within the output data. Any discrepancies in the validation will be noted in reviewer's guides accompanying the final data transfers.

Define.xml will be created for SDTM and ADaM using the Define-XML version 2.0 model.

7. Analysis Populations

7.1 Intent-to-Treat

The intent-to-treat (ITT) population will include all subjects who have been randomized to receive study drug.

7.2 Modified Intent-to-Treat

The mITT population will include all subjects who have been randomized to receive study drug and have at least one non-missing value at baseline and at least one recorded value in the EAP for both serum total 25D and for plasma iPTH. The mITT population will be analyzed according to the randomized treatment.

The key secondary efficacy analyses will be performed on the mITT population.

7.3 Per Protocol

The PP population will be defined as all subjects for whom at least two serum total 25D and two plasma iPTH determinations are included in the calculated baseline value and in the EAP, and who do not have a major protocol deviation.

Secondary efficacy analysis and additional secondary efficacy analyses will be conducted using the PP population.

7.4 Safety

The Safety population will include all subjects who have received at least one dose of study drug and will be used for assessing safety. The Safety population will be analyzed according the treatment received.

7.5 Pharmacokinetic and Pharmacodynamic

The PK population will include subjects who have at least one PK sample from a post-baseline collecting timepoint. Subjects that have documented dosing errors or deviations, or insufficient measurable concentration versus time data for generating PK parameters, will be included in the listings, but may be removed from the group summaries as appropriate.

The PD population will include subjects who have any post-baseline PD data.

[redacted]

8. General Statistical Considerations

8.1 Missing or Inconclusive Data Handling

In general, there will be no imputation of missing data except for partial or missing dates. For AE and medication missing or partial dates, dates will be imputed for the purpose of determining whether the AE is treatment-emergent and whether a medication was concomitant with study treatment. If the event or medication could have been concurrent with study treatment based on the available information, then it will be considered either treatment-emergent or concomitant.

Partial/missing start and end dates for AEs and concomitant medications will be imputed as follows:

Partial/missing start date:

- Dates with missing day only will be imputed as the 1st of the month unless month and year are same as month and year of first dose of study medication in which case missing day will be imputed as the first dose day.
- Dates with both day and month missing will be imputed as 1 Jan unless year is same as year of first dose of study medication in which case missing day and month will be imputed as the first dose day and month.
- Completely missing dates will be imputed as first dose date unless end date indicates it could have started prior to this in which case missing date will be impute as 1 Jan of the same year as the end date.

Partial/missing end date:

- Dates with missing day only will be imputed as the last day of the month unless month and year are same as month and year of the last dose in which case missing day will be imputed as the last dose date.
- Dates with both day and month missing will be imputed as 31 Dec unless year is same as year of the last dose in which case missing day and month will be imputed as the last dose day and month.
- If the ongoing flag is missing or “Yes” then date will not be imputed. If ongoing is “No” then it will be imputed as the last dose date.

The original dates will be displayed in data listings and the imputed dates will be used in derivations only (study day, treatment-emergent status, etc.).

AEs with missing onset date will be treated as TEAEs and missing onset date will be imputed as the date of Visit 3, unless the event end date indicates that the event resolved prior to Visit 3, 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 the investigational study drug, in which case it will be documented in medical history.

Pharmacokinetic concentration data:

- There will be no imputation of missing data or values designated as not reportable.
- All concentrations reported as below the lower limit of the assay (BLQ, <LLOQ, etc.) will be considered 0 for the purpose of generating the concentration versus time tabular and graphical summaries.
- Concentrations reported as below the lower limit of the assay (BLQ, <LLOQ, etc.) that occur before any measurable concentration will be considered 0 for the purpose of the PK analysis. Concentration reported as below the lower limit of the assay that occur between two timepoints with measurable concentrations, or at the end of the concentration versus time profile, will be not be imputed (i.e., treated as missing) for the purpose of the PK analysis.

8.2 Definition of Baseline, EAP and Follow-Up Assessment Period (FAP)

- Baseline for non-PK analyses- The last non-missing assessment at Visit 2 prior to first dose at Visit 3. If multiple assessments are taken at Visit 2, the average of those assessments will be used as baseline.
- Baseline for PK analysis- Baseline serum calcifediol concentration for PK analysis is defined as the average concentration obtained at t=-12, t=-3 and t=0 at the first PK dose.
- Baseline adjusted calcifediol concentration - Post baseline serum calcifediol concentration minus the average baseline calcifediol concentration.
- EAP – The efficacy assessment period is the last 6 weeks of the first 26 weeks of treatment. i.e., the assessments taken at Visits 21, 22, 23, and 24. Serum 25D and iPTH values at EAP are defined as the average of the assessments taken at these visits.
- FAP – the follow-up assessment period is the follow-up period after initiation of cinacalcet. Serum 25D and iPTH values at FAP are defined as the average of the assessments taken during the follow-up period.

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, the more recent non-missing result 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 will be used unless otherwise specified.

8.3 Data Analysis Conventions

All data analysis will be performed by SDC after the study is completed and the database has been locked and released for unblinding. Statistical programming and analyses will be performed using SAS® Version 9.4 or higher. Output will be provided in rich text format (RTF) for tables and portable document format (PDF) for tables, listings, and figures using landscape orientation. All study data will be listed by subject, treatment, treatment subgroup, and visit (as applicable) based on all randomized subjects unless otherwise specified.

All data collected on eCRFs and from clinical laboratory evaluations will be grouped and listed by population subgroup (PK subgroup, non-PK subgroup), subject, visit, and date and time as feasible. Summary tables will be presented by subgroup (PK subgroup, non-PK subgroup) as appropriate. Descriptive summaries of categorical outcomes will include the proportion of subjects. Denominators for percentage of subject calculations will be based on the number of subjects with nonmissing data in the subgroup and selected population unless otherwise specified. All percentages will be rounded to one decimal place (i.e., XX.X%).

Descriptive summaries of quantitative measures will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum or as appropriate. In PK and PD summaries, 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 x (SD/[Arithmetic Mean]). Arithmetic means, SDs, medians, and geometric means will be reported with the same number of significant figures as the reported values.. The %CV will be rounded to 1 decimal place.

Differences between active treatment groups and placebo will be calculated as Active minus Placebo and change from baseline will be calculated as post-baseline minus baseline. Continuous descriptive statistics (n, mean [SD], median, minimum, maximum) of measurements at each visit will be presented and t-test will be performed to compare active group from placebo. The mean difference between the CTAP101 group and placebo, the corresponding 95% CIs, and the p-values will be presented for each

visit. The changes from baseline to each visit will also be presented using descriptive analysis. Treatment group differences for changes from baseline will be evaluated using a mixed model repeated measures (MMRM) model fitted with treatment group, visit, and the treatment by visit interaction as categorical variables and baseline value as a covariate, with contrasts included for each visit.

All statistical tests will be two-sided with a significance level of 0.05 ($\alpha = 0.05$) unless otherwise specified. Confidence intervals (CI) for differences between treatment groups will be two-sided at 95% confidence. Confidence limits should have one more decimal place than the raw data. All p-values will be rounded to four decimal places; p-values less than 0.0001 will be presented as "<0.0001"; p-values greater than 0.9999 will be presented as ">0.9999."

8.4 Adjustments for Multiplicity

No adjustments for multiplicity will be made in this phase 2 study.

8.5 Unscheduled Data

Unscheduled data, such as information from unscheduled visits, repeat laboratory tests, or Investigator comments, will be included in the data listings. When there are multiple measures in a scheduled visit window, summary tables will use the worst-case value for safety and the scheduled visit data for efficacy.

9. Disposition of Subjects

Subject disposition will be tabulated and descriptively summarized for all randomized subjects by subgroup (PK subgroup, non-PK subgroup) and CTAP101 study drug treatment group, separately and combined. Subject disposition will be summarized by presenting the total number and the percentage of subjects in each of the analysis populations (ITT, mITT, PP, and Safety) using randomized subjects (i.e., the ITT population) as the denominator. The percentage of subjects who completed the study and subjects who discontinued prematurely from the study will also be summarized.

The number and percentage of subjects prematurely discontinued from study and the primary reason for premature study discontinuation will be summarized by subgroup (PK subgroup, non-PK subgroup) and treatment group for all randomized subjects. The reasons for study discontinuation include: AE, protocol violation, physician decision, sponsor termination of the study, subject choice, other, lost-to FU, pregnancy, lack of efficacy. Lack of efficacy will be further categorized as: 100% increase in plasma iPTH after 26 weeks of treatment from pre-treatment baseline, plasma iPTH above 1,200 pg/mL on consecutive visits (if at least 2 weeks apart) after 12 weeks of treatment, and other. Additionally, COVID-19 related discontinuations will also be summarized. A subject listing will be provided that includes the date of and reason for premature study discontinuation.

The number and percentage of subjects with any Major/Minor and COVID-19 related protocol deviations will be summarized by subgroup and treatment group for all randomized subjects. A subject listing will be provided that includes the date of the deviation, the deviation code, the deviation description, and the classification of whether the deviation was judged to be major or minor.

Additionally, the number and percentage of subjects electing cinacalcet treatment will be summarized by subgroup (PK subgroup, non-PK subgroup) and treatment group, separately and combined. The proportion of subjects who become ineligible after initiating cinacalcet due to iPTH < 150 pg/mL or serum calcium < 7.5 mg/dL will be summarized by subgroup and treatment group for all subjects who initiate cinacalcet treatment.

9.1 Screen and Pre-Treatment Failures

All screen and pre-treatment failures will be summarized by treatment group. Subjects who have consented and did not meet eligibility criteria at the conclusion of the Visit 1 (Screening Visit) are considered a Screen Failure. Subjects who are eligible after Visit 1 but do not meet eligibility criteria at either Visit 2 (Week -2) or Visit 3 (Day 1) are considered a Pre-Treatment Failure. Subjects who are terminated due to study enrollment goal met will be summarized in a separate category.

10. Demographic and Baseline Characteristics

10.1 Demographics

Demographic characteristics will be summarized for the mITT, PP and safety populations by subgroup (PK subgroup, non-PK subgroup) separately and combined. The demographic variables collected in this study include age, gender, race and ethnicity. Subjects who record more than one race will be grouped into a single category denoted as Multiple Race. Percentages will be based on all subjects in the respective analysis population and treatment group.

Age (years) will be summarized, overall and by treatment, using continuous descriptive statistics (n, mean [SD], median, minimum, maximum). Age will also be categorized as follows: <65 years and ≥65 years. Age will be defined in years according to the age reported at the screening visit

A subject listing that includes all demographic variables will be provided.

10.2 Baseline Characteristics

Baseline characteristics will be summarized separately for the mITT, PP, safety populations by subgroup (PK subgroup, non-PK subgroup) separately and combined on the treatments subjects randomized: placebo vs 900 mcg. The baseline characteristic variables that will be summarized include:

- Using continuous descriptive statistics (n, mean [SD], median, minimum, maximum) for height, weight, body mass index (BMI), plasma iPTH, and serum 25(OH)D, 1,25D, calcium and phosphorus
- Tobacco history (never, former, current) including time (months) since last use for former users. Time will be calculated relative to first dose date.
- Alcohol history (never, former, current)
- Time (months) since diagnosis of CKD and time (months) since diagnosis of SHPT will be calculated from the medical history case report form. Time will be calculated relative to first dose date.
- Prior use of calcitriol, 1α-hydroxyvitamin D analogs, calcimimetics, and prior use of 1α-hydroxyvitamin D analogs and/or calcimimetics will be summarized from concomitant medication data.

All pretreatment variables will be listed with their respective FU data, and subject listings of disease history will also be provided.

11. Medical History and Concomitant Medications

11.1 Medical History

Medical history will be summarized for the Safety population by subgroup (PK subgroup, non-PK subgroup) separately and combined. Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 21.0 or higher and will be summarized using discrete summary statistics and presented by treatment group at the subject and event level by System Organ Class (SOC) and Preferred Term (PT). Subjects who have more than one medical history within a given SOC or PT are only counted once within that SOC or PT. All SOCs are listed in alphabetical order; PTs within a SOC are listed in order of descending frequency across all subjects. Percentages are based on the total number of subjects in each respective treatment group.

Medical history will be displayed in a data listing.

11.2 Prior and Concomitant Medications

Prior medications are defined as any continuing or new medication used within 12 weeks and discontinued before study treatment. Concomitant medications are defined as any continuing or new medication taken from study treatment or anytime thereafter until the end of the study. Medications that start before study treatment and continue anytime during study treatment will be defined as both prior and concomitant medications. Type and dose of concomitant medications used for phosphate binder

therapy will be displayed in a listing. Concomitant medications will be summarized for the Safety population by subgroup (PK subgroup, non-PK subgroup) separately and combined.

World Health Organization (WHO) Drug Dictionary (Global Enhanced B3, March 2021 is used to code concomitant and prior medications. Medications will be coded and summarized to the therapeutic drug class (Anatomical Therapeutic Chemical [ATC] 4 classification) and Preferred Name using frequency counts and percentages. If the ATC 4 classification is not provided, the next lowest classification that is provided in the coding dictionary will be used. The preferred name is defined as the active ingredient; if the active ingredient is not provided or includes more than two ingredients (e.g., multivitamins), then the drug name will be summarized as the preferred name. Any uncoded terms are summarized under the ATC classification and preferred name of "Uncoded." Subjects will be counted only once under each ATC Class or Preferred Name for which they have at least one medication. The ATC Classes and Preferred Names within ATC Classes will be ordered by descending frequency values based on all subjects. Percentages will be based on the number of subjects in each treatment group.

Listings of prior and concomitant medications will be generated. A listing of concomitant phosphate binder therapy medication will be presented separately. For the purpose of inclusion in prior or concomitant medication tables, incomplete medication start and stop dates will be imputed in order to categorize medications into prior or concomitant categories.

11.3 Concomitant Procedures

Concomitant procedures will be summarized for the Safety population by subgroup (PK subgroup, non-PK subgroup) separately and combined Concomitant procedures will be coded using MedDRA, version 21.0 summarized using discrete summary statistics, and presented by treatment group at the subject and event level by SOC and PT. Subjects who have more than one concomitant procedure within a given SOC or PT are only counted once within that SOC or PT. All SOCs are listed in alphabetical order; PTs within a SOC are listed in order of descending frequency across all subjects. Percentages are based on the total number of subjects in each respective treatment group.

Concomitant procedures will be displayed in the medical history data listing.

12. Dosing Compliance and Treatment Exposure

12.1 Dosing Compliance

Dosing compliance will be summarized with continuous descriptive statistics for the Safety population by subgroup (PK subgroup, non-PK subgroup) separately and combined. The table will be summarized

separately and combined by the four treatment groups in EAP: 0 mcg (placebo), 1-300 mcg, 301-600 mcg and 601-900 mcg.

Dosing compliance (% compliance) will be assessed by calculating the number of actual doses received and comparing that to the number of expected doses (number of capsules that should have been taken versus actual number taken as evidenced by the number of capsules remaining in bottles of study drug assigned to each subject). The following formula is for dosing compliance (%) calculation:

$$\text{Compliance (\%)} = \frac{\text{Number of Actual Doses Received}}{\text{Number of Expected Doses}} \times 100\%$$

Dosing compliance at <80% or >120% should be reported as a major protocol deviation. Compliance will be summarized as <80%, 80-120%, and >120% compliant categories. A subject listing of overall dosing compliance will also be produced.

Dosing compliance for cinacalcet will be calculated and summarized as above but cinacalcet compliance will not be included as a protocol deviation. Unlike CTAP101 dosing, not all subjects were able to participate in voluntary cinacalcet dosing due to late addition to protocol at which time subjects had already completed study, subject not eligible or subject did not consent to participate in this aspect of the study.

12.2 Treatment Exposure

Extent of treatment exposure (days) will be summarized with continuous descriptive statistics for the Safety population by subgroups (PK subgroup, non-PK subgroup) separately and combined for each treatment group. The table will be summarized by the initial treatment groups: 0 mcg (placebo) and 900 mcg per week.

Extent of treatment exposure for completed or discontinued subjects will be calculated in days using the following:

Extent of Treatment Exposure (days) = (Date of Last Dose – Date of Visit 3 [Day 1]) + 1

Extent of treatment exposure for subjects who were lost to FU will be calculated in days using the following:

Extent of Treatment Exposure (days) = (Date of Last Recorded Dose – Date of Visit 3 [Day 1]) + 1

A subject listing of treatment exposure will be produced.

Similarly, extent of sub-therapeutic exposure to cinacalcet for subjects who elected to participate during the FAP will be calculated in days using the following:

Extent of Cinacalcet Exposure (days) = (Date of Last Recorded Cinacalcet Dose – Date of First Cinacalcet Dose) + 1

In addition to dose compliance and treatment exposure, listings of dose adjustments, study drug assignment, study drug administration, study drug titration, study drug replacement and study meals will be provided.

13. Efficacy Analyses

13.1 Primary Analysis

There is no primary efficacy endpoint for Cohort 1, as efficacy in this part of the study is merely observational.

13.2 Secondary Analyses

The key secondary efficacy endpoint for Cohort 1 is the proportion of subjects in the mITT population attaining both (a) mean serum total 25D ≥50 ng/mL and (b) mean plasma iPTH reduction by at least 30% from baseline during the EAP by treatment group.

A subject who reached these criteria is considered to be a "responder." The response rate in the CTAP101 group and the placebo group is calculated as (Number of Responders)/(Number of Total Subjects) in the respective group.

The key secondary efficacy analysis will compare the placebo group to all CTAP101 subjects.

The analysis will be performed using a Pearson chi-square test statistic (alpha=0.05) comparing the placebo subjects to all CTAP101 treated subjects. Note that the protocol states a Cochran-Mantel-Haenszel (CMH) test will be used; however, there are no stratification factors in the analysis; therefore, the CMH test is equivalent to a Pearson chi square test.

Additionally, two alternative responder criteria endpoints (using 20%, 10% thresholds for mean decrease of plasma iPTH from baseline) during the EAP will be examined. The same methods used for the key secondary efficacy endpoint will be used to compare each active dose group versus the placebo group attaining these alternative responder criteria endpoints.

The 20% criteria requires the following:

a. increasing mean serum 25D by ≥50 ng/mL from pre-treatment baseline; and

b. decreasing mean plasma iPTH by ≥20% from pre-treatment baseline

The 10% criteria requires the following:

a. increasing mean serum 25D by ≥50 ng/mL from pre-treatment baseline; and

b. decreasing mean plasma iPTH by ≥10% from pre-treatment baseline

As a supportive descriptive analysis of the secondary endpoint, the proportion of patients attaining each component of the response criteria will be presented.

Table 3. Reference Table of Visits / Days

Visit #	Day# NPK and PK Placebo	Day# PK Active
1	-83 to -69	-83 to -69
2	-13 to -7	-13 to -7
3	1	1
4	NA	2-3 Hours relative to PK Dose -3 to 42
5	4	4 Hours relative to PK Dose 48
6	6	6
7	NA	8
8	NA	11
9	NA	15
10	8	22
11	15	29
12	22	36
13	29	43
14	43	57
15	57	71
16	71	85
17	85	99
18	99	113

Visit #	Day# NPK and PK Placebo	Day# PK Active
19	113	127
20	127	141
21	141	155
22	155	169
23	159	183
24	183	197 Hours relative to PK Dose -12
25	NA	198-99 Hours relative to PK Dose 0 to 42
26	186	200 Hours relative to PK Dose 48
27	188	202
28	190	204
29	193	207
30	197	211
31	211	225
32	225	239
ET		

13.2.1 Continuous Mean Serum 25D

Summary statistics for Serum 25D at baseline and EAP and change and percent change from baseline at EAP will be displayed. Statistical analysis methods for both mean observed serum 25D and mean change in serum 25D will follow Sections 8.3A scatter plot will be generated to show the observed and the change in serum 25D at each visit.

This analysis will be performed using visits where mean serum 25D is intended to be measured on all subjects. In non-PK group, this will include Baseline visits [Visits 2 (Days -13 to -7) and 3 (Day 1)], Visits 10-16 (Days 8-71), Visit 17 (Day 85), Visits 18-23 (Days 99-169), Visit 24 (Day 183)/ET, Visits 30-31 (Days 197-211), and Visit 32 (Day 225). In PK group, the visits include Baseline visits [Visits 2 (Days -

13 to -7) and 3 (Day 1)], Visit 9 (Day 15 for active), Visit 10-16 (Days 8-71 for placebo, Days 22-85 for active), Visit 17 (Day 85 for placebo, Day 99 for active), Visits 18-23 (Days 99-169 for placebo, Days 113-183 for active), Visit 24 (Day 183 for placebo, Day 197 for active)/ET, Visits 30-31 (Days 197-211 for placebo, Days 211-225 for active) and Visit 32 (Day 225 for placebo, Day 239 for active).

Continuous Mean Serum 25D is collected as follows:

Non-PK and PK Placebo	
Visit#	**Day#**
1	-83 to -69
2	-13 to -7
3	1
4	NA
5	4
6	6
7	NA
8	NA
9	NA
10	8
11	15
12	22
13	29
14	43
15	57
16	71
17	85
18	99
19	113
20	127
21	141
22	155
23	169
24	183

PK Active	
Visit#	**Day#**
1	-83 to -69
2	-13 to -7
3	1
4	2-3
5	4
6	6
7	8
8	11
9	15
10	22
11	29
12	36
13	43
14	57
15	71
16	85
17	99
18	113
19	127
20	141
21	155
22	169
23	183
24	197

Non-PK and PK Placebo			PK Active	
Visit#	**Day#**		**Visit#**	**Day#**
25	NA		25	198-199
26	186		26	200
27	188		27	202
28	190		28	204
29	193		29	207
30	197		30	211
31	211		31	225
32	225		32	239
ET			ET	

The analysis will be performed in non-PK and PK subgroups separately and combined, including only those visits where all subjects in the summary were planned to have the visit. At visits where both non-PK and PK subgroups collected serum 25D and for summaries of all subjects, p-values will be generated. Otherwise, due to small numbers of subjects in each subgroup, the model may be underpowered and p-values will not be calculated. An analysis of serum 25D which utilizes fewer visits will also be performed as part of the PD analysis (Section 16).

13.2.2 Change from Baseline in Plasma iPTH

Statistical analysis methods for plasma iPTH will follow section 8.5 and 8.6. Additionally, a scatter plot will be generated to show the plasma iPTH change at each visit.

This analysis will be performed using visits where plasma iPTH is measured on all subjects (following the same visit schedule as serum 25D collection described in Section 13.2.1).

Plasma iPTH is collected as follows:

Non-PK and PK Placebo			PK Active	
Visit#	**Day#**		**Visit#**	**Day#**
1	-83 to -69		1	-83 to -69
2	-13 to -7		3 Before Dialysis	1
3	1		3 PM	NA

Non-PK and PK Placebo			PK Active	
Visit#	**Day#**		**Visit#**	**Day#**
			9	15
10	8		10	22
11	15		11	29
12	22		12	36
13	29		13	43
14	43		14	57
15	57		15	71
16	71		16	85
17	85		17	99
18	99		18	113
19	113		19	127
20	127		20	141
21	141		21	155
22	155		22	169
23	169		23	183
24	183		24	197
			24 PM	NA
30	197		30	211
31	211		31	225
32	225		32	239
ET			ET	

The analysis will be performed in non-PK and PK subgroups separately and combined, including only those visits where all subjects in the summary were planned to have the visit. At visits where both non-PK and PK subgroups collected plasma iPTH and for summaries of all subjects, p-values will be generated. Otherwise, due to small numbers of subjects in each subgroup, the model may be underpowered and p-values will not be calculated. An analysis of plasma iPTH which utilizes fewer visits will also be performed as part of the PD analysis (Section 16).

13.2.4 Subgroup Analyses of Key Secondary Outcomes

The following key secondary efficacy outcomes will also be compared on below subgroups within the mITT population, using all subjects in both the non-PK and PK subgroups:

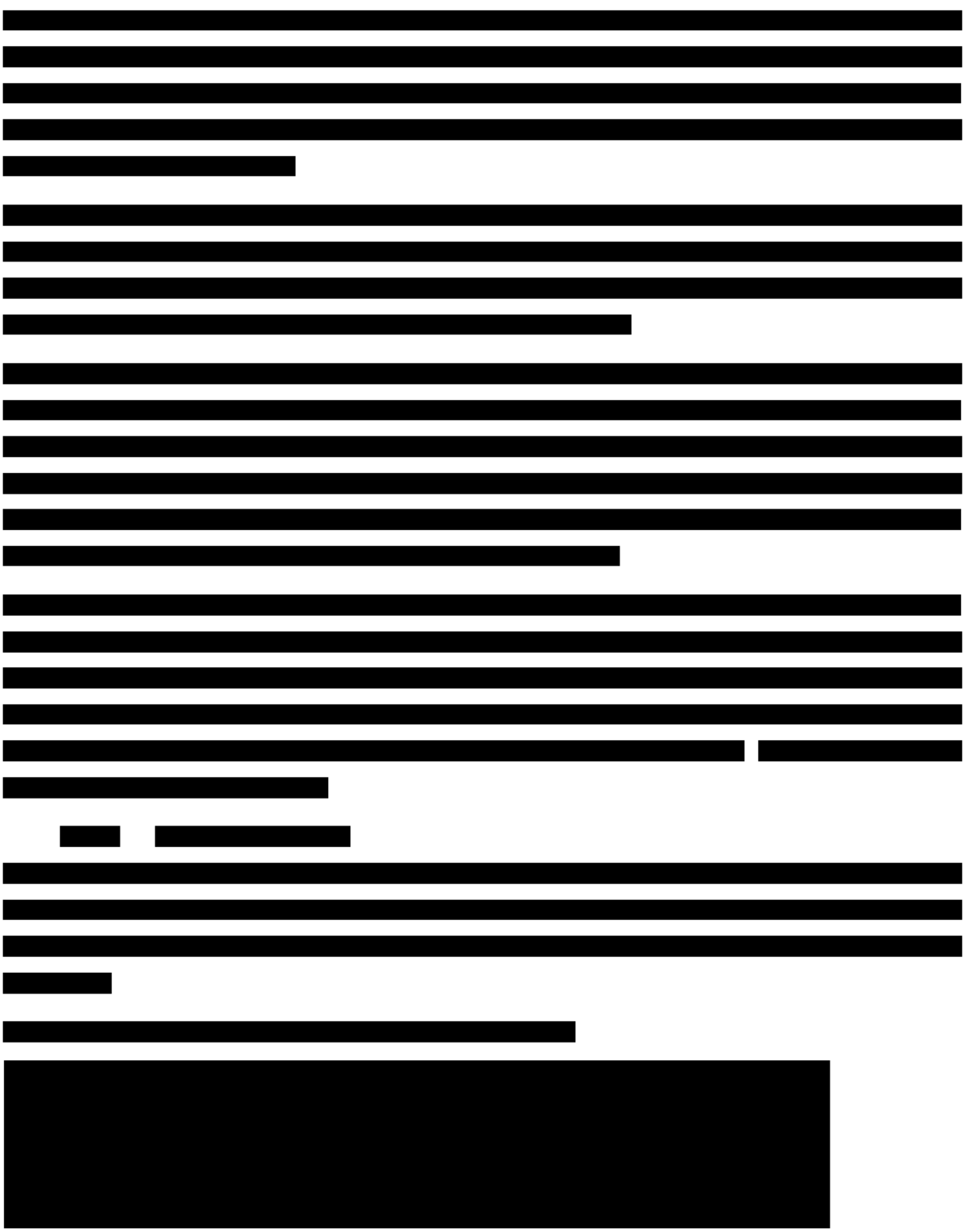
- BMI and body weight (<median, ≥median)
- Age (<median, ≥median)
- Gender
- Race (white, non-white)
- Time since initiation of dialysis (<median, ≥median)
- Baseline serum phosphorus (<median, ≥median)
- Baseline corrected serum calcium (<median, ≥median)
- Baseline plasma iPTH (<median, ≥median)
- Etiology of CKD
- Prior Calcimimetics (Yes, No)
- Prior treatment with 1α-hydroxyvitamin D analogs and cinacalcet.

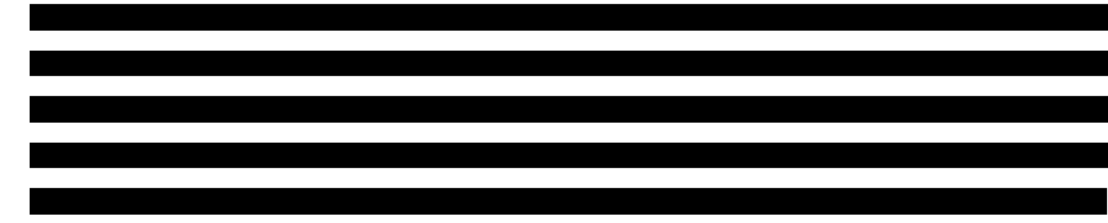
Within each level of the subgroup, the sample size, number of responders, and percent responders for each treatment group will be displayed as well as differences in response rates between active group and placebo with corresponding 95% CIs. CMH tests will be performed for each subgroup category to assess a relationship between treatment (placebo vs. all CTAP101 subjects) and each category with respect to responders. In addition, a logistic regression analysis will be performed with the explanatory variables of treatment and the subgroup category.

Similar subgroup analyses will be performed for the response criteria using alternative responder criteria based on modifying the efficacy endpoint by changing the mean percent decrease in plasma iPTH criteria (mean decrease of 20% and 10% thresholds).

[redacted]

[redacted]





[redacted]

14. Safety Analyses

All subjects in Safety population will be included in the safety summaries. Statistical summaries of safety data will be descriptive and performed by study arm. No inferential hypothesis testing will be performed on the safety variables.

14.1 Primary Safety Analyses

14.1.1 Adverse Events

14.1.1.1 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. Any pre-existing medical condition that worsens after first administration of the study drug will also be considered a new AE. The AE reporting period ends upon study exit. 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 and resolution (or ongoing), seriousness and reason for seriousness, description, severity, relationship of the AE to the investigational study drug, action(s) taken, expectedness, and outcome. All AEs will be collected on the eCRF and coded via SOC and PT using MedDRA version 20.0 or later.

The intensity of the AE will be rated by the Investigator per Common Terminology Criteria for Adverse Events (CTCAE), version 5.0. The level of severity include: Grade 1, Grade 2, Grade 3, Grade 4 and Grade 5. It should be noted that the clinical severity and seriousness of an AE are not synonymous, e.g., a severe headache is not classified as serious until it meets the required elements as an SAE. Adverse events with missing severities will be counted as severe and Grade 4.

The relationship or association of the study drug in causing or contributing to the AE will be characterized by the Investigator using the classifications: Not Related, Unlikely Related, Possibly Related, and Related. Adverse events with missing relationships are counted as related.

14.1.1.2 Serious Adverse Events

An SAE (Serious Adverse Event) is defined by the Investigator or Sponsor as any AE occurring during an investigational study that result 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 events that may not result in death, may be life threatening, or may 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.

All SAEs 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 or Investigator Brochure (IB) for CTAP101 Capsules. Categories are:

- Unexpected - nature or severity of the event is not consistent with the product information;
- Expected - event is known based on the product information.

14.1.1.3 Treatment-Emergent Adverse Events

A treatment-emergent adverse event (TEAE) is defined as any AE with onset or worsening reported by a subject from the time that the first dose of study drug is taken in this study until 30 days following discontinuation of study drug administration. Adverse events which began prior to treatment or 30 or more days after treatment will not be included in the TEAE summary tables but will be included in the AE data listings.

14.1.1.4 Summaries of Adverse Events

An overall summary will be presented to summarize the number of events and subjects with AEs, TEAEs, treatment-related TEAEs (related or possibly related), Death, SAEs excluding Death, TEAEs Leading to Early Treatment Discontinuation or Death, TEAEs by relationship to study drug (related, possibly related, unlikely related, not related) and TEAEs by severity. This overall summary will be include dosing groups according to section 8.4.

Additional summaries of TEAEs will be provided showing the number and percentage of subjects who experienced at least one TEAE. The summaries will be grouped by the actual dose subjects received when the AE first occurred: Placebo, 900 mcg, 900 reduce to 600 mcg, 600 reduce to 300 mcg and 300 reduce to 0 mcg.. The TEAEs will be sorted in descending order of total incidence for each SOC and for each PT within SOCs. The percentages will be based on the number of subjects in each treatment group after dose adjustment. If a subject has more than one TEAE that coded to the same PT, the subject will

be counted only once for that PT. Similarly, if a subject has more than one TEAE within a SOC category, the subject will be counted only once in that SOC category.

Similar summaries will be provided for the following categories of TEAEs by SOC and PT:

- Any Treatment-related TEAEs (related or possibly related),
- Treatment-related TEAEs (related or possibly related) during treatment period,
- Cinacalcet treatment-related TEAEs (related or possibly related) during FU period,
- SAEs,
- TEAEs leading to study discontinuation,
- TEAEs by CTCAE Grade: Grade 1, Grade 2, Grade 3, Grade 4, Grade 5,
- TEAEs by Relationship to Study Drug: Related, Possibly Related, Unlikely Related, Not Related,
- TEAEs by Relationship to Cinacalcet: Related, Possibly Related, Unlikely Related, Not Related, and,
- TEAEs CTCAE Grade 3 or Greater

All AEs and SAEs will be presented in a subject listing. The TEAEs leading to study discontinuation will be listed separately as well as TEAEs grade 3 (severe) or greater.

14.1.2 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, and heart rate [HR]) will be collected at all visits where procedures are performed.

Observed values will be summarized descriptively at baseline (the average of measurements at pre-dose Visit 2 and Visit 3) and each following visits by dose groups that subjects actually received before the visit (see section 8.5). Descriptive summaries will include n, mean (SD), median, minimum, and maximum. Change from baseline will also be summarized at each post-baseline visit. Additionally, for each measurement, the lowest and the highest post-baseline value and change from baseline value will be presented. A listing of vital signs will be provided.

14.1.3 Physical Examination

Physical examinations (including height, weight, and BMI) will be performed as follows:

Non-PK and PK Placebo			PK Active	
Visit#	**Day#**		**Visit#**	**Day#**
1	-83 to -69		1	-83 to -69
24	183		24	197

Non-PK and PK Placebo	
Visit#	Day#
32	225
ET	

PK Active	
Visit#	Day#
32	239
ET	

All results will be summarized by actual dose groups received at each visit.

The physical examination results, graded as normal, abnormal not clinically significant (NCS), or abnormal clinically significant (CS), Height, weight, and BMI will be summarized descriptively according to section 8.6. A subject listing of the physical examination results will also be produced.

14.1.4 Electrocardiogram

The 12-Lead ECG will be performed as follows:

Non-PK and PK Placebo	
Visit#	Day#
3	1
24	183
ET	

PK Active	
Visit#	Day#
3	1
24	197
ET	

Heart rate, RR, PR, QRS, QT, and QTcF (Fridericia's) intervals will be summarized using descriptive statistics by actual dose group at each visit. If not already calculated, QTcF will be derived using the following formula:

$$QTcF = QT(uncorrected)/[(60/HR)^(1/3)]$$

Change from baseline to each post-baseline visit will also be summarized by treatment group. Additionally, for each measurement, the lowest and the highest post-baseline value will be provided. The shift from baseline in overall ECG interpretation (normal; abnormal, not clinically significant; and abnormal, clinically significant) will also be summarized by FU visit.

A subject listing of the ECG results will also be produced.

14.1.5 Clinical Laboratory Data

Clinical laboratory data including hematology, serum chemistry, and partial serum chemistry are collected at specified visits. The results will be listed in a data listing and summarized in tables. The quantitative variables will be summarized by actual dose group with continuous descriptive statistics. Change from baseline will also be summarized by actual dose group. Additionally, for each applicable

analyte of blood chemistry, the lowest and the highest post-baseline value and change from baseline value will be presented. Laboratory analytes are listed in Table 4.

Table 4. List of Laboratory Tests

Hematology:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- White blood cell count

Serum b-hCG Pregnancy Test (only for females of childbearing potential, defined as either not surgically sterile or not diagnosed as postmenopausal)

[redacted] **PD and PK parameters:**
- Serum total 1,25-dihydroxyvitamin D
- Serum 1,25-dihydroxyvitamin D_3
- [redacted]
- Serum total 25-hydroxyvitamin D (blinded*)
- [redacted]
- Serum 24,25-dihydroxyvitamin D_3
- Vitamin D binding protein (DBP)
- Serum myostatin

Serum Chemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Blood urea nitrogen
- Calcium (corrected)
- 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)
- Phosphorus
- Albumin

14.1.5.1 The Full Blood Chemistry Panel will be performed at the following visits:

Non-PK and PK Placebo	
Visit#	Day#
1	-83 to -69
2	-13 to -7
3	1
17	85
24	183

PK Active	
Visit#	Day#
1	-83 to -69
2	-13 to -7
3	1
17	99
24	197

Non-PK and PK Placebo	
Visit#	**Day#**
32	225
ET	

PK Active	
Visit#	**Day#**
32	239
ET	

14.1.5.2 The Partial Blood Chemistry Panel, (consisting of calcium corrected for albumin, phosphorus and albumin) will be performed at the following visits:

Non-PK and PK Placebo	
Visit#	**Day#**
10	8
11	15
12	22
13	29
14	43
15	57
16	71
18	99
19	113
20	127
21	141
22	155
23	169

PK Active	
Visit#	**Day#**
4	2-3
5	5
6	6
7	8
8	11
9	15
10	22
11	29
12	36
13	43
14	57
15	71
16	85
18	113
19	127
20	141
21	155
22	169
23	183
25	198-199

Non-PK and PK Placebo	
Visit#	Day#
30	197
31	211
32	225
ET	

PK Active	
Visit#	Day#
26	200
27	202
28	204
29	207
30	211
31	225
32	239
ET	

14.1.5.3 Hematology will be performed at the following visits:

Non-PK and PK Placebo	
Visit#	Day#
1	-83 to -69
3	1
17	85
24	183
32	225
ET	

PK Active	
Visit#	Day#
1	-83 to -69
3	1
17	99
24	197
32	239
ET	

14.1.5.4 The serum pregnancy test will be performed (only for women of childbearing potential) at the following visits:

Non-PK and PK Placebo	
Visit#	Day#
1	-83 to -69
3	1
17	85
24	183
32	225
ET	

PK Active	
Visit#	Day#
1	-83 to -69
3	1
17	99
24	197
32	239
ET	

[redacted]

15. Pharmacokinetic Analyses

In Cohort 1, serum samples for the evaluation of calcifediol concentration will be obtained at the following nominal time points:

Single Dose PK Assessments:

PK Timepoint (hr)	Visit#	Day#
-12	V3	1
-3	V4	2-3
0	V4	2-3
0 - DOSE	V4	2-3
4	V4	2-3
8	V4	2-3
12	V4	2-3
16	V4	2-3
20	V4	2-3
24	V4	2-3
30	V4	2-3
36	V4	2-3
42	V4	2-3
48	V5	4

Repeat-Dose PK Assessments:

PK Timepoint (hr)	Visit#	Day#
-12	V24	197
-3	V25	198-199
0	V25	198-199
0 - DOSE	V25	198-199
4	V25	198-199
8	V25	198-199
12	V25	198-199
16	V25	198-199
20	V25	198-199
24	V25	198-199
30	V25	198-199

36	V25	198-199
42	V25	198-199
48	V26	200

Serum calcifediol and baseline-adjusted calcifediol concentrations (as defined in Section 8.2 will be listed and a summary by nominal time point will be presented; the summary will consist of the number of subjects (n), mean, SD, minimum, median, maximum, percent coefficient of variation (%CV), geometric mean, and the 25th and 75th percentiles.

Linear and semi-logarithmic plots of the individual serum calcifediol and baseline-adjusted concentrations versus actual time and mean (SD) serum concentrations and baseline-adjusted concentrations versus nominal time will be generated.

PK parameters based on serum calcifediol concentration versus time data, as well as baseline-adjusted serum calcifediol concentration versus time data, will be estimated for each subject from the PK sites by applying a non-compartmental approach using Phoenix WinNonlin® 8.3 (Certara, Princeton, NJ) or higher. Actual sampling times will be used for the calculation of PK parameters.

Where the data allow, the following PK parameters will be calculated using both observed and baseline-adjusted serum calcifediol concentrations.

Table 5. Pharmacokinetic Parameters

Parameter Estimated:	Parameter Description:
C_{max}	Maximum observed serum concentration
C_{max}/BW	Maximum observed serum concentration divided by body weight
T_{max}	Time of observed maximum serum concentration
T_{last}	Timepoint with the last observed measurable concentration
AUC_{0-t}	Area under the serum concentration time curve from time zero to the timepoint with the last measurable concentration, calculated by linear up-log down trapezoidal method
AUC_{0-t}/BW	AUC_{0-t} divided by body weight

AUC_{inf}	Area under the serum concentration time curve from time zero extrapolated to time infinity, estimated as $AUC_{0-t} + C_{pred}/\lambda_z$, where C_{pred} is the predicted concentration at T_{last}
λ_z	Terminal rate constant, determined by linear regression of the terminal points of the log-linear serum concentration-time curve.
$t_{1/2}$	Terminal half-life, estimated as ln (2)/ λ_z.
CL/F	Clearance divided by the bioavailable fraction, estimated as dose/AUC_{inf}.
V_z/F	Volume of distribution based on the terminal phase divided by the bioavailable fraction, estimated as dose/(AUC_{inf} x λ_z).

AUC parameters will not be generated unless there are at least three measurable calcifediol concentrations in the PK profile. Parameters based on sufficient characterization of the terminal phase of the concentration versus time profile (λ_z, $t_{1/2}$, CL/F, and V_z/F) will only be reported if the goodness-of-fit parameter R^2 is greater than 0.8 and the percent of AUC extrapolated to time infinity ($AUC_{\%extrap}$) is less than 25%. Additional PK parameters, such as partial AUCs or accumulation ratios, may be generated to aid with interpretation of the data if needed.

PK parameters will also be summarized relative to BMI, body weight, age, gender, race, severity of SHPT and dialysis vintage, etiology of CKD and prior treatment with calcimimetics. For each of these factors when appropriate, the PK parameters will be summarized by PK period for subgroups, where the median values are based on the PK population only.

All parameters will be reported to three significant figures. The following descriptive statistics will be calculated for the PK parameters: number of subjects (n), arithmetic mean, SD, minimum, median, maximum, geometric mean, %CV and the 25th and 75th percentiles. Listings and summary tables of the concentration versus time data and PK parameters will be generated using SAS 9.4 or higher.

16. Pharmacodynamic Analyses

PD profiles for serum DBP, [redacted] total free 25D, 1,25D, $1,25D_3$, and $24,25D_3$ will be collected at the following visits:

Non-PK and PK Placebo			**PK Active**	
Visit#	**Day#**		**Visit#**	**Day#**
2	-13 to -7		2	-13 to -7

Non-PK and PK Placebo	
Visit#	Day#
3	1
4	NA
5	4
6	6
7	NA
8	NA
9	NA
17	85
24	183
25	NA
26	186
27	188
28	190
29	193
30	197
31	211
32	225
ET	

PK Active	
Visit#	Day#
3	1
4	2-3
5	4
6	6
7	8
8	11
9	15
17	99
24	197
25	198-199
26	200
27	202
28	204
29	207
30	211
31	225
32	239
ET	

These will be presented as descriptive statistics and compared between the study arms. Analysis method will follow sections 8.2 and 8.3. Correlations between total 25D and calcifediol and the listed PD parameters (excluding DBP, [redacted], total free 25D) will be examined graphically and correlation coefficients calculated. Values below LLOQ will be set to 0.

17. Interim Analyses

No interim analysis will be done for Cohort 1.

18. Changes from Protocol-Stated Analyses

1. The protocol states that the ITT population will be used for efficacy analysis, but then also states that subjects who do not have at least one recorded value at baseline for serum total 25D and for

plasma iPTH will be excluded from all efficacy analyses. The mITT population is defined to include subjects in the ITT population with at least one post-baseline value recorded during EAP for both serum total 25D and for plasma iPTH. Efficacy analyses will be based on the mITT population.

2. The protocol lists severity of SHPT and VDI and etiology of CKD as subgroups for analysis; however, these data were not collected on the eCRF. They will be excluded from analysis.

3. Partial AE dates imputed as date of treatment start will be imputed using Visit 3 date and not Visit 1 as stated in the protocol.

19. References

[redacted]

2 CTAP101-CL-2010 Protocol Version 11.0

20. Revision History

Documentation of revision to the SAP will commence after approval of the Final version 1.0.

21. Tables

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	PD

[redacted]

22. Listings

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	All Randomized Subjects
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[redacted]	[redacted]	[redacted]
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23. Figures

[redacted]		

Figure Number	Title	Population
[redacted]	[redacted]	[redacted]

24. Appendix

1.Cohort 1 - Non-PK Sites

[a] Last dose of CTAP101/Placebo treatment administered on Day 181; [b]Last dose of cinacalcet administered on Day 209.

Subjects Randomized to Placebo (n=~4)	Follow-up								ET
Subjects Randomized to Active (n=~12)	Follow-up								
Study Visit	25	26	27	28	29	30	31	32	
Treatment Week		**26**	**26**	**26**	**26**	**26**	**26**	**26**	
Day of Week (M, W, F dialysis schedule; W is acceptable for all visits shaded in blue)		M	W	F	M	F	F	F	
Day of Week (T, Th, Sa dialysis schedule; Th is acceptable for all visits shaded in blue)		T	Th	Sa	T	Sa	Sa	Sa	
Randomization to Active or Placebo Treatment (Prior to First HD dose)									
SUBJECTS RANDOMIZED TO PLACEBO OR ACTIVE		No study procedures							
CTAP101/Placebo Treatment Dose Number – TIW dose administration, once during each HD session		**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	
Study Week		27	27	27	28	28	30	32	
Study Day		186[b]	188	190	193	197	211	225	
Cinacalcet Treatment Dose Number – TIW dose adminstration during each HD during three weeks of the 6-week FU period				1	2	4[b]	**No Dose**	**No Dose**	
SUBJECTS RANDOMIZED TO PLACEBO OR ACTIVE									
Sign ICF									
Review/confirm inclusion/exclusion criteria									
Medical history and demographics									
Prior/concomitant medications						1	1	1	1
Adverse events						1	1	1	1
Physical exam (including height, weight, BMI and nutritional status)								1	1
Vital Signs (blood pressure and heart rate)						1	1	1	1
12-Lead ECG									1
[redacted]									1
Serum pregnancy test								1	1
Clinical chemistry (full panel)								1	1
Clinical chemistry (partial panel)						1	1		
Hematology								1	1
Plasma iPTH and serum 25D						1	1	1	1
Serum DBP[redacted]25D3, 1,25D3 and 24,25D3									1

No Visit

a Last dose of CTAP101/Placebo treatment administered on Day 181; [b]Last dose of cinacalcet administered on Day 209.

2. Cohort 1 PK Sites

Subjects Randomized to Placebo (n=7)		Screen	WO	Baseline			Dose Level = 0 mcg/week																					
Subjects Randomized to Active (n=21)		Screen	WO	Baseline			Single-dose PK Assessment (for subjects randomized to active)						Dose Level = 900 mcg/week															
Study Visit		1		2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	
Treatment Week		**0**		**0**	**0**		**0**	**0**	**0**	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	
Day of Week (M, W, F dialysis schedule; W is acceptable for all visits shaded in blue)					F		Sa-S	M	W	F	M	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	
Day of Week (T, Th, Sa dialysis schedule; Th is acceptable for all visits shaded in blue)					Sa		S-M	T	Th	Sa	T	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	
Randomization to Active or Placebo Treatment (Prior to First HD or PK Dose)																												
SUBJECTS RANDOMIZED TO PLACEBO								No Study Procedures																				
Placebo Treatment Dose Number - TIW dose administration, once during each HD session						First HD		2	3	No Visits			4	7	10	13	19	25	31	37	43	49	55	61	67	73	No Dose [a]	
Study Week		-11 to -10		-2	-1	-1	No Visit						1	2	3	4	6	8	10	12	14	16	18	20	22	24	26	
Study Day		-83 to -69		-13 to -7	1	1		4	6				8	15	22	29	43	57	71	85	99	113	127	141	155	169	183	
Cinacalcet Treatment Dose Number - TIW dose administration during each HD during three weeks of the 6-week FU period																												
SUBJECTS RANDOMIZED TO ACTIVE																												
PK Dose							First PK Dose [a]																					
CTAP101 Treatment Dose Number - TIW dose administration, once during each HD session												First HD	4	7	10	13	19	25	31	37	43	49	55	61	67	73	No Dose [b]	
Study Week		-11 to -10		-2	-1		1	1	1	1	2	2	3	4	5	6	8	10	12	14	16	18	20	22	24	26	28	
Study Day		-83 to -69		-13 to -7	1		2-3	4	6	8	11	15	22	29	36	43	57	71	85	99	113	127	141	155	169	183	197	
Hours relative to PK dose					-24 to -12		-3 to 42	48																			-12	
							(GORC or equivalent)																					
Cinacalcet Treatment Dose Number - TIW dose administration during each HD during three weeks of the 6-week FU period			Washout																									
SUBJECTS RANDOMIZED TO PLACEBO OR ACTIVE																												
Sign ICF		1																										
Review/confirm inclusion/exclusion criteria		1		1	1																							
Medical history and demographics		1																										
Prior/concomitant medications		1		1	1								1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Adverse events		1		1	1								1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Physical exam (including height, weight, BMI)		1																									1	
Vital Signs (blood pressure and heart rate)		1		1	1								1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
12-Lead ECG					1																						1	
[redacted]					1																						1	
Serum pregnancy test		1			1															1							1	
Clinical chemistry (full panel)		1		1	1															1							1	
Clinical chemistry (partial panel)													1	1	1	1	1	1	1		1	1	1	1	1	1		
Hematology		1			1															1							1	
Plasma iPTH and serum 25D		1		1	1								1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3					1															1							1	
ONLY SUBJECTS RANDOMIZED TO ACTIVE																												
Concomitant medications						[f]		1	1	1	1	1															[f]	
Vital Signs (blood pressure and heart rate)						[f]	[e, g]	[f], 1	1	1	1	1															[f]	
Adverse events						[f]	[c, g]	[f], 1	1	1	1	1															[f]	
Clinical chemistry (partial panel)						[f]	[f]	[f]	1	1	1	1															[f]	
Plasma iPTH and serum 25D												1																
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3						[f]	[f]	[f]	1	1	1	1															[f]	

[a]Last dose of CTAP101/Placebo Treatment administered on Day 181; [b]Last dose administered on Day 195; [c]First PK dose (900 mcg) administered at t=0 on Day 2; [d]Second PK dose administered at t=0 on Day 198; [e]Vital Signs taken three times per day on Days 2 and 3; [f]Adverse Events assessed daily at Days 2 and 3; [g]Activity performed at Phase 1 unit or equivalent; [h]Last dose administered on Day 209 for Placebo; [i]Last dose administered on Day 223 for Active.

[redacted]

Subjects Randomized to Placebo (n=~7)		Follow-up								ET
Subjects Randomized to Active (n=~21)		Repeated-dose PK Assessment/Follow-up for subjects randomized to active								
Study Visit		25	26	27	28	29	30	31	32	
Treatment Week		**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	
Day of Week (M, W, F dialysis schedule; W is acceptable for all visits shaded in blue)		Sa-S	M	W	F	M	F	F	F	
Day of Week (T, Th, Sa dialysis schedule; Th is acceptable for all visits shaded in blue)		S-M	T	Th	Sa	T	Sa	Sa	Sa	
Randomization to Active or Placebo Treatment (Prior to First HD or PK Dose)										
SUBJECTS RANDOMIZED TO PLACEBO		No study procedures for subjects randomized to placebo								
Placebo Treatment Dose Number - TIW dose administration, once during each HD session		**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	
Study Week		27	27	27	27	28	28	30	32	
Study Day		184-185	186[k]	188	190	193	197	211	225	
Cinacalcet Treatment Dose Number - TIW dose administration during each HD during three weeks of the 6-week FU period					1	2	4[h]	**No Dose**	**No Dose**	
SUBJECTS RANDOMIZED TO ACTIVE										
PK Dose		**2nd PK Dose[d]**								
CTAP101 Treatment Dose Number - TIW dose administration, once during each HD session			**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	**No Dose**	
Study Week		29	29	29	29	30	30	32	34	
Study Day		198-199	200	202	204	207	211	225	239	
Hours relative to PK dose		0-42	48							
		(GCRC or equivalent)								
Cinacalcet Treatment Dose Number - TIW dose administration during each HD during three weeks of the 6-week FU period					1	2	4[i]	**No Dose**	**No Dose**	
SUBJECTS RANDOMIZED TO PLACEBO OR ACTIVE										
Sign ICF										
Review/confirm inclusion/exclusion criteria										
Medical history and demographics										
Prior/concomitant medications							1	1	1	1
Adverse events							1	1	1	1
Physical exam (including height, weight, BMI)									1	1
Vital Signs (blood pressure and heart rate)							1	1	1	1
12-Lead ECG										1
[redacted]										1
Serum pregnancy test									1	1
Clinical chemistry (full panel)									1	1
Clinical chemistry (partial panel)							1	1		
Hematology									1	1
Plasma iPTH and serum 25D							1	1	1	1
Serum DBP[redacted]ee 25D, 25D3, 125D, 1,25D3, 24,25D3										1
ONLY SUBJECTS RANDOMIZED TO ACTIVE										
Concomitant medications			1	1	1	1				
Vital Signs (blood pressure and heart rate)		6[c,g]	1[f], 1	1	1	1				
Adverse events		2[c,g]	1[f], 1	1	1	1				
Clinical chemistry (partial panel)		1[f]	1[f]	1	1	1				
Plasma iPTH and serum 25D										
Serum DBP, [redacted], free 25D, 25D3, 125D, 1,25D3, 24,25D3		1[f]	1[f]	1	1	1	1	1	1	

[a]Last dose of CTAP101/Placebo Treatment administered on Day 181; [b]Last dose administered on Day 195; [c]First PK dose (900 mcg) administered at t=0 on Day 2; [d]Second PK dose administered at t=0 on Day 198; [e]Vital Signs taken three times per day on Days 2 and 3; [f]Adverse Events assessed daily at Days 2 and 3; [g]Activity performed at Phase 1 unit or equivalent; hLast dose administered on Day 209 for Placebo; [i]Last dose administered on Day 223 for Active