PROTOCOL CTAP101-CL-2010

Study Title:	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.
Study Number:	CTAP101-CL-2010
Short Title:	Safety, Efficacy, PK and PD of CTAP101 (calcifediol) ER Capsules for SHPT in HD Patients VDI
Study Phase:	2
Product Name:	CTAP101 Capsules
Investigators:	Multi-center

Sponsor:

OPKO Ireland Global Holdings Ltd.
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Miami, FL 33137

Sponsor Contact:

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Study Medical Monitor:

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Study Contact:

[redacted]

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

	Date
Version 11.0	05 May 2020

Confidentiality Statement

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SYNOPSIS

Sponsor:

OPKO Ireland Global Holdings Ltd.

Name of Finished Products:

CTAP101 Capsules (150 mcg strength)
Cinacalcet Tablets (30 mg strength)

Name of Active Ingredients:

Calcifediol, calcidiol, 25-hydroxyvitamin D_3
Hydrochloride salt of cinacalcet

Test Products, Dose, and Mode of Administration:

CTAP101 Capsules (300, 600 and 900 mcg/week) or matching placebo by the oral route.

Cinacalcet (30 mg tiw) by the oral route.

Study Title:

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.

Study Number:

CTAP101-CL-2010

Study Phase: 2

Primary Objectives:

The primary objectives of this study are:

1. To evaluate the efficacy of repeated dosing with three dose levels of CTAP101 extended-release (ER) Capsules versus placebo in raising mean serum total 25-hydroxyvitamin D 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 three dose levels of CTAP101 Capsules; and,
3. To assess the pharmacokinetic (PK) profiles and PK linearity of serum calcifediol after single and repeated doses of CTAP101 Capsules at three dose levels 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).

Secondary Objectives:

The secondary objectives of this study are:

1. To evaluate the efficacy of repeated dosing with three dose levels of CTAP101 ER Capsules versus placebo in raising mean serum total 25-hydroxyvitamin D 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 25-hydroxyvitamin D and plasma iPTH during administration of repeated doses of CTAP101 Capsules at three dose levels;
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 D analogs and/or calcimimetics on the efficacy and safety of repeated doses of CTAP101 Capsules at three dose levels versus placebo in raising serum total 25-hydroxyvitamin D 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 of CTAP101 Capsules at three dose levels versus placebo on mean serum calcium (corrected for albumin), phosphorus, vitamin D binding protein (DBP), total free 25-hydroxyvitamin D, total 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_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]

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 [redacted] 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 this protocol. Subjects in Cohort 2 will participate in a randomized, double-blinded, placebo-controlled repeated-dose, dose-ranging safety and efficacy study of CTAP101 Capsules administered at three different dose levels (300, 600 or 900 mcg per week).

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. Randomization will be accomplished in blocks of four subjects using two computer-generated codes, one for the PK sub-group (n=28) and one for the non-PK sub-group (n=16).

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

In Cohort 2, approximately 480 subjects will be screened to randomize approximately 212 eligible subjects, stratified for severity of SHPT, in a 1:1:1:1 ratio into four groups receiving the following treatments in a double-blinded fashion for 26 weeks: (aa) CTAP101 Capsules at 300 mcg per week, (bb) CTAP101 Capsules at 600 mcg per week, (cc) CTAP101 Capsules at 900 mcg per week or (dd) matching placebo. Randomization will be accomplished in blocks of four subjects using two computer-generated codes, one for the PK sub-group (n=72) and one for the non-PK sub-group (n=140). A subset of subjects will undergo a subsequent 26 weeks of open-label treatment (for a total of 52 weeks) depending on their prior participation in the PK assessments described below.

An Interactive Response Technology system (IRT) will provide study treatment group assignments for both cohorts (using computer-generated randomization codes provided by the IRT vendor) and dosing adjustments. For Cohort 2 only, an independent, unblinded Data Safety Monitoring Board (DSMB) will be established to oversee the IRT and verify the appropriateness of all dosing adjustments, to monitor subject safety and the effectiveness of CTAP101 Capsules at regular intervals. Specific responsibilities and activities of the DSMB will be defined in the charter ratified at a pre-Cohort 2 organizational meeting. Also, for Cohort 2 only, subjects, dialysis facilities, study personnel and the sponsor will be blinded to the administered treatments and to plasma iPTH, serum total 25-hydroxyvitamin D and serum calcifediol data until the last subject completes the first 26 weeks of treatment.

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 calcimimetics 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 period prior to baseline assessments. Subjects will undergo a 6-week FU period after completing treatment with CTAP101 Capsules or corresponding placebo.

On two occasions, a subset of subjects (n=~21) from Cohort 1 who are assigned to treatment with CTAP101 Capsules and, on one or two occasions, a subset of subjects (n=~18) from each of the four treatment groups in Cohort 2 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 (all groups) and repeated-dose (active groups only) PK profiles of serum calcifediol and associated PD profiles for serum calcium (corrected), phosphorus, DBP, total free 25-hydroxyvitamin D, total 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3. Subjects receiving CTAP101 Capsules will complete a 26-week treatment period between the two PK profile assessments. Subjects in Cohort 2 receiving treatment with placebo will complete a 26-week treatment period after the single-dose PK assessment, and then receive CTAP101 Capsules at a dose of 300, 600 or 900 mcg per week, assigned randomly with stratification by severity of SHPT, during a second 26-week treatment period, after which they will complete a 6-week follow-up period. Blood samples for the first PK profile assessment will be collected at -12, -3, 0, 4, 8, 12, 16, 20, 24, 30, 36 and 42 hours, and on Days 4, 6, 8, 11 and 15 following a single dose (0, 300, 600 or 900 mcg) administered as 6 capsules (CTAP101 and/or placebo) 2 weeks prior to the start of the first 26-week treatment period. Blood samples for the second PK profile assessment will be collected at -12, -3, 0, 4, 8, 12, 16, 20, 24, 30, 36 and 42 hours, and on Days 4, 6, 8, 11 and 15 following the last administered dose in treatment week 26 for subjects receiving dosages of 300 or 600 mcg per week of CTAP101 Capsules, and at -12, -3, 0, 4, 8, 12, 16, 20, 24, 30, 36 and 42 hours, and on Days 4, 6, 8, 11, 15, 22, 29 and 43 following the last administered dose in treatment week 26 for subjects receiving 900 mcg per week of CTAP101 Capsules. On specified and subsequent HD days, blood samples will be collected just before dialysis. Subjects who received treatment with CTAP101Capsules at 900 mcg per week will terminate further participation in the study after the second PK profile assessment. Subjects who received treatment with CTAP101 Capsules at 300 or 600 mcg per week will resume dosing, as before, and complete a second 26-week treatment period and a subsequent 6-week follow-up period.

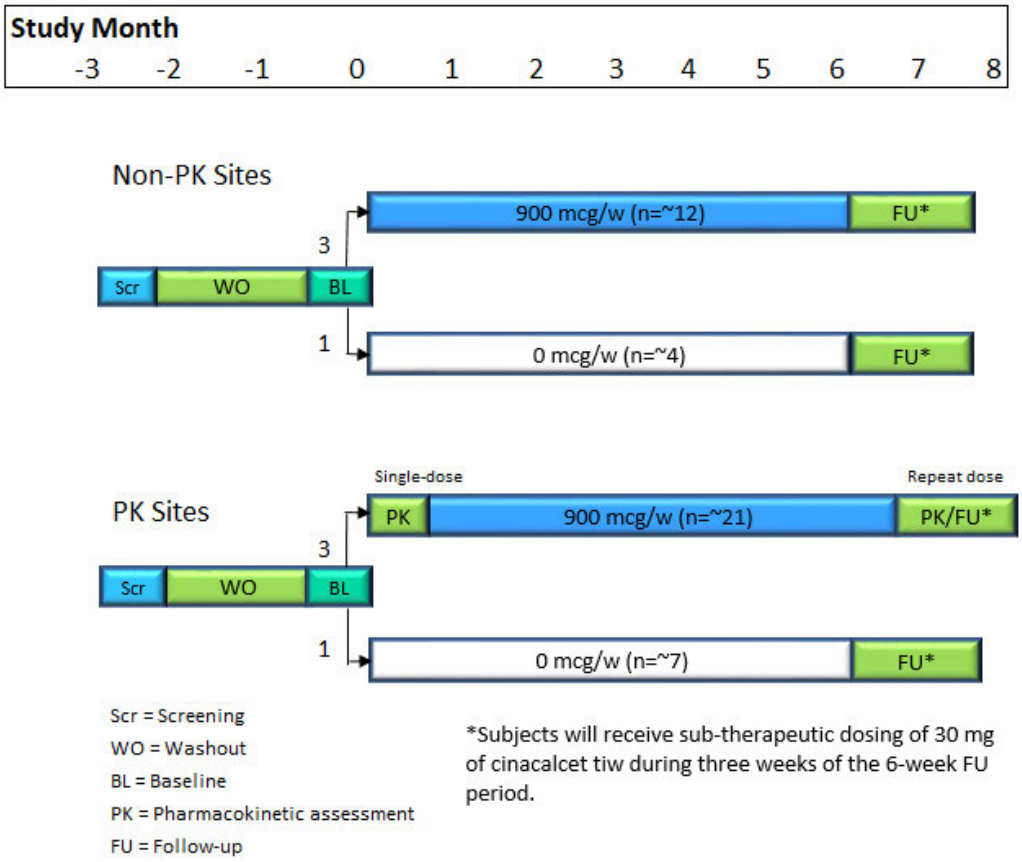
The remaining subjects from each treatment group will forgo all PK assessments and complete 26 or 52 weeks of treatment. Subjects assigned to CTAP101 Capsules will remain on this study drug for the entire period. Subjects assigned to placebo will be treated with placebo for the 26 weeks of treatment and, subsequently, if in Cohort 2, with CTAP101 Capsules at a dose of 300, 600 or 900 mcg per week, assigned randomly with stratification for severity of SHPT, during another 26 weeks of treatment. All of these subjects will complete a 6-week follow-up period at the end of treatment with CTAP101 Capsules or placebo.

Subjects in Cohort 1 only, 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 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.

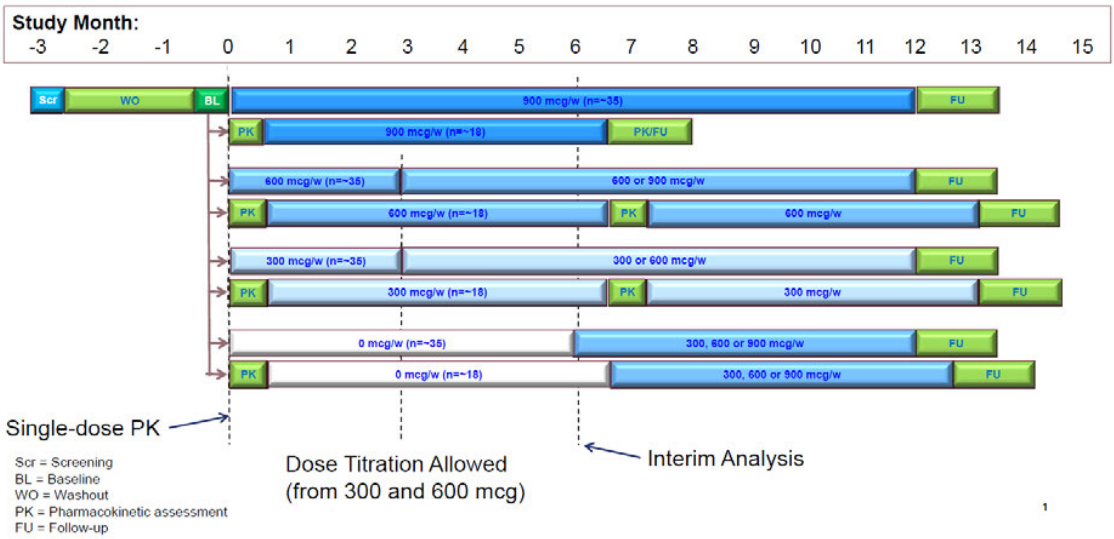
For all subjects, pre-dialysis blood samples will be collected at weekly, biweekly or monthly intervals (see Section 7 Study Activities) during the pre-treatment washout period, the 26- and 52-week treatment periods and the 6-week post-treatment follow-up period. These samples will be collected at the start of either the 2nd or 3rd HD session of the week (Wednesday/Thursday or Friday/Saturday). Key parameters to be analyzed in the collected samples include: plasma iPTH, serum calcium (corrected for serum albumin), serum phosphorus, serum total 25-hydroxyvitamin D, serum total 1,25-dihydroxyvitamin D, serum calcifediol, serum 1,25-dihydroxyvitamin D_3, and serum 24,25-dihydroxyvitamin D_3. 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) and clinical laboratory tests (hematology and clinical chemistries). ECGs (12-lead) will be obtained at baseline and the end of treatment (EOT) only, or at early termination (ET). [redacted]

A diagram of the study design is shown below:

Cohort 1 (randomized, single-blinded design):



Cohort 2 (randomized, double-blinded placebo-controlled design for the first 6 months of the treatment period followed by open-label, non-placebo-controlled design for the second 6 months of the treatment period):



Dosing Plan:

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. After 12 weeks of treatment, subjects in Cohort 2 who are receiving 300 or 600 mcg per week of CTAP101 Capsules and who are not participating in PK determinations will undergo upward dose titration provided that (a) the plasma iPTH has not decreased by at least 30% from pretreatment baseline and remains >300 pg/mL, (b) corrected serum calcium is <9.8 mg/dL, and (c) serum phosphorus is <6.0 mg/dL. Subjects in Cohorts 1 or 2 who are receiving 900 mcg per week of CTAP101 Capsules or placebo, or are participating in PK assessments, will not undergo upward dose titration at any time. Upward dose titration will occur in a single increment of 300 mcg (two CTAP101 Capsules). After 26 weeks of treatment, subjects who were assigned to placebo will commence treatment with 300, 600 or 900 mcg of CTAP101 Capsules, assigned randomly with stratification for severity of SHPT.

Subjects will reduce the dose at any time in increments of 300 mcg (two CTAP101 Capsules) per week in the event that plasma iPTH is confirmed 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, provided that that the investigator has deemed the elevated serum phosphorus to be related to study drug administration and has previously taken appropriate and persistent actions to control serum phosphorus by initiating or adjusting phosphate binder therapy. In the event that a dose reduction is required for a subject receiving the minimum dosage of 300 mcg per week, the subject will suspend dosing and resume when plasma iPTH is ≥150 pg/mL and corrected serum calcium is <9.8 mg/dL at the minimum dosage of 300 mcg per week. Subjects assigned to treatment with CTAP101 Capsules will suspend dosing if plasma iPTH is confirmed to be <100 pg/mL or corrected serum calcium is confirmed to be >11.0 mg/dL, and will resume when plasma iPTH is ≥150 pg/mL and corrected serum calcium is <9.8 mg/dL at a dose that has been reduced by 300 mcg per week or at the minimum dosage of 300 mcg per week.

After 12 weeks of treatment, subjects who have experienced more than a 100% increase in plasma iPTH from pre-treatment baseline or whose plasma iPTH has increased above 1,200 pg/mL on two consecutive visits (if at least 2 weeks apart) will terminate dosing with study drugs and further participation in the treatment period and immediately enter the 6-week post-treatment follow-up period. Such subjects may be immediately removed from the study and placed on standard of care therapy, at the discretion of the Investigator.

Subjects in Cohort 1 only, 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 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.

Duration of Treatment:

Subjects will participate in Cohort 1 of the study for up to the following number of weeks:

- **PK sub-group randomized to CTAP101 Capsules:** 46 weeks (2 weeks screening, 8 weeks washout, 2 weeks baseline, 2 weeks for single-dose PK determination, 26 weeks of treatment with CTAP101 Capsules, and 6 weeks for repeated-dose/steady-state PK determination and follow-up (FU) evaluation from CTAP101 treatment and inclusive of 3 weeks of cinacalcet dosing).
- **PK sub-group randomized to placebo and Non-PK sub-group:** 44 weeks (2 weeks screening, 8 weeks washout, 2 weeks baseline, 26 weeks of treatment with either CTAP101 Capsules or matching placebo, and 6 weeks of follow-up (FU) evaluation from CTAP101/placebo treatment and inclusive of 3 weeks of cinacalcet dosing).
- Subjects who participate in Cohort 1 will not be eligible for participation in Cohort 2.

Subjects will participate in Cohort 2 of the study for up to the following number of weeks:

- **PK sub-groups:** 74 weeks (2 weeks screening, 8 weeks washout, if required, 2 weeks baseline, 2 weeks for single-dose PK determination, 26 weeks of treatment with either CTAP101 Capsules or matching placebo, 0-6 weeks for repeated-dose (steady-state) PK determination, 26 weeks of further treatment with CTAP101 Capsules, and 6 weeks of follow-up evaluation).
- **Non-PK sub-groups:** 70 weeks (2 weeks screening, 8 weeks washout, if required, 2 weeks baseline, 26 weeks of treatment with either CTAP101 Capsules or matching placebo followed by 26 weeks of treatment with CTAP101 Capsules only, and 6 weeks of follow-up evaluation).

Primary Efficacy Endpoint:

There is no primary efficacy endpoint for Cohort 1, as efficacy in this part of the study is merely observational. The primary efficacy endpoint for Cohort 2 is the proportion of subjects in the intent-to-treat (ITT) population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline, defined in Section 9.10.1, during the first efficacy assessment period (EAP), defined as the average of values obtained in the last 6 weeks of the first 26 weeks of treatment.

Primary Safety Endpoints:

The safety and tolerability will be evaluated for both cohorts in the Safety population (defined as all subjects who have received at least one dose of study drug) by AEs, PEs, VS, hematology and clinical chemistries, and ECGs.

Pharmacokinetic and Pharmacodynamic Endpoints:

Single-dose and repeated-dose (steady-state) PK determinations will be performed by analyzing serum calcifediol concentrations versus time recorded in both cohorts after (a) a single, initial dose of 0 mcg (placebo) or 300, 600 or 900 mcg (CTAP101 Capsules) and (b) after the last administered dose in the first 26 weeks of treatment in a subset of approximately 21 (Cohort 1) or 18 (Cohort 2) subjects in each active treatment group. The following PK parameters will be calculated using observed and baseline-adjusted serum calcifediol

concentrations: area under the concentration curve (AUC), maximum concentration, (C_{max}), time to maximum concentration (t_{max}), steady-state concentration (C_{ss}), time to steady-state concentration (t_{ss}), terminal elimination half-life ($t_{½}$) in subjects treated with CTAP101 Capsules at a dose of 900 mcg per week, clearance (CL/F), and volume of distribution (Vd/F), as feasible. Relative exposure and dose proportionality will be examined, if possible.

In an effort to characterize the dose-exposure-response relationships and to determine the impact of intrinsic and extrinsic factors on these relationships, population PK and PD models will be developed from pooled serum calcifediol data collected from subjects in both cohorts. PD markers to be considered in the population PD analysis include: plasma iPTH, and serum calcium (corrected), phosphorus and 1,25-dihydroxyvitamin D_3. The effect of the following covariates will be examined: body weight, age, gender, race, SHPT severity, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics.

Secondary Endpoints:

The key secondary efficacy endpoint for Cohort 1 is the proportion of subjects in the intent-to-treat (ITT) population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline, defined in Section 9.10.1, during the EAP, defined as the average of values obtained in the last 6 weeks of the 26 weeks of treatment, calculated for each treatment group and for each final dose group, defined in Section 9.11.

Secondary efficacy endpoints for Cohorts 1 and 2 include the proportion of subjects in the per-protocol (PP) population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline during the first EAP. Additional secondary endpoints include the proportion of subjects in the PP population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 10, 20 or 30% from pre-treatment baseline during the first and/or second EAP, as applicable, the latter being defined as the average of values obtained in the last 6 weeks of the second 26 weeks of treatment; the time courses of mean absolute changes from pre-treatment baseline in serum total 25-hydroxyvitamin D 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, DBP, total free 25-hydroxyvitamin D, total 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3, and 24,25-dihydroxyvitamin D_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.

[redacted]

Sample Size Estimation:

Formal power calculations have not been undertaken for Cohort 1. For Cohort 2, sample size has been calculated to provide power of 80% for a two-sided, alpha 0.05 level test of equal proportions comparing the numbers of subjects attaining both a mean serum total 25-hydroxyvitamin D level of ≥50 ng/mL and a mean decrease from pre-treatment baseline of at least 30% in plasma iPTH (averaged over the last 6 weeks of the first 26-week treatment period) on each of the three different weekly dosages of CTAP101 Capsules (active) versus placebo. Assuming response rates of at least 0.4 (CTAP101 Capsules) versus 0.1 (placebo), and using a 1:1 ratio of each dose of CTAP101 Capsules:placebo subjects with an estimated 30% dropout rate over the course of the study, a sample size of 53 subjects is required in each treatment arm of the study, allocated as 53 to CTAP101 Capsules at 300 mcg per week, 53 to CTAP101 Capsules at 600 mcg per week, 53 to CTAP101 Capsules at 900 mcg per week, and 53 to placebo.

Statistical Analyses:

Efficacy analyses will be performed for the ITT and PP populations in both cohorts, as indicated. The ITT population will be defined as all subjects (up to approximately 212) who have been randomized to receive study medication. Subjects who do not have at least one recorded value at baseline, defined in Section 9.10.1, for serum total 25-hydroxyvitamin D and for plasma iPTH will be excluded from all efficacy analyses. The PP population will be defined as all subjects for whom at least two serum total 25-hydroxyvitamin D and two plasma iPTH determinations are included in the calculated baseline value, and in the respective EAP, and who do not have a major protocol deviation.

Primary efficacy will be assessed in the ITT population of Cohort 2 by comparing the proportions of subjects in all three active groups versus those in the placebo group and, subsequently, each active dose group versus placebo (in the order of dose group bb, then cc, then aa versus dose group dd) attaining both a mean serum total 25-hydroxyvitamin D level of ≥50 ng/mL and a mean decrease from baseline in plasma iPTH of ≥30% in the first EAP using the Cochran-Mantel-Haenszel test statistic (alpha=0.05). Subjects who do not have at least two serum total 25-hydroxyvitamin D and plasma iPTH determinations in the EAP will be deemed non-responders. Dose groups will be defined for analysis of the first 26 weeks of treatment by the average weekly dose administered in the first EAP, as follows: dose group dd = 0 mcg; dose group aa = 1-300 mcg, dose group bb = 301-600 mcg and dose group cc = 601-900 mcg. Statistical comparisons will not be made between the active treatment groups receiving different average weekly dosages of CTAP101 Capsules.

Key secondary efficacy for Cohort 1 will be assessed in the ITT population by comparing the proportions of subjects in the active group versus those in the placebo group attaining both a mean serum total 25-hydroxyvitamin D level of ≥50 ng/mL and a mean decrease from baseline in plasma iPTH of at least 30% in the EAP using the Cochran-Mantel-Haenszel test statistic (alpha=0.05). Subjects who do not have at least two serum total 25-hydroxyvitamin D and plasma iPTH determinations in the EAP will be deemed non-responders.

Secondary efficacy will be assessed in the PP population of Cohort 2 by comparing the proportions of subjects in each active dose group versus those in the placebo group attaining a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease from baseline in plasma iPTH of at least 10, 20 or 30% in the first and/or second EAP, as applicable, using the Cochran-Mantel-Haenszel test statistic (alpha=0.05). Dose groups will be defined as described above. Statistical comparisons will not be made between the active treatment groups receiving different average weekly dosages of CTAP101 Capsules.

Primary safety analyses will be conducted in the Safety populations of both cohorts, and the statistical summary will be descriptive and performed by dose group (defined above). No inferential hypothesis testing between each active group and the placebo group will be performed on the safety parameters with the exception of mean serum calcium and phosphorus.

Secondary safety analyses in both cohorts will compare the proportions of subjects with confirmed corrected serum calcium >10.4 mg/dL or confirmed serum phosphorus >6.5 mg/dL (deemed to be study drug related) between the CTAP101 Capsules and placebo dose groups using the Cochran-Mantel-Haenszel test statistic (alpha=0.05).

In addition to assessing the safety and efficacy evaluations for the full study population in Cohort 2, categorical comparisons (by dose group) will be conducted for sub-groups based on body weight, age, gender, race, dose and severity of SHPT and VDI, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics. Also, mean plasma iPTH in the EAP of Cohort 1 and in the first EAP of Cohort 2 will be compared, by treatment group, to the mean pre-washout screening value for subjects who were previously treated with 1α-hydroxylated vitamin D analogs and/or calcimimetics. An interim analysis of safety and efficacy will be completed for Cohort 2 after the last subject has completed the first 26 weeks of treatment.

Inclusion Criteria

Each subject must meet the following criteria to be enrolled into the two cohorts of this study:

1. Be at least 18 years of age.
2. Be diagnosed with CKD requiring in-center HD tiw for the preceding 6 months, as confirmed by medical history.
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; and,
   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.
4 Be receiving calcimimetic therapy (either etelcalcetide or cinacalcet) and/or calcitriol or other 1α-hydroxylated vitamin D analog (paricalcitol or doxercalciferol) for at least 1 month at the time of screening for enrollment in Cohort 1. Approximately 50% of enrolled subjects will have been receiving calcimimetic therapy.
5. Exhibit during the initial screening visit:

a. Plasma iPTH ≥150 pg/mL and <600 pg/mL if receiving etelcalcetide, cinacalcet, calcitriol or other 1α-hydroxylated vitamin D analog (paricalcitol or doxercalciferol); or
b. Plasma iPTH ≥300 pg/mL and <900 pg/mL if not receiving etelcalcetide, cinacalcet, calcitriol or other 1α-hydroxylated vitamin D analog; and,
c. Serum total 25-hydroxyvitamin D <50 ng/mL if not receiving vitamin D supplementation.

6. When otherwise confirmed eligible at Visit 1, must forgo any further treatment with etelcalcetide and cinacalcet for the duration of the study and undergo an 8-week washout period.
7. When otherwise confirmed eligible at Visit 1, must forgo any further treatment with calcitriol or other 1α-hydroxylated vitamin D analogs or vitamin D supplements for the duration of the study and undergo an 8-week washout period.
8. Exhibit after the 8-week washout period (if required due to prior use of etelcaclcetide, cinacalcet, calcitriol or other 1α-hydroxylated vitamin D analogs, or vitamin D supplementation):

   Cohort 1:

   a. Plasma iPTH increased by at least 50%; and,
   b. Plasma iPTH ≥300 pg/mL and <1,200 pg/mL; or,

   Cohort 2:

   f. Plasma iPTH ≥300 pg/mL and <1,200 pg/mL (approximately half of the subjects will be enrolled in each of these two plasma iPTH strata: ≥300 to <600 and ≥600 to <1,200 pg/mL); and

   Cohorts 1 and 2:

   c. Corrected serum calcium <9.8 mg/dL;
   d. Serum total 25-hydroxyvitamin D <50 ng/mL; and,
   e. Serum phosphorus <6.5 mg/dL.

9. When otherwise confirmed eligible at Visit 1, if taking more than 1,000 mg per day of elemental calcium, reduce calcium use (to ≤1,000 mg per day) and/or use non-calcium based phosphate binder therapies (as needed) for the duration of the study.
10. When otherwise confirmed eligible at Visit 1, if taking bone metabolism therapies that may interfere with study endpoints, must discontinue use of these agents for the duration of the study.
11. Willing and able to comply with study instructions and commit to all clinic visits for the duration of the study.
12. Female subjects of childbearing potential must be neither pregnant nor lactating and must have a negative serum beta-human chorionic gonadotropin (b-hCG) pregnancy test at the first screening visit and at other scheduled times.
13. 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.

14. Be able to read, understand and sign the subject Informed Consent Form (ICF) or have a legal representative sign the ICF.

Exclusion Criteria

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

1. Scheduled kidney transplant or parathyroidectomy.
2. History (prior 2 months) of corrected serum calcium ≥9.8 mg/dL or serum phosphorus ≥6.5 mg/dL if not receiving calcitriol or other 1α-hydroxylated vitamin D analog.
3. Receipt of bisphosphonate therapy or other bone modifying treatment (eg, denosumab) within 6 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, intestinal malabsorption disorder, hepatitis or cardiovascular event that in the opinion of the investigator may worsen or reduce life expectancy, and/or interfere with participation in the study.
5. History of neurological/psychiatric disorder, including psychotic disorder or dementia, or any reason which, in the opinion of the investigator makes adherence to a treatment or follow-up schedule unlikely.
6. Known or suspected hypersensitivity to any of the constituents of the study drugs.
7. Currently participating in, or has participated in, an interventional/investigational study within 30 days prior to study screening.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1,25D_3	1,25-dihydroxyvitamin D_3, calcitriol
24,25D_3	24,25-dihydroxyvitamin D_3
25D_3	25-hydroxyvitamin D_3, calcifediol, calcidiol
[redacted]	[redacted]
AE	adverse event
ALT	alanine transferase
AST	aspartate aminotransferase
AUC	area under the (concentration) curve
BA	Bioavailability
[redacted]	[redacted]
b-hCG	beta-human chorionic gonadotropin
BMI	body mass index
CFR	Code of Federal Regulations
[redacted]	[redacted]
CKD	chronic kidney disease
CL/F	Clearance
C_{max}	maximum concentration
[redacted]	[redacted]
C_{ss}	steady-state concentration
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
CV	coefficient of variation
[redacted]	[redacted]
DBP	vitamin D binding protein
DSMB	data safety monitoring board
EAP	efficacy assessment period
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment
ER	extended-release

ET	early termination
FDA	Food and Drug Administration
[redacted]	[redacted]
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HD	Hemodialysis
HDPE	high-density polyethylene
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
[redacted]	[redacted]
IP	investigational product
iPTH	intact parathyroid hormone
IRB/EC	Institutional Review Board/Ethics Committee
IRT	interactive response technology
ITT	intent-to-treat
K/DOQI	Kidney Disease Outcomes Quality Initiative
KDIGO	Kidney Disease Improving Global Outcomes
LAR	legally authorized representative
MBD	mineral and bone disorder
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
[redacted]	[redacted]
PD	pharmacodynamic(s)
PE	physical examinations
PK	pharmacokinetic(s)
PP	per-protocol
PTH	parathyroid hormone
SAE	serious adverse event
SD	standard deviation
SGOT	serum glutamic oxaloacetic transaminase

SGPT	serum glutamic pyruvic transaminase
SHPT	secondary hyperparathyroidism
SOC	system organ class
SOP	standard operating procedure
[redacted]	[redacted]
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent adverse events
tiw	three times per week
t_{max}	time to maximum concentration
[redacted]	[redacted]
t_{ss}	time to steady-state concentration
US	United States
Vd/F	volume of distribution
VDI	vitamin D insufficiency
VS	vital signs
WO	wash-out

1 INTRODUCTION

1.1 Chronic Kidney Disease and Vitamin D Insufficiency

CTAP101 is an extended-release (ER) oral formulation of calcifediol which OPKO Ireland Global Holdings Ltd. (OPKO) is developing as a treatment for secondary hyperparathyroidism (SHPT) in patients with vitamin D insufficiency (VDI) and stage 5 chronic kidney disease (CKD) requiring regular hemodialysis (HD).

Calcifediol is 25-hydroxyvitamin D_3, the physiological precursor to the vitamin D hormone, 1,25-dihydroxyvitamin D_3 (calcitriol). This prohormone is synthesized by the liver from vitamin D_3 (cholecalciferol) 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 vitamin D_2 (ergocalciferol), which cannot be produced endogenously but is obtained only from the 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.

It is widely accepted that serum total 25-hydroxyvitamin D is the best indicator of a patient's vitamin D status. Serum total 25-hydroxyvitamin D levels of ≥30 ng/mL are currently considered adequate in CKD patients while levels of <30 ng/mL are considered "insufficient" [Holick et al 2011]. The commonly used reference range for serum total 25-hydroxyvitamin D is 30 to 100 ng/mL [Souberbielle et al 2010]. Observational studies suggest that in CKD patients, as glomerular filtration rate (GFR) declines, higher 25-hydroxyvitamin D levels may be required to achieve plasma intact parathyroid hormone (iPTH) targets [Ennis et al 2016]. A secondary analysis of two prospective randomized clinical trials conducted in patients with stage 3 or 4 CKD concluded that 25-hydroxyvitamin D levels above 50 ng/mL were required for significant plasma iPTH reduction [Strugnell et al 2019]. Levels of serum total 25-hydroxyvitamin D in the general population vary according to many factors, including intensity of sunlight (varying with geographic location and season), exposure to sunlight (affected by skin pigmentation, use of sunscreen and other cultural factors), age and dietary intake [Holick 1995]. Levels tend to be lower during the winter and at higher latitudes. In patients with CKD, low serum total 25-hydroxyvitamin D levels (VDI) are unrelated to season or latitude and become more prevalent as kidney disease advances.

1.2 Chronic Kidney Disease, SHPT and Vitamin D Insufficiency

CKD is a steadily-increasing health problem in the United States (US) driven by an aging population and an increasing prevalence of obesity with associated complications of hypertension and diabetes mellitus. CKD is categorized into five stages, each defined by a GFR range that progressively decreases from stage 1 to 5. Aberrations in mineral metabolism and bone histology begin early in the course of CKD, worsening as GFR declines [Levin et al 2007]. Even minimal reductions in GFR have been linked to increased risk of bone loss (osteoporosis), and the incidence of hip fracture increases as CKD progresses. Co-morbidities associated with CKD include SHPT, VDI, pervasive soft tissue calcification, cardiovascular disease, infections and reduced quality of life [Souberbielle et al 2010].

VDI in patients with CKD is driven by nutritional inadequacy, decreased exposure to sunlight, proteinuria, decreased hepatic synthesis of calcifediol and excessive expression of the vitamin D

catabolic enzyme, CYP24 [Helvig et al 2010]. Because renal and extra-renal production of 1,25-dihydroxyvitamin D_3 is dependent on an adequate supply of calcifediol, VDI causes inadequate 1,25-dihydroxyvitamin D_3 production. Declining renal function further impairs the conversion of calcifediol to 1,25-dihydroxyvitamin D_3 by the renal 1α-hydroxylase (CYP27B1). Chronically low circulating 1,25-dihydroxyvitamin D_3 results in decreased intestinal absorption of dietary calcium, increased secretion of parathyroid hormone (PTH) by the parathyroid glands and, ultimately, SHPT.

Clinical practice guidelines for the treatment of metabolic bone disease in CKD recommend regular screening for elevated PTH beginning in patients with stage 3 CKD. The guidelines, issued by the National Kidney Foundation from the Kidney Disease Outcomes Quality Initiative (K/DOQI) [National Kidney Foundation. KDOQI Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease 2003, Guideline 8A], the more recent Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) [Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group 2009] and the recent update to the KDIGO guideline [KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of CKD-MBD], also recommend testing for VDI when elevated PTH is encountered, and correcting with aggressive vitamin D supplementation. However, the medical literature documents that low serum total 25-hydroxyvitamin D is inconsistently or inadequately treated in patients with stage 3 or 4 CKD by vitamin D (ergocalciferol or cholecalciferol) supplementation, and that elevated PTH remains uncorrected. More than 30 studies have been published since 1973 in which ergocalciferol or cholecalciferol was administered to patients with stage 3 to 5 CKD. The overall conclusion from this body of work is summarized by Kalantar-Zadeh and Kovesdy: *"Most of these studies have shown either no or minimal to inadequate changes in PTH levels, usually only in some stages of CKD, or changes that still would not satisfy the K/DOQI recommended target ranges for PTH"* [Kalantar-Zadeh and Kovesdy 2009]. A more recent review of the published randomized clinical trials concluded that vitamin D had no efficacy in lowering plasma iPTH levels in patients with stage 3 to 5 CKD [Agarwal and Georgianos 2016]. Hence, there is a need for effective treatment to increase serum total 25-hydroxyvitamin D and control elevated plasma iPTH in this patient population.

1.3 Nonclinical Experience

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 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.

To study the toxicity of CTAP101 Capsules, an earlier formulation of CTAP101 Capsules was administered to dogs for 3 months 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 per day and were associated with serum calcifediol levels >450 ng/mL following 1 month of treatment.

Using the current formulation of CTAP101 Capsules, dogs were treated daily for three months with doses up to 45 µg (~4.5 µg/kg/day). No signs of toxicity were observed at the highest dose tested which was associated with serum calcifediol levels >150 ng/mL.

Calcifediol administration (orally through addition to the diet) to rats for 6 months 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) demonstrate 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 immediate-release capsule preparation. Further, a delay in the release of the active ingredient (time of maximum concentration or t_{max} >7 hours) was observed as compared to the immediate-release formulation (t_{max} ~4 hours).

1.4 Previous Clinical Experience

CTAP101 Capsules (30 mcg/capsule) have been approved by the US Food and Drug Administration (FDA) for the treatment of SHPT in adults with stage 3 or 4 CKD and VDI, defined as serum total 25-hydroxyvitamin D levels less than 30 ng/mL. The clinical studies which supported FDA approval are described below.

There have been three previous single-dose phase 1 studies with CTAP101 Capsules (CTAP101-CL-1005, CTAP101-CL-1011 and CTAP101-CL-1016), two phase 2 studies, of which one was a single-dose study (CTAP101-CL-2004) and one was a repeat-dose study (CTAP101-CL-2008), and three phase 3 studies (CTAP101-CL-3001, CTAP101-CL-3002 and CTAP101-CL-3003). Studies CTAP101-CL-1011, CTAP101-CL-1016 and CTAP101-CL-2008 were conducted with the current formulation of CTAP101 Capsules (30 mcg per capsule). Two of the phase 3 studies (CTAP101-CL-3001 and CTAP101-CL-3002) were identical double-blind, placebo-controlled pivotal trials and the third (CTAP101-CL-3003) was a follow-on open-label extension trial.

The single-dose studies confirmed the ER characteristics of the investigational drug product and that the current formulation has a BA of approximately 25% when administered in the fasting state. Administration of a single pharmacologic dose of CTAP101 Capsules following a high-fat, high calorie meal resulted in a significantly higher exposure of calcifediol compared to when administered in a fasted state. An approximate 5-fold increase in C_{max} and a 3.5-fold increase in area under the concentration curve (AUC) was observed in the fed group compared to the fasted group (CTAP101-CL-1016).

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 iPTH from baseline and compared to

placebo during 6 weeks of treatment. The mean % decrease in plasma iPTH from baseline in the per-protocol (PP) population was related to the administered dose: -20.9, -32.8, and -39.3 for the 30, 60 and 90 mcg groups, respectively.

The efficacy was confirmed in the phase 3 program with nearly all subjects (97%) treated with CTAP101Capsules who completed the program without a major protocol deviation, achieving a normal serum total 25-hydroxyvitamin D level and with 50% of such subjects achieving a mean reduction in plasma iPTH from baseline of at least 30%. Fewer than 9% of placebo subjects achieved a 30% reduction in plasma 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 investigational study drug.

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

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 three dose levels of CTAP101 ER Capsules versus placebo in raising mean serum total 25-hydroxyvitamin D to ≥50 ng/mL and in reducing mean plasma iPTH by at least 30% from pre-treatment baseline;
2. To investigate the safety and tolerability of repeated dosing with three dose levels of CTAP101 Capsules;
3. To assess the pharmacokinetic (PK) profiles and PK linearity of serum calcifediol after single and repeated doses of CTAP101 Capsules at three dose levels in subjects with SHPT, VDI and CKD who are undergoing HD three times per week (tiw).

2.1.2 Secondary Objectives

The secondary objectives of this study are:

1. To evaluate the efficacy of repeated dosing with three dose levels of CTAP101 ER Capsules versus placebo in raising mean serum total 25-hydroxyvitamin D to ≥50 ng/mL and in reducing mean plasma iPTH by at least 10 and 20% from pre-treatment baseline;
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 at three dose levels;
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 doses of CTAP101 Capsules at three dose levels versus placebo in raising serum total 25-hydroxyvitamin D 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 of CTAP101Capsules at three dose levels versus placebo on mean serum calcium (corrected for albumin), phosphorus, vitamin D binding protein (DBP), total free 25-hydroxyvitamin D, total 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_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]

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

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 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 this protocol. Subjects in Cohort 2 will participate in a randomized, double-blinded, placebo-controlled repeated-dose, dose-ranging safety and efficacy study of CTAP101 Capsules administered at three different dose levels (300, 600 or 900 mcg per week).

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 (subjects only) fashion for 26 weeks: (a) CTAP101 Capsules at 900 mcg per week or (b) matching placebo. Randomization will be accomplished in blocks of four subjects using two computer-generated codes, one for the PK sub-group (n=28) and one for the non-PK sub-group (n=16).

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

In Cohort 2, approximately 480 subjects will be screened to randomize approximately 212 eligible subjects, stratified for severity of SHPT, in a 1:1:1:1 ratio into four groups receiving the following treatments in a double-blinded fashion for 26 weeks: (aa) CTAP101 Capsules at 300 mcg per week, (bb) CTAP101 Capsules at 600 mcg per week, (cc) CTAP101 Capsules at 900 mcg per week or (dd) matching placebo. Randomization will be accomplished in blocks of four subjects using two computer-generated codes, one for the PK sub-group (n=72) and one for the non-PK sub-group (n=140). A subset of subjects will undergo a subsequent 26 weeks of treatment (for a total of 52 weeks) depending on their participation in the PK determinations described below.

An Interactive Response Technology system (IRT) will provide study treatment group assessments for both cohorts (using computer-generated randomization codes provided by the IRT vendor) and dosing adjustments. For Cohort 2 only, an independent, unblinded Data Safety Monitoring Board (DSMB) will be established to oversee the IRT and verify the appropriateness of all dosing adjustments, to monitor subject safety and the effectiveness of CTAP101 Capsules at regular intervals. Specific responsibilities and activities of the DSMB will be defined in the charter ratified at the pre-Cohort 2 organizational meeting. Also, for Cohort 2 only, subjects, dialysis facilities, study personnel and the sponsor will be blinded to the administered treatments

and to plasma iPTH, serum total 25-hydroxyvitamin D and serum calcifediol 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.

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 period prior to baseline assessments. Subjects will undergo a 6-week FU observation period after completing treatment.

On two occasions, a subset of subjects (n=~21) from Cohort 1 who are assigned to treatment with CTAP101 Capsules and, on one or two occasions, a subset of subjects (n=~18) from each of the four treatment groups in Cohort 2 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 (all groups) and repeated dose (active groups) PK profiles of serum calcifediol and associated PD profiles for serum calcium (corrected), phosphorus, DBP, total free 25-hydroxyvitamin D, total 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3. Subjects receiving CTAP101 Capsules will complete a 26-week treatment period between the two PK profile assessments. Subjects in Cohort 2 receiving treatment with placebo will complete a 26-week treatment period after the single-dose PK assessment, and then receive CTAP101 Capsules at a dose of 300, 600 or 900 mcg per week, assigned randomly with stratification by severity of SHPT, during a second 26-week treatment period, after which they will complete a 6-week follow-up period. Blood samples for the first PK profile assessments will be collected at -12, -3, 0, 4, 8, 12, 16, 20, 24, 30, 36 and 42 hours, and on Days 4, 6, 8, 11 and 15 following a single dose (0, 300, 600 or 900 mcg) administered as 6 capsules (CTAP101 and/or placebo) 2 weeks prior to the start of the first 26-week treatment period and, again, after the last administered dose in treatment week 26. Blood samples for the second PK profile assessment will be collected at -12, -3, 0, 4, 8, 12, 16, 20, 24, 30, 36 and 42 hours, and on Days 4, 6, 8, 11 and 15 following the last administered dose in treatment week 26 for subjects receiving dosages of 300 or 600 mcg per week of CTAP101 Capsules, and at -12, -3, 0, 4, 8, 12, 16, 20, 24, 30, 36 and 42 hours, and on Days 4, 6, 8, 11, 15, 22, 29 and 43 following the last administered dose in treatment week 26 for subjects receiving 900 mcg per week of CTAP101 Capsules. On specified and subsequent HD days, blood samples will be collected just before dialysis. Subjects who received treatment with CTAP101 Capsules at 900 mcg per week will terminate further participation in the study after the second PK profile assessment. Subjects who received treatment with CTAP101 at 300 or 600 mcg per week will resume dosing, as before, and complete a second 26-week treatment period and a subsequent 6-week follow-up period.

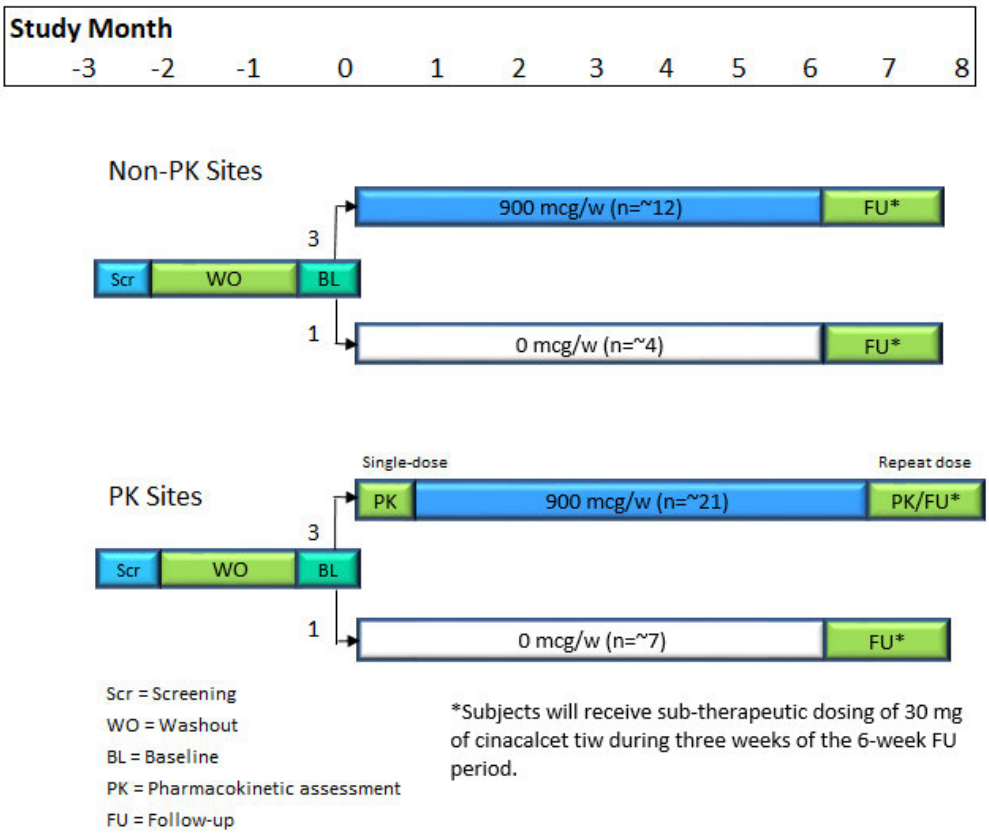
The remaining subjects from each treatment group will forgo all PK assessments and complete 26 or 52 weeks of treatment. Subjects assigned to CTAP101 Capsules will remain on this study drug for the entire period. Subjects assigned to placebo will be treated with placebo for the 26 weeks of treatment and, subsequently, if in Cohort 2, with CTAP101 Capsules at a dose of 300, 600 or 900 mcg per week, assigned randomly with stratification by severity of SHPT, during another 26 weeks of the treatment. All of these subjects will complete a 6-week follow-up period at the end of treatment.

Subjects in Cohort 1 only, 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.

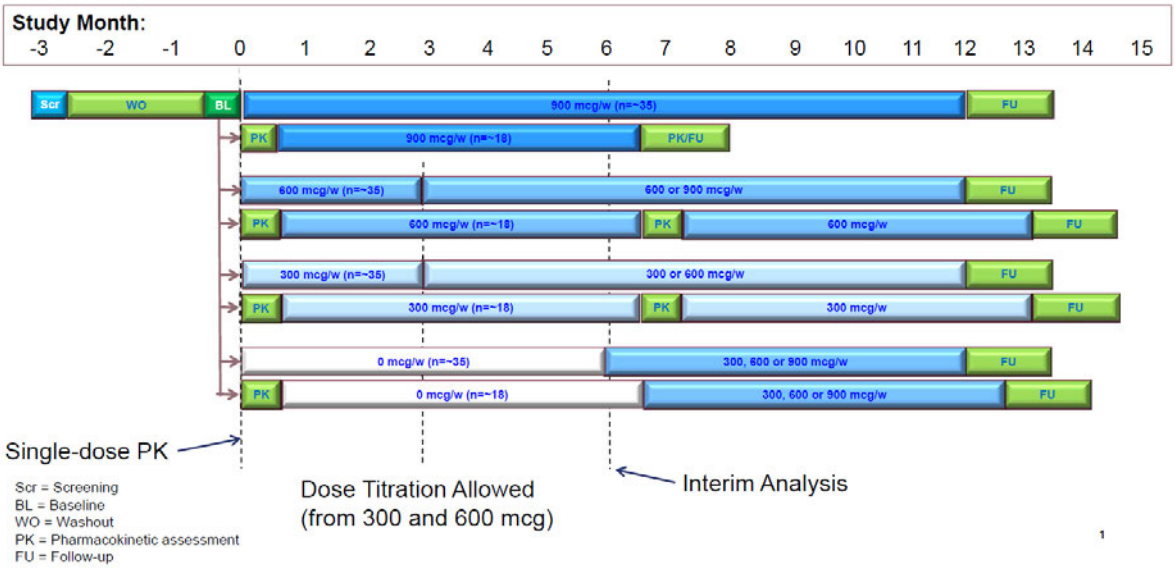
For all subjects, pre-dialysis blood samples will be collected at weekly, biweekly or monthly intervals (see Section 7 Study Activities) during the pre-treatment washout period, the 26- and 52-week treatment periods and the 6-week post-treatment follow-up period. These samples will be collected at the start of either the 2nd or 3rd HD session of the week (Wednesday/Thursday or Friday/Saturday). Key parameters to be analyzed in the collected samples include: [redacted] corrected serum calcium (adjusted for serum albumin), serum phosphorus, serum total 25-hydroxyvitamin D, serum total 1,25-dihydroxyvitamin D, [redacted] serum 1,25-dihydroxyvitamin D_3, and serum 24,25-dihydroxyvitamin D_3. VS and AEs will be monitored at each study visit. Other parameters to be monitored less frequently include brief PEs and clinical laboratory tests (hematology and clinical chemistries). 12-lead ECGs will be obtained at baseline and end of treatment (EOT) only, or at early termination (ET). [redacted]

A diagram of the study design is shown below:

Cohort 1 (randomized, single-blinded design):



Cohort 2 (randomized, double-blinded placebo-controlled design for the first 6 months of the treatment period followed by open-label, non-placebo-controlled design for the second 6 months of the treatment period):



3.2 Rationale for Study Design and Control Group

OPKO is developing CTAP101 Capsules for the treatment of SHPT in patients with VDI and stage 5 CKD requiring regular HD. The active ingredient in CTAP101 Capsules is calcifediol, which is formulated as ER capsules for oral administration. The formulation is designed to raise serum total 25-hydroxyvitamin D in a gradual (physiological) manner. Raising blood levels of 25-hydroxyvitamin D too rapidly produces a surge in 1,25-dihydroxyvitamin D production which increases the expression of CYP24 in both the kidney and in peripheral target tissues and has significant adverse effects on the expression of other key factors associated with bone and mineral metabolism, including FGF23, CYP27B1, calcium and phosphorus [Petkovich et al 2015].

The principal aim of the present study is to:

1) Explore, in Cohort 1, the safety, efficacy, PK and PD of CTAP101 Capsules administered for 26 weeks at a weekly dose of 900 mcg to treat SHPT in subjects aged 18 years or older with VDI and stage 5 CKD receiving regular HD; and, if appropriate (based on a review of the data obtained by the Sponsor and the FDA),
2) Further evaluate, in Cohort 2, the safety, efficacy, PK and PD of CTAP101 Capsules administered for up to 52 weeks.

Cohort 2 of the present study is designed to evaluate the efficacy of CTAP101 Capsules with regard to raising mean serum total 25-hydroxyvitamin D to ≥50 ng/mL and reducing mean plasma iPTH levels by at least 30% from pre-treatment baseline. The study also will examine the safety and tolerability of CTAP101 Capsules. This placebo-controlled study provides the best means to evaluate safety, efficacy and tolerability of CTAP101 Capsules because no therapy has yet been approved to treat elevated plasma iPTH levels associated with low serum total 25-hydroxyvitamin D levels in patients with stage 5 CKD. Single-dose and repeated-dose PK profiles of serum calcifediol and associated PD profiles for serum DBP, total free 25-hydroxyvitamin D, total 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3 will be determined in a subset of subjects in Cohort 2.

The starting dose and dose titration criteria are based on the results from prior repeat-dose, placebo-controlled, double-blind studies with CTAP101 Capsules (30 mcg) in patients with VDI and stage 3-4 CKD. These studies demonstrated that CTAP101 Capsules increased mean serum total 25-hydroxyvitamin D and decreased mean plasma iPTH in a dose-proportional manner. CTAP101 Capsules administered at daily doses of 30, 60 and 90 mcg (or 210, 420 and 630 µg/week) for six weeks produced mean plasma iPTH changes from baseline of -20.9, -32.8 and -39.3%, respectively, and elevated serum total 25-hydroxyvitamin D levels ≥30 ng/mL in almost all subjects (CTAP101-CL-2008). AE rates were comparable across the treatment groups, indicating that therapy with CTAP101 Capsules had no adverse effect on mean serum calcium or phosphorus or on any other monitored parameters during the 6-week treatment period. PK analyses determined that the terminal elimination half-life $t_{1/2}$ after repeat dosing was approximately 30 days but that steady state was not yet achieved after 6 weeks of treatment. Steady state in phase 3 studies was attained after 12 weeks of treatment (CTAP101-CL-3001 and CTAP101-CL-3002). Thus, in the present study (CTAP101-CL-2010), subjects will complete up to 52 weeks of therapy with a tiw dose of CTAP101 Capsules of 300, 600 and 900 mcg/week. Study drug will be reduced or discontinued for confirmed excessive elevations in serum calcium or phosphorus or for confirmed over suppression of plasma iPTH.

The pivotal phase 3 studies (CTAP101-CL-3001 and CTAP101-CL-3002) showed that CTAP101 Capsules suppressed plasma iPTH to the same degree in both stage 3 and stage 4 CKD, a finding which is at odds with conventional wisdom that 25-hydroxyvitamin D is less likely to be converted to 1,25-dihydroxyvitamin D as CKD advances, due to declining expression of CYP27B1 in the failing kidneys. This finding indicates that (a) there is adequate renal CYP27B1 activity in predialysis patients to activate 25-hydroxyvitamin D and/or that (b) 25-hydroxyvitamin D is activated by CYP27B1 expressed outside the kidneys. It is well established that CYP27B1 is expressed and functional in the parathyroid glands and in many other extra-renal tissues [Adams et al 2014], presumably for local hormone production, and that extra-renal expression of CYP27B1 can be stimulated by further cinacalcet therapy [Ritter el al 2012]. Further, it has been demonstrated that serum levels of 1,25-dihydroxyvitamin D rise in response to administered calcifediol in anephric patients [Dusso et al 1990]. It is plausible, therefore, that CTAP101 Capsules raise serum total 25-hydroxyvitamin D to high enough levels to enable sufficient extra-renal 1,25-dihydroxyvitamin D production for PTH control.

3.3 Study Duration

Cohort 1 of the study is expected to be conducted in approximately 14 months from time of initial subject enrollment (first subject consented) to study completion for the last subject (last subject out/last visit complete). Cohort 2 is expected to be conducted in approximately 27 months. Subjects will participate in the study for up to approximately:

- **PK sub-group randomized to CTAP101 Capsules:** 46 weeks (2 weeks screening, 8 weeks washout, 2 weeks baseline, 2 weeks for single-dose PK determination, 26 weeks of treatment with CTAP101 Capsules, and 6 weeks for repeated-dose/steady-state PK determination and follow-up (FU) evaluation from CTAP101 treatment and inclusive of 3 weeks of cinacalcet dosing).
- **PK sub-group randomized to placebo and Non-PK sub-group:** 44 weeks (2 weeks screening, 8 weeks washout, 2 weeks baseline, 26 weeks of treatment with either CTAP101 Capsules or matching placebo, and 6 weeks of follow-up (FU) evaluation from CTAP101/placebo treatment and inclusive of 3 weeks of cinacalcet dosing).
- Subjects who participate in Cohort 1 will not be eligible for participation in Cohort 2.

Subjects will participate in Cohort 2 of the study for up to approximately:

- **PK sub-groups:** 74 weeks (2 weeks screening, 8 weeks washout, if required, 2 weeks baseline, 2 weeks for single-dose PK determination, 26 weeks of treatment with either CTAP101 Capsules or matching placebo, 0-6 weeks for repeated-dose (steady-state) PK determination, 26 weeks of further treatment with CTAP101 Capsules, and 6 weeks of follow-up evaluation); or,
- **Non-PK sub-groups:** 70 weeks (2 weeks screening, 8 weeks washout, if required, 2 weeks baseline, 26 weeks of treatment with either CTAP101 Capsules or matching placebo followed by 26 weeks of treatment with CTAP101 Capsules only, and 6 weeks of follow-up evaluation).

3.4 Study Endpoints

3.4.1 Pharmacokinetic Endpoints

Single-dose and repeated-dose (steady-state) PK determinations will be performed by analyzing serum calcifediol concentrations versus time recorded in both cohorts after (a) a single, initial dose of 0 mcg (placebo) or 300, 600 or 900 mcg (CTAP101 Capsules) and (b) after the last administered dose in the first 26 weeks of treatment in a subset of approximately 21 (Cohort 1) or 18 (Cohort 2) subjects in each active treatment group. The following PK parameters will be calculated using observed and baseline-adjusted serum calcifediol concentrations: AUC, C_{max}, time to maximum concentration (t_{max}), steady-state concentration (C_{ss}), time to steady-state concentration (t_{ss}), terminal elimination half-life ($t_{½}$) in subjects treated with CTAP101 Capsules at a dose of 900 mcg per week), clearance (CL/F), and volume of distribution (Vd/F), as feasible. Relative exposure and dose proportionality will be examined, if possible.

3.4.2 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 PK and PD models will be developed from serum calcifediol data collected from subjects in Cohort 2. PD markers to be considered in the population PD analysis include: plasma iPTH, and serum calcium (corrected), phosphorus, and 1,25-dihydroxyvitamin D_3. The effect of the following covariates will be examined: body weight, age, gender, race, CKD stage, SHPT severity, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics.

3.4.3 Primary Safety Endpoints

The safety and tolerability of CTAP101 Capsules will be evaluated for both cohorts in the intent-to-treat Safety population (defined as all subjects who received at least on dose of study drug) by AEs, physical examinations (PEs), vital signs (VS), hematology and clinical chemistries, and 12-lead electrocardiograms (ECGs).

3.4.4 Efficacy Endpoints

There is no primary efficacy endpoint for Cohort 1, as this part of the study is merely observational. The primary efficacy endpoint for Cohort 2 is the proportion of subjects in the ITT population attaining both a mean serum 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline during the first efficacy assessment period (EAP), defined as the average of values obtained in the last 6 weeks of the first 26-weeks of treatment.

The key secondary efficacy endpoint for Cohort 1 is the proportion of subjects in the intent-to-treat (ITT) population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline, defined in Section 9.10.1, during the EAP, defined as the average of values obtained in the last 6 weeks of the 26 weeks of treatment, calculated for each treatment group and for each final dose group, defined in Section 9.11.

Secondary efficacy endpoints for Cohorts 1 and 2 include the proportion of subjects in the per-protocol (PP) population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline during the first EAP. Additional secondary endpoints include the proportion of subjects in the PP population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 10, 20 or 30% from pre-treatment baseline during the first and/or second EAP, as applicable, the latter being defined as the average of values obtained in the last 6 weeks of the second 26-weeks of treatment; the time courses of mean absolute changes from pre-treatment baseline in serum total 25-hydroxyvitamin D 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, DBP, total free 25-hydroxyvitamin D, total 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_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 lα-hydroxylated vitamin D analogs and/or calcimimetics.

[redacted]

4 STUDY POPULATION SELECTION

4.1 Study Population

The target population for this study is subjects at least 18 years old diagnosed with SHPT, VDI (serum total 25-hydroxyvitamin D <50 ng/mL) and stage 5 CKD requiring regular HD tiw for at least the prior six months. All subjects will be U.S. residents.

For Cohort 1, approximately 100 subjects will be screened to randomize in a 3:1 ratio approximately 44 eligible subjects into two groups receiving the following treatments in a single-blinded (subjects only) fashion for 26 weeks: (a) CTAP101 Capsules at 900 mcg per week or (b) matching placebo. An attempt will be made to enroll 4 Japanese subjects (first, second or third generation in the U.S.). Randomization will be accomplished in blocks of four subjects using two computer-generated codes, one for the PK sub-group (n=28) and one for the non-PK sub-group (n=16). 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 sub-group.

For Cohort 2, approximately 480 subjects will be screened to randomize in a 1:1:1:1 ratio approximately 212 eligible subjects, stratified for severity of SHPT, into four treatment groups receiving the following treatments in a double-blinded fashion for 26 weeks: (aa) CTAP101 Capsules at 300 mcg per week, (bb) CTAP101 Capsules at 600 mcg per week, (cc) CTAP101 Capsules at 900 mcg per week or (dd) matching placebo. Randomization will be accomplished in blocks of four subjects using two computer-generated codes, one for the PK sub-group (n=72) and one for the non-PK sub-group (n=140). In this cohort, approximately half of the subjects will have baseline plasma iPTH values in the range of ≥300 to <600 pg/mL, and approximately half will have values in the range of ≥600 to <900 pg/mL.

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled into the two cohorts of this study:

1. Be at least 18 years of age.
2. Be diagnosed with CKD requiring in-center HD tiw for the preceding 6 months, as confirmed by medical history.
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; and,
   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.
4. Be receiving calcimimetic therapy (either etelcalcetide or cinacalcet) and/or calcitriol or other 1α-hydroxylated vitamin D analog (paricalcitol or doxercalciferol) for at least 1 month at the time of screening for enrollment in Cohort 1. Approximately 50% of enrolled subjects will have been receiving calcimimetic therapy.
5. Exhibit during the initial screening visit:

a. Plasma iPTH ≥150 pg/mL and <600 pg/mL if receiving etelcalcetide, cinacalcet, calcitriol or other 1α-hydroxylated vitamin D analog (paricalcitol or doxercalciferol); or
b. Plasma iPTH ≥300 pg/mL and <900 pg/mL if not receiving etelcalcetide, cinacalcet, calcitriol or other 1α-hydroxylated vitamin D analog; and,
c. Serum total 25-hydroxyvitamin D <50 ng/mL if not receiving vitamin D supplementation.

6. When otherwise confirmed eligible at Visit 1, must forgo any further treatment with etelcalcetide and cinacalcet for the duration of the study and undergo an 8-week washout period.
7. When otherwise confirmed eligible at Visit 1, must forgo any further treatment with calcitriol or other 1α-hydroxylated vitamin D analogs or vitamin D supplements for the duration of the study and undergo an 8-week washout period.
8. Exhibit after the 8-week washout period (if required due to prior use of etelcalcetide, cinacalcet, calcitriol or other 1α-hydroxylated vitamin D analogs, or vitamin D supplementation):

   Cohort 1:

   a. Plasma iPTH increased by at least 50%; and,
   b. Plasma iPTH ≥300 pg/mL and <1,200 pg/mL; or,

   Cohort 2:

   f. Plasma iPTH ≥300 pg/mL and <1,200 pg/mL (approximately half of the subjects will be enrolled in each of these two plasma iPTH strata: ≥300 to <600 and ≥600 to <1,200 pg/mL); and

   Cohorts 1 and 2:

   c. Corrected serum calcium <9.8 mg/dL;
   d. Serum total 25-hydroxyvitamin D <50 ng/mL; and,
   e. Serum phosphorus <6.5 mg/dL.

9. When otherwise confirmed eligible at Visit 1, if taking more than 1,000 mg per day of elemental calcium, reduce calcium use (to ≤1,000 mg per day) and/or use non-calcium based phosphate binder therapies (as needed) for the duration of the study.
10. When otherwise confirmed eligible at Visit 1, if taking bone metabolism therapies that may interfere with study endpoints, must discontinue use of these agents for the duration of the study.
11. Willing and able to comply with study instructions and commit to all clinic visits for the duration of the study.
12. Female subjects of childbearing potential must be neither pregnant nor lactating and must have a negative serum beta-human chorionic gonadotropin (b-hCG) pregnancy test at the first screening visit and at other scheduled times.
13. 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.

14. Be able to read, understand and sign the subject Informed Consent Form (ICF) or have a legal representative sign the ICF.

4.3 Exclusion Criteria

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

1. Scheduled kidney transplant or parathyroidectomy.
2. History (prior 2 months) of corrected serum calcium ≥9.8 mg/dL or serum phosphorus ≥6.5 mg/dL if not receiving calcitriol or other 1α-hydroxylated vitamin D analog.
3. Receipt of bisphosphonate therapy or other bone modifying treatment (eg, denosumab) within 6 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, intestinal malabsorption disorder, hepatitis or cardiovascular event that in the opinion of the investigator may worsen or reduce life expectancy, and/or interfere with participation in the study.
5. History of neurological/psychiatric disorder, including psychotic disorder or dementia, or any reason which, in the opinion of the investigator makes adherence to a treatment or follow-up schedule unlikely.
6. Known or suspected hypersensitivity to any of the constituents of the study drugs.
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 CTAP101 Capsules

Dosage form:	Soft gel capsule
Dose strength:	150 mcg calcifediol ER capsule
Product description:	Blue oval capsules printed single-sided, centered with the logo O in white. Each bottle contains 30 capsules.
Active component:	Calcifediol
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) and ink (white, which may contain titanium dioxide, isopropyl alcohol, propylene glycol, hydroxypropylmethyl cellulose 2910)
Storage conditions:	25°C (77°F); excursions allowed to 15°C to 30°C (59°F to 86°F); protect from light and heat.

5.2 Description of Placebo Capsules

Dosage form:	Soft gel capsule
Dose strength:	0 mcg calcifediol ER capsule
Product description:	Blue oval capsules printed single-sided, centered with the logo O in white. Each bottle contains 30 capsules.
Active component:	None
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) and ink (white, which may contain titanium dioxide, isopropyl alcohol, propylene glycol, hydroxypropylmethyl cellulose 2910)
Storage conditions:	25°C (77°F); excursions allowed to 15°C to 30°C (59°F to 86°F); protect from light and heat

5.3 Description of Cinacalcet

Dosage form:	Film-coated tablet
Dose strength:	30 mg cinacalcet tablet
Product description:	Light-green, film-coated, oval-shaped biconvex tablets marked with “CL” on one side and “410” on the opposite side. Each bottle

	contains 30 tablets, or an equivalent, U.S approved generic alternate source.
Active component:	cinacalcet hydrochloride
Non-active components:	microcrystalline cellulose, corn starch, povidone K30, isopropyl alcohol, magnesium stearate, crospovidone, lactose monohydrate, titanium dioxide, triacetin, FD&C blue #2, ferric oxide yellow, and hypromellose 2910.
Storage conditions:	25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F). (See USP controlled room temperature)

For product information, refer to Appendix 2.

5.4 Treatments Administered

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 (see Table 1 below). 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. After 12 weeks of treatment, subjects in Cohort 2 who are receiving 300 or 600 mcg per week of CTAP101 Capsules and who are not participating in PK determinations will undergo upward dose titration provided that (a) the plasma iPTH has not decreased by at least 30% from pretreatment baseline and remains >300 pg/mL, (b) corrected serum calcium is <9.8 mg/dL, and (c) serum phosphorus is <6.0 mg/dL. Subjects in Cohorts 1 or 2 who are receiving 900 mcg per week of CTAP101 Capsules or placebo, or are participating in PK assessments, will not undergo upward dose titration at any time. Upward dose titration will occur in a single increment of 300 mcg (two CTAP101 Capsules). After 26 weeks of treatment, subjects in Cohort 2 who were assigned to placebo will commence treatment with 300, 600 or 900 mcg of CTAP101 Capsules, assigned randomly with stratification by severity of SHPT.

Subjects in Cohort 1 only, 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 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.

Table 1 Initial Weekly Dosing Schedule for Study Drugs

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

5.5 Dose Reduction Criteria

Subjects will reduce the dose at any time 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, provided that that the investigator has deemed the elevated serum phosphorus to be related to study drug administration and has previously taken appropriate and persistent actions to control serum phosphorus by initiating or adjusting phosphate binder therapy. A new dose reduction should not occur within a month of a previous dose reduction. In the event that a dose reduction is required for a subject receiving the minimum dosage of 300 mcg per week, the subject will suspend dosing and resume when plasma iPTH is ≥150 pg/mL and corrected serum calcium is <9.8 mg/dL at the minimum dosage of 300 mcg per week.

Subjects assigned to treatment with CTAP101 Capsules will suspend dosing if plasma iPTH is confirmed to be <100 pg/mL or corrected serum calcium is confirmed to be >11.0 mg/dL, and will resume when plasma iPTH is ≥150 pg/mL and corrected serum calcium is <9.8 mg/dL at a dose that has been reduced by 300 mcg per week or at the minimum dosage of 300 mcg per week.

After 12 weeks of treatment, subjects who have experienced more than a 100% increase in plasma iPTH from pre-treatment baseline or whose plasma iPTH has increased above 1,200 pg/mL on consecutive visits (if at least 2 weeks apart) will terminate dosing with study drugs and further participation in the treatment period and immediately enter the 6-week post-treatment follow-up period. Such subjects may be immediately removed from the study and placed on standard of care therapy, at the discretion of the Investigator.

Subjects who have received cinacalcet (30 mg tiw at the end of HD) during 3 weeks of the 6-week FU observation period (Study Weeks 27-29 for non-PK active and placebo and PK placebo subjects and Study Weeks 29-31 for PK active subjects) who have a serum calcium <7.5 mg/dL or a plasma iPTH <150 pg/mL should discontinue cinacalcet immediately. The investigator should continue to monitor and evaluate these laboratory values until values have stabilized and follow the standard of care.

5.5.1 Overdose and Toxicity

Excessive administration of calcifediol can cause hypercalcemia, hyperphosphatemia, or over suppression of intact PTH. Common symptoms of vitamin D overdosage may include constipation, decreased appetite, dehydration, fatigue, irritability, muscle weakness, or vomiting. Treatment of acute accidental overdosage with calcifediol should consist of general supportive measures. If the overdosage is discovered within a short time, induce emesis or perform gastric lavage to prevent further absorption. Obtain serial serum calcium measurements and assess any electrocardiographic abnormalities due to hypercalcemia. Discontinue supplemental calcium. Treat with standard medical care if persistent and markedly elevated serum calcium levels occur.

5.6 Method of Assigning Subjects to Treatment Groups

After signing the 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 cohort (one for the PK sub-group and one for the non-PK sub-groups) provided by the IRT vendor. 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 (see Section 4.1 Study Population), they will be randomized within in the same block to treatment arms in the PK sub-group. 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.

5.7 Prior and Concomitant Therapy

Subjects should not take any vitamin D and/or bone metabolism therapy other than the study drug. Excluded therapies include 1α-hydroxylated vitamin D analogs (calcitriol, paricalcitol and doxercalciferol), calcimimetics, bisphosphonates, denosumab, teriparatide, preotact, calcitonin and other drugs that may affect bone metabolism. Glucocorticoids and hormone replacement therapy should remain at the same dose throughout the study.

All medication usage from 12 weeks prior to Visit 1, during study and until completion of the study will be recorded.

Cytochrome P450 inhibitors, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole, may inhibit enzymes involved in vitamin D metabolism (CYP24A1 and CYP27B1), and may alter serum levels of calcifediol. Dose adjustment of CTAP101 Capsules may be required if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor.

Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins and may impair the absorption of calcifediol, the active ingredient in CTAP101 Capsules. Dose adjustment of CTAP101 Capsules may be required if a patient initiates or discontinues therapy with cholestyramine.

Phenobarbital and other anticonvulsants or other compounds that stimulate microsomal hydroxylation reduce the half-life of calcifediol. Dose adjustment of CTAP101 Capsules if a patient initiates or discontinues therapy with phenobarbital or other anticonvulsants.

5.7.1 Phosphate Binder and Elemental Calcium Therapy

Use of calcium-based phosphate binders or antacid therapies such as calcium carbonate or calcium acetate are allowed up to 1000 mg per day of elemental calcium. Non calcium-based phosphate binder therapy such as sevelamer HCL or lanthanum carbonate and non-calcium-based antacids can be used at the discretion of the investigator. Any changes in phosphate binder therapy should be captured in the electronic case report form (eCRF).

5.7.2 Dialysate Calcium Concentration

The dialysate calcium concentration should remain unchanged throughout the study. Any changes in dialysate calcium concentration will be captured in the eCRF.

5.7.3 Diet 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.

Subjects who participate in PK determinations will receive standardized meals while housed in the phase 1 unit. These meals will be administered at approximately 12 hours prior to dosing and 5, 10, 23, 28 and 33 hours post-dose.

5.7.4 Subject Activity Restrictions

Subjects should maintain their usual pattern of sun exposures and activities.

5.8 Treatment Compliance

Study treatment compliance will be assessed at all specified visits. The Investigator, or assigned designee will perform drug accountability and dosing compliance calculations for all study drugs (number of capsules that should have been taken versus actual number taken as evidenced by written dosing records and the number of capsules remaining in bottles of study drug assigned to each subject). Dosing compliance at <80% or >120% should be reported as a major protocol deviation.

5.9 Packaging and Labeling

CTAP101 Capsules and matching placebo capsules will be provided in white, round, wide-mouth, high-density polyethylene (HDPE) bottles with aluminum heat-induction safety seals with white, polypropylene, child-resistant (push down and turn) caps, 30 capsules per bottle.

For Cohort 1 cinacalcet dosing in FU period of study, cinacalcet will be provided in bottles, 30 tablets per bottle.

All study drug labels will include the protocol number, sponsor identification and address, bottle contents, bottle number, area for subject and investigator identification as applicable, investigational use statements, storage conditions and instructions for use.

5.10 Storage and Accountability

CTAP101 Capsules, matching placebo capsules and cinacalcet will be shipped to sites using standardized shipment and temperature monitoring procedures. While at the study site, study drugs will be stored at controlled room temperature (25°C or 77°F) with excursions allowed to 15°C to 30°C (59°F to 86°F), and protected from light and heat per label instructions 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. Accountability for all study drugs, 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 throughout the course of the study. Specifically, the investigator or assigned designee will confirm that 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 by site, to whom and amount dispensed\returned and accounts of any drug accidentally destroyed, or not returned, or lost. The site's overall inventory of study drug supplies will be verified routinely throughout the course of the study. All opened and unopened bottles of study drug capsules are to be retained at the site until the sponsor or designee has performed a complete accountability, following which study drug will be returned to the sponsor or designee.

5.11 Investigational Product Retention at Study Site

At the conclusion of the study, a final accountability of all study IP 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 return records must be maintained by the investigator.

6 STUDY PROCEDURES

6.1 Informed Consent

A signed ICF will be obtained prior to any study related procedures. The subject or their legally authorized representative (LAR) 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 LAR 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 or the subject's willingness to participate in the study, the subject or LAR 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 and/or their LAR, and answer all questions regarding this study, prior to obtaining informed consent.

The process for obtaining consent will be in accordance with all applicable regulatory requirements. The subject or his/her LAR 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 is 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 or patient information 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/Ethics Committee (IRB/EC) and use of the amended form (including ongoing subjects).

6.2 Medical History and Concomitant Medications

A detailed medical history, including demographics and concomitant medications, will be recorded at Visit 1/Screening.

6.3 Physical Examination, Vital Signs and Electrocardiogram

VS and PE will be performed by a licensed physician or by another suitably-qualified person where permitted by local regulations. Evaluations are presented in Table 2.

Table 2 Evaluations

Physical Examination:	PE including BMI determination and excluding a urogenital examination at the following visits: o Cohort 1: Visits 1, 24, 32 or ET; o Cohort 2: Visits 1, 26 and 35 or 43 or ET.
Vital Sign measurements:	Blood pressure and heart rate will be measured and recorded before dialysis after the subject has been sitting for at least 2 minutes prior to any scheduled blood draws at every study visit. As part of standard of care, blood pressure will also be monitored during dialysis. Symptomatic episodes of hypotension will be recorded. Subjects assigned to single dose or repeated dose PK assessments will have their vital signs assessed throughout their stay in the phase 1 unit.
12-Lead Electrocardiogram (ECG)	Each 12-lead ECG will be started after the subject has been in recumbent position for at least 5 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. Interval measures and rhythm will also be reported. 12-lead ECG will be performed at the following visits: o Cohort 1: Visits 3, 24 or ET; o Cohort 2: Visits 3, 26, and 35 or 43 or ET. For consistency of ECG data, every effort will be made to utilize the same facility and reader for all ECGs at each site.
Body height	Body height will be recorded in centimeters to the nearest 1.0 cm during every scheduled PE.
Body weight:	Body weight will be recorded in kilograms to the nearest 0.1 kg during every scheduled PE.
Other Assessments:	[redacted]: o Cohort 1: Visits 3, 24 or ET; o Cohort 2: Visits 3, 26 and 35 or 43 or ET.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

Blood will be drawn before dialysis and analyzed as specified in Table 3. [redacted]

All serum calcium values will be adjusted based on serum albumin level of <4.0 g/dL.

All clinically significant abnormal laboratory values should be recorded as AEs and the investigator will follow-up according to Section 6.6.6 Clinical Significance.

Please refer to Appendix 1 Schedule of Events for specific time points.

Subjects will be in a seated or supine position during blood collection. Clinical laboratory tests are listed in Table 3.

Table 3 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 child bearing 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
- Plasma iPTH (blinded*)
- Serum total 25-hydroxyvitamin D (blinded*)
- Serum calcifediol (blinded*)
- Serum 24,25-dihydroxyvitamin D_3
- [redacted]
- Vitamin D binding protein (DBP)
- [redacted]

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

[redacted]

6.4.2 Sample Collection, Storage, and Shipping

Missed blood samples should not be redrawn or recollected (unless the investigator considers the sample necessary for subject safety) and should be noted as "not done" in source documentation along with a reason.

A central laboratory experienced in clinical research trials 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.

[redacted] In Cohort 1, up to approximately 230 mL of blood will be drawn from each subject who is assigned to treatment with placebo or is assigned to treatment with CTAP101 Capsules in one of the non-PK sites, and up to approximately 691 mL will be drawn from each subject who is assigned to treatment with CTAP101 Capsules in one of the PK sites. These amounts of blood will be drawn in increments over a period of approximately 44-46 weeks. In Cohort 2, up to 382 mL of blood will be drawn from each subject who does not participate in the PK assessments, and up to 775 mL will be drawn from each subject who does participate in the PK assessments, over approximately 70-74 weeks. Additional blood draws may be needed for unscheduled or repeat visits. Every effort has been made to minimize the total amount of blood to be drawn.

Samples are to be shipped to the central laboratory for each subject as visits are completed.

6.4.3 Clinical Supplies

The sponsor or their assigned designee will supply vacutainers, blood collection tubes, needles, pipettes, 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

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 eCRF.

All subjects in Cohorts 1 and 2 will be blinded to CTAP101 Capsule and placebo treatment group assignments and to plasma iPTH, serum total 25-hydroxyvitamin D, and serum calcifediol data until the last subject completes 26 weeks of treatment and the data have been locked. For Cohort 1 cinacalcet dosing in the FU period of study only, subjects, dialysis study personnel and sponsor (and its' designee) will be unblinded to this treatment.

For Cohort 2 only, dialysis staff, study personnel and the sponsor (and its' designees) will be blinded to treatment group assignments and to plasma iPTH, serum total 25-hydroxyvitamin D, and serum calcifediol data until after the last subject has completed 26 weeks of treatment and the data have been locked, or until a decision has been made to break the blind (eg, as a result of an emergent event).

For Cohort 2 only, an independent, unblinded DSMB will be established to oversee the IRT and verify the appropriateness of all dosing adjustments, to monitor subject safety and the effectiveness of CTAP101 Capsules at regular intervals. Specific responsibilities and activities of the DSMB will be defined in the charter ratified at the pre-Cohort 2 organizational meeting.

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 the investigational study drug, 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 will be 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 description of the event (event term), date of onset, date of resolution, investigator-specified assessment of severity and relationship to the investigational study drug, 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, x-ray or ECG findings) or symptoms should NOT be recorded as

additional AEs. If a diagnosis is unknown, then sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory values, [redacted] assessments or ECGs 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, [redacted] 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 pre-existing 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 (including thought processes around the reason for the elective procedure) 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) by submitting the Pregnancy Reporting Form to [redacted] Pharmacovigilance:

Fax: [redacted]

E-mail: s[redacted]

Pregnancies will be considered 'events of special interest' and will not be captured as serious adverse events (SAEs). Investigators should follow specific procedures for reporting them to [redacted] Pharmacovigilance. 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 per Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

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 the investigational 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 classifications and criteria outlined in Table 4.

Table 4 Adverse Event Relationship Criteria

Relationship	Criteria
Not related	• The temporal sequence of the AE onset relative to administration of the investigational product is not reasonable. • Disease or other drugs provide plausible explanations. • Dechallenge (if performed) is negative or ambiguous.
Unlikely related	• The temporal sequence of the AE onset relative to the administration of the investigational product is reasonable. • Could also be explained by disease or other drugs. • Dechallenge (if performed) is positive or uncertain. • Rechallenge is negative.
Possibly related	• The temporal sequence of the AE onset relative to administration of the investigational product is reasonable. • Unlikely to be attributed to disease or other drugs. • Dechallenge (if performed) is positive.
Related	• The temporal sequence of the AE onset relative to administration of the investigational product is reasonable. • Cannot be explained by disease or other drugs. • Dechallenge (if performed) is positive and pharmacologically/ pathologically plausible. • Rechallenge (if feasible) is positive. • The AE shows a pattern consistent with previous knowledge of the investigational product or product class, i.e., pharmacologically or phenomenologically recognized/plausible or an objective and specific medical disorder.

6.6.6 Clinical Significance

Changes in laboratory values, [redacted], vital signs, ECG findings 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 considered clinically significant unless the investigator indicates not clinically significant directly on the laboratory paperwork or source documentation.

6.6.7 Serious Adverse Events

6.6.7.1 Definition

An SAE 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.

Hospitalizations to conduct diagnostic procedures will be captured separately from AEs in the eCRF.

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.

6.6.7.2 Expectedness

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.

6.6.7.3 Reporting Serious Adverse Events

Any AE considered serious (see Section 6.6.7 Serious Adverse Events) by the investigator that meets the previously mentioned criteria must be reported to [redacted] Pharmacovigilance at the following number within 24 hours from the time when site personnel first learn about the event.

SAFETY REPORTING Contact: [redacted] Pharmacovigilance

Fax: [redacted]

E-mail: [redacted]

A written report should be provided consisting of the SAE Form and other necessary source documents. 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 update the SAE Form and eCRFs and provide any additional documentation to [redacted] Pharmacovigilance immediately or within 1 working day of receipt.

The sponsor or designee will notify the appropriate regulatory agencies of any serious and unexpected SAEs associated with the use of the investigational study drug according to

regulations. Copies of any reports to regulatory agencies regarding serious and unexpected SAEs will be provided to the investigators by the sponsor or designee for review and submission to the IRB/EC.

If using a local IRB/EC, the investigator is responsible for informing his or her IRB/EC per its requirements of any SAEs at that site. Copies of SAE correspondence with the IRB/EC, regulatory authorities, and other physicians must be provided to the Study Contact.

A subject experiencing one or more SAEs will receive treatment and follow-up evaluations by the investigator, or they will be referred to another appropriate physician for treatment and follow-up. 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 investigational study drug administration and subsequently all events will be closed.

6.6.8 Treatment-Emergent Adverse Events

A 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.

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 on a separate page 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 (e.g., failure to record at least one baseline value for serum total 25-hydroxyvitamin D and for plasma iPTH);
- A serious or intolerable AE occurs;
- A clinically significant change in a laboratory parameter occurs;
- The sponsor or investigator terminates the study;
- 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 becomes pregnant;
- A subject experiences more than a 100% increase in plasma iPTH after 12 weeks of treatment from pre-treatment baseline; or
- A subject exhibits plasma iPTH above 1,200 pg/mL on consecutive visits (if at least 2 weeks apart) after 12 weeks of treatment.
- Dosing with cinacalcet will be discontinued if a subject has a serum calcium of <7.5 mg/dL or a plasma iPTH <150 pg/mL..

Subjects who are withdrawn from the study prematurely for any reason, should have the noted assessments completed for the Early Termination Visit. No subject replacement is planned.

6.9 Appropriateness of Measurements

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 analyzing AEs, serum calcium and phosphorus.

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 summarizing the effect of CTAP101 Capsules to lower elevated iPTH levels and to normalize vitamin D levels. Pre and post-dose averages will be used to minimize the effect of any intrasubject and interassay variability.

7 STUDY ACTIVITIES

7.1 Cohort 1

7.1.1 Non-PK Sites

Note: Any subject who terminates participation in the study prematurely will complete the procedures listed under Visit 24 (Day 183) at the ET Visit.

7.1.1.1 Screening and Baseline Periods

Subjects will not discontinue any medications or adjust any medications as noted in the inclusion criteria until they are confirmed as eligible (including confirmation of clinical laboratory parameters) to begin the washout period. If subject is found to be a screen failure after Visit 1, the subject may be rescreened one additional time.

7.1.1.1.1 Visit 1 (Days -83 to -69)

- A signed ICF will be obtained from the subjects prior to any study-related procedures
- Review of inclusion/exclusion criteria
- Medical history and demographics
- Review of prior medications
- AE assessment
- PE (including weight, height and BMI)
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following:
  - Clinical chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D

7.1.1.1.2 Washout Period (Days -68 to -14)

7.1.1.1.3 Visit 2 (Days -13 to -7)

- Must be within ±3 days of scheduled visit
- Review of inclusion/exclusion criteria
- Review of concomitant medications
- AE assessment
- VS Assessment
- Blood samples will be drawn for the following:
  - Clinical chemistry (full panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3

7.1.1.2 Treatment Period (26 weeks)

- Study drug (CTAP101 Capsules or placebo) is administered tiw at each HD session throughout the Treatment Period beginning with Visit 3 (Day 1) and continuing through Day 181. No study drug will be administered at Visit 24 (Day 183) or on later study Visits/Days.

7.1.1.2.1 Visit 3 (Day 1)

- Must be within ±3 days of scheduled visit
- Review of inclusion/exclusion criteria
- Subjects randomized to treatment with active or placebo drug product
- Review of concomitant medications
- AE assessment
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- 12-Lead ECG
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3
- [redacted]
- Subjects will receive initial dose of study drug during HD and will continue thrice weekly dosing during each successive HD session through Day 181.

7.1.1.2.2 Visit 4

- All subjects skip Visit 4.

7.1.1.2.3 Visits 5 and 6 (Days 4 and 6)

- No study procedures are scheduled on Visits 5 and 6.

7.1.1.2.4 Visits 7-9

- All subjects skip Visits 7-9.

7.1.1.2.5 Visits 10-16 (Days 8-71)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)

- Plasma iPTH and serum total 25-hydroxyvitamin D

7.1.1.2.6 Visit 17 (Day 85)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3

7.1.1.2.7 Visits 18-23 (Days 99-169)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D
- Note: The last dose of study drug will be administered on Day 181.

7.1.1.2.8 Visit 24 (Day 183) or Early Termination (ET)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- PE (including height, weight and BMI)
- VS assessment
- 12-Lead ECG
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted] 1,25-dihydroxyvitamin D_3 and 24,25-dihydroxyvitamin D_3

- [redacted]
- Subjects will not receive study drug (CTAP101 Capsules or placebo) during this visit or any later visits.

7.1.1.3 Follow-up Period

Study drug (cinacalcet) is administered at a sub-therapeutic dose of 30 mg tiw at the end each HD session to all subjects, previously treated with CTAP101 Capsules/placebo study drug, during 3 weeks of the 6-week FU observation period (Weeks 27-29), specifically beginning with Week 27 (Day 190) and continuing through Week (Day 209) for non-PK active and placebo subjects. Subjects must have a serum calcium of ≥8.6 mg/dL and a plasma iPTH of ≥300 pg/mL prior to beginning cinacalcet dosing. No cinacalcet will be administered at Visit 31 (Day 211) or any subsequent days for non-PK active and and PK placebo subjects. Subjects will proceed with FU period schedule and activities listed below.

7.1.1.3.1 Visit 25

- All subjects skip Visit 25.

7.1.1.3.2 Visits 26-29 (Days 186-193)

- No study procedures are scheduled for Visits 26-29.

7.1.1.3.3 Visits 30-31 (Days 197-211)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D

  Placebo and active subjects will receive cinacalcet on Day 209, but will not receive cinacalcet during Visit 31 (Day 211).

7.1.1.3.4 Visit 32 (Day 225)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- PE (including height, weight and BMI)
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)

- Blood samples drawn for:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D

- No active or placebo subject will receive cinacalcet during this visit.
- Subjects terminate further participation in the study.

7.1.2 PK Sites

7.1.2.1 Screening and Baseline Periods

Subjects will not discontinue any medications or adjust any medications as noted in the inclusion criteria until they are confirmed as eligible (including confirmation of clinical laboratory parameters) to begin the washout period. If subject is found to be a screen failure after Visit 1, the subject may be rescreened one additional time.

Note: Any subject who terminates participation in the study prematurely will complete the procedures listed under Visit 24 (Day 183 for subjects randomized to placebo; Day 197 for subjects randomized to active) at the ET Visit.

7.1.2.1.1 Visit 1 (Days -83 to -69)

- A signed ICF will be obtained from the subjects prior to any study-related procedures
- Review of inclusion/exclusion criteria
- Medical history and demographics
- Review of prior medications
- AE assessment
- PE (including weight, height and BMI)
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following:
  - Clinical chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D

7.1.2.1.2 Washout Period (Days -68 to -14)

7.1.2.1.3 Visit 2 (Days -13 to -7)

- Must be within ±3 days of scheduled visit
- Review of inclusion/exclusion criteria
- Review of concomitant medications
- AE assessment
- VS Assessment
- Blood samples will be drawn for the following:

- Clinical chemistry (full panel)
- Plasma iPTH and serum total 25-hydroxyvitamin D

7.1.2.2 Treatment Period (26 weeks)

Placebo study drug is administered tiw at each HD session throughout the Treatment Period beginning with Visit 3 (Day 1) and continuing through Day 181. No study drug will be administered at Visit 24 (Day 183) or on later study Visits/Days.

Active study drug is administered for single-dose PK assessments at t=0 on Visit 4 (Day 2), tiw at each HD session throughout the Treatment Period beginning with Visit 9 (Day 15) and continuing through Day 195, and for repeat-dose PK assessments at t=0 on Visit 25 (Day 198). No study drug will be administered at Visit 26 (Day 200) or on later study Visits/Days.

7.1.2.2.1 Visit 3 (Day 1)

- Review of inclusion/exclusion criteria
- Subjects randomized to treatment with active or placebo drug product
- Review of concomitant medications
- AE assessment
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- 12-Lead ECG
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- [redacted]
- Subjects randomized to placebo will:
  - Receive initial dose of study drug during HD.
  - Receive additional doses of study drug at every subsequent HD until Visit 24.
  - Will skip Visits 4-9 and complete Visit 10 one week later.
- Subjects randomized to active study drug will:
  - Receive no study drug or food in the hemodialysis clinic.
- Be transported to/admitted into a nearby phase 1 unit (for 3 successive nights).
  - Receive a standardized dinner.
  - Review of concomitant medications
  - AE assessment
  - VS assessment

- Provide blood samples at t=~-12 hours for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Receive no further food after dinner and remain in the phase 1 unit overnight.

7.1.2.2.2 Single-dose PK Assessment (Only Subjects Randomized to Active Drug)

7.1.2.2.2.1 Visit 4 (Days 2-3)

- Subjects assigned to placebo treatment will skip this visit.
- AE assessment (once per day)
- VS assessment (3 times per day)
- Fasting blood samples will be drawn from subjects housed in the phase 1 unit at t=~-3 hours, and t=0 hours and precisely (plus or minus 5 minutes, with exact time noted) at t=4, 8, 12, 16, 20, 24, 30, 36 and 42 hours post-dose for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects take first dose of study drug (900 mcg given as 6 CTAP101 Capsules of 150 mcg strength) with a sufficient quantity of a non-alcoholic beverage to enable swallowing of the capsules immediately after the t=0 blood draw, with the exact time of dosing noted.
- Standardized meals will be administered at approximately t=5 hours (lunch), 10 hours (dinner), 23 hours (breakfast), 28 hours (lunch) and 33 hours (dinner) post-dose.
- Subjects will remain in the phase 1 unit for a second and third night.

7.1.2.2.2.2 Visit 5 (Day 4)

- No study procedures are scheduled at this visit for subjects assigned to placebo treatment.
- Subjects will receive a standardized meal (breakfast) in the phase 1 unit at approximately t=47 hours post-dose.
- AE assessment
- VS assessment
- Blood samples will be drawn precisely at t=48 hours for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects will be discharged from the phase 1 unit and transported to the clinic for the regularly scheduled HD session.

- Once at the dialysis clinic and prior to HD session:
  - Review of concomitant medications
  - AE assessment
  - VS assessment

7.1.2.2.2.3 Visits 6-8 (Days 6-11)

- No study procedures are scheduled at Visit 6 for subjects assigned to placebo treatment.
- Subjects assigned to placebo treatment will skip Visits 7-8.
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn (with exact time noted) for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total free 25-hydroxyvitamin D, [redacted], and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

7.1.2.2.2.4 Visit 9 (Day 15)

- Subjects assigned to placebo treatment will skip this visit.
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn (with the time noted) for the following analyses:
  - Chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects receive initial thrice weekly dose of study drug during HD
- Subjects will receive additional doses of study drug at every subsequent HD until Visit 24.

7.1.2.2.3 Visits 10-16 (Days 8-71 for subjects randomized to placebo; Days 22-85 for subjects randomized to active)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)

- Plasma iPTH and serum total 25-hydroxyvitamin D

7.1.2.2.4 Visit 17 (Day 85 for subjects randomized to placebo; Day 99 for subjects randomized to active)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], total free 25-hydroxyvitamin D, [redacted], and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

7.1.2.2.5 Visits 18-23 (Days 99-169 for subjects randomized to placebo; Days 113-183 for subjects randomized to active)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D

7.1.2.2.6 Visit 24 (Day 183 for subjects randomized to placebo; Day 197 for subjects randomized to active) or Early Termination (ET)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- PE (including height, weight and BMI)
- VS assessment
- 12-Lead ECG
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D

- [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
- Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

- [redacted]

[Note: the remaining instructions for this Visit do not apply to an Early Termination Visit.]

- Subjects randomized to placebo will:
  - Not receive a dose of study drug (CTAP101 placebo) during this HD session and will stop all further dosing with study drug.
  - Skip Visits 25-29 and complete Visit 30 two weeks later.
- Subjects randomized to active study drug will:
  - Receive no study drug (CTAP101 Capsules) or food in the HD clinic
  - Be transported to/admitted into a nearby phase 1 unit (for 3 successive nights)
  - Review of concomitant medication
  - AE assessment
  - VS assessment
  - Receive a standardized dinner.
  - Provide blood samples at t=~-12 hours for the following analyses:
    - Chemistry (partial panel)
    - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
    - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
  - Receive no further food after dinner and remain in the phase 1 unit overnight.

7.1.2.3 Follow-up Period

Note: No study procedures are scheduled on Visits 25-29 (Days 184-193) for subjects assigned to placebo treatment.

Study drug (cinacalcet) is administered at a sub-therapeutic dose of 30 mg tiw at the end each HD session to all subjects, previously treated with CTAP101 Capsules/placebo study drug, during 3 weeks of their respective 6-week FU observation periods, specifically beginning with Week 27 (Day 190) and continuing through Week 29 (Day 209) for PK placebo subjects or beginning with Week 29 (Day 204) and continuing through Week 31 (Day 223) for PK active subjects. Subjects must have a serum calcium of ≥8.6 mg/dL and a plasma iPTH of ≥300 pg/mL prior to beginning cinacalcet dosing. No cinacalcet will be administered at Visit 31 (Day 211) or any subsequent days for PK placebo subjects or Visit 32 (Day 225) for PK active subjects. Subjects will proceed with FU period schedule and activities listed below.

7.1.2.3.1 Repeated-dose PK Assessment (Only Subjects Randomized to Active)

7.1.2.3.1.1 Visit 25 (Days 198-199)

- AE assessment (once per day)
- VS assessment (3 times per day)
- Fasting blood samples will be drawn from subjects housed in the phase 1 unit at t=~-3 hours, and t=0 hours and precisely (plus or minus 5 minutes, with exact time noted) at t=4, 8, 12, 16, 20, 24, 30, 36 and 42 hours post-dose for the following analyses:
  - Chemistry (partial panel)
  - [redacted], free 25-hydroxyvitamin D, [redacted], and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects take last dose of study drug (current dose given as 2 capsules) with a sufficient quantity of a non-alcoholic beverage to enable swallowing of the capsules immediately after the t=0 blood draw, with the exact time of dosing noted.
- Standardized meals will be administered at approximately t=5 hours (lunch), 10 hours (dinner), 23 hours (breakfast), 28 hours (lunch) and 33 hours (dinner) post-dose.
- Subjects will remain in the phase 1 unit for a second and third night.

7.1.2.3.1.2 Visit 26 (Day 200)

- Subjects will receive a standardized meal (breakfast) in the phase 1 unit at approximately t=47 hours post-dose.
- AE assessment
- VS assessment
- Blood samples will be drawn precisely at t=48 hours for the following analyses:
  - Chemistry (partial panel)
  - [redacted], free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects will be discharged from the phase 1 unit and transported to the clinic for the regularly scheduled HD session
- Once at the dialysis clinic and prior to HD session:
  - Review of concomitant medications
  - AE assessment
  - VS assessment
- No study drug (CTAP101 Capsules) will be administered during this HD session or at any subsequent visit.

7.1.2.3.1.3 Visits 27-29 (Days 202-207)

- Review of concomitant medication
- AE assessment

- VS assessment
- Blood samples will be drawn (with the time noted) for the following analyses:
  - Chemistry (partial panel)
  - [redacted] total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

7.1.2.3.2 Visits 30-31 (Days 197-211 for subjects randomized to placebo; Days 211-225 for subjects randomized to active)

- Must be within ±3 days of scheduled visit
- Review of concomitant medication
- AE assessment
- VS assessment
- Blood samples will be drawn (with the time noted) for the following analyses:
  - Chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D
- Additional blood samples will be drawn from subjects randomized to active for:
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Placebo subjects will receive cinacalcet on Day 209, but will not receive cinacalcet during Visit 31 (Day 211).
- Active subjects will receive cinacalcet on Day 223, but will not receive cinacalcet during Visit 32 (Day 225).

7.1.2.3.3 Visit 32 (Day 225 for subjects randomized to placebo; Day 239 for subjects randomized to active)

- Must be within ±3 days of scheduled visit
- Review of concomitant medication
- AE assessment
- PE (including height, weight and BMI)
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Serum b-hCG pregnancy test (for females of child bearing potential)
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
- Additional blood samples will be drawn (with the time noted) from subjects randomized to active for:

- [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
- Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

- No placebo or active subjects will receive cinacalcet during this visit.
- Subjects terminate further participation in the study.

7.2 Cohort 2

Note: Any subject who terminates participation in the study prematurely will complete the procedures listed under Visit 26 (Day 197) at the ET Visit.

7.2.1 Screening and Baseline Periods

Subjects will not discontinue any medications or adjust any medications as noted in the inclusion criteria until they are confirmed as eligible (including confirmation of clinical laboratory parameters) to begin the washout period.

7.2.1.1 Visit 1 (Days -83 to -69)

- A signed ICF will be obtained from the subjects prior to any study-related procedures
- Review of inclusion/exclusion criteria
- Medical history and demographics
- Review of prior medications
- AE assessment
- PE (including weight, height and BMI)
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following:
  - Clinical chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D

7.2.1.2 Visit 2 (Days -13 to -7)

- Must be within ±3 days of scheduled visit
- Review of inclusion/exclusion criteria
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following:
  - Clinical chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted]
- Blood samples will be drawn for non-PK subjects for:

- [redacted], total free 25-hydroxyvitamin D, [redacted]; and 24,25-dihydroxyvitamin D_3
- Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

7.2.2 Treatment Period (26 weeks)

7.2.2.1 **Visit 3 (Day 1*)***

- Review of inclusion/exclusion criteria
- Subjects randomized to treatment with active or placebo drug product
- Review of concomitant medications
- AE assessment
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- 12-Lead ECG
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], total free 25-hydroxyvitamin D, [redacted]; and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
  - [redacted]
- [redacted]
- [redacted]
- Non-PK subjects will:
  - Skip Visits 4 through 9 and complete Visit 10 one week later
  - Receive initial dose of study drug during HD
  - Receive additional doses of study drug at every subsequent HD until Visit 43
- Subjects in the PK sub-groups will:
  - Receive no study drug or food prior to departure from the clinic, and will be transported to/admitted into a nearby phase 1 unit (for 3 successive nights)
  - Review of concomitant medications
  - AE assessment
  - VS assessment
  - Receive a standardized dinner
  - Provide blood samples at t=~-12 hours for the following analyses:
    - Chemistry (partial panel)
    - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3

    - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
  - Receive no further food after dinner and remain in the phase 1 unit overnight.

7.2.2.2 Single-dose PK Assessment (PK Sub-Groups Only)

7.2.2.2.1 Visit 4 (Days 2-3, Saturday-Sunday or Sunday-Monday)

- AE assessment (once daily)
- VS assessment (3 times per day)
- Fasting blood samples will be drawn from subjects housed in the phase 1 unit at t=~-3 hours, and t=0 hours and precisely (plus or minus 5 minutes, with exact time noted) at t=4, 8, 12, 16, 20, 24, 30, 36 and 42 hours post-dose for the following analyses:
  - Chemistry (partial panel)
  - [redacted] total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects take assigned dose of study drug with up to 250 mL of water immediately after the t=0 blood draw, with the exact time of dosing noted.
- Standardized meals will be administered at approximately t=5 hours (lunch), 10 hours (dinner), 23 hours (breakfast), 28 hours (lunch) and 33 hours (dinner) post-dose.
- Subjects will remain in the phase 1 unit for a second and third night.

7.2.2.2.2 Visit 5 (Day 4, Monday or Tuesday)

- Subjects will receive a standardized meal (breakfast) in the phase 1 unit at approximately t=47 hours post-dose.
- AE assessment
- VS assessment
- Blood samples will be drawn precisely at t=48 hours for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects will be discharged from the phase 1 unit and transported to the clinic for the regularly scheduled HD session.
- Once at the dialysis clinic and prior to HD session:
  - Review of concomitant medications
  - AE assessment
  - VS assessment

7.2.2.2.3 Visits 6-8 (Days 6-11)

- Review of concomitant medications

- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Chemistry (partial panel)
  - [redacted] total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

7.2.2.2.4 Visit 9 (Day 15)

- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects receive initial dose of study drug during HD
- Subjects will receive additional doses of study drug at every subsequent HD until Visit 26.

7.2.2.3 Visits 10-16 (Days 22-85)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D

7.2.2.4 Visit 17 (Day 99)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D

- [redacted] total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
- Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- [redacted]

- Qualified subjects will titrate dose upwards, starting with this visit.

7.2.2.5 Visits 18-25 (Days 106-183)

- Visits 18 and 20 are not required for subjects who do not undergo upward dose titration at Visit 17.
- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D

7.2.2.6 Visit 26 (Day 197) or Early Termination (ET)

- Must be within ±3 days of scheduled visit
- Review of concomitant medication
- AE assessment
- VS assessment
- Physical exam (height, weight and BMI)
- 12-Lead ECG (only for subjects in the PK sub-group receiving 900 mcg per week or ET)
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
  - [redacted]
- [redacted]
- [redacted]

[Note: the remaining instructions for this Visit do not apply to an Early Termination Visit.]

- Non-PK subjects will:
  - Continue dosing with study drugs

- Skip Visits 27 through 35
- Complete Visit 36 after 4 weeks

- Subjects who have been treated with placebo will:
  - Skip Visits 27 through 35
  - Complete Visit 36 after 4 weeks
  - Commence dosing with CTAP101 Capsules at a dosage of 300, 600 or 900 mcg per week, assigned randomly with stratification by severity of SHPT, and continue dosing through Day 419.
- Subjects in the active PK sub-groups will:
- Receive no study drug or food prior to departure from the clinic, and will be transported to/admitted into a nearby phase 1 unit (for 3 successive nights)
- Once at the dialysis clinic and prior to HD session:
  - Review of concomitant medications
  - AE assessment
  - VS assessment
  - Receive a standardized dinner
  - Provide blood samples at t=~-12 hours for the following analyses:
    - [redacted], free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
    - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
  - Receive no further food after dinner and remain in the phase 1 unit overnight.

7.2.2.7 Repeated-dose PK Assessment (Active PK Sub-Groups Only)

7.2.2.7.1 Visit 27 (Days 198-199, Saturday-Sunday or Sunday-Monday)

- AE assessment (once daily)
- VS assessment (3 times per day)
- Fasting blood samples will be drawn from subjects housed in the phase 1 unit at t=~-3 hours, and t=0 hours and precisely (plus or minus 5 minutes, with exact time noted) at t=4, 8, 12, 16, 20, 24, 30, 36 and 42 hours post-dose for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total 25-hydroxyvitamin D, free 25-hydroxyvitamin D, [redacted], and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects take assigned dose of study drug with up to 250 mL of water immediately after the t=0 blood draw, with the exact time of dosing noted.
- Standardized meals will be administered at approximately t=5 hours (lunch), 10 hours (dinner), 23 hours (breakfast), 28 hours (lunch) and 33 hours (dinner) post-dose.
- Subjects will remain in the phase 1 unit for a second and third night.

7.2.2.7.2 Visit 28 (Day 200, Monday or Tuesday)

- Subjects will receive a standardized meal (breakfast) in the phase 1 unit at approximately t=47 hours post-dose.
- AE assessment
- VS assessment
- Blood samples will be drawn precisely at t=48 hours for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total 25-hydroxyvitamin D, free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects will be discharged from the phase 1 unit and transported to the clinic for the regularly scheduled HD session.
- Once at the dialysis clinic and prior to HD session:
  - Review of concomitant medications
  - AE assessment
  - VS assessment

7.2.2.7.3 Visits 29-34 (Days 202-225)

- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Chemistry (partial panel)
  - [redacted], total free 25-hydroxyvitamin D, [redacted], and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects who had been receiving CTAP101 Capsules at weekly doses of 300 or 600 mcg during the first 26 weeks of treatment will:
  - Skip Visits 32-35
  - Complete Visit 36 4 days after Visit 31

7.2.2.7.4 Visit 35 (Day 239)

- Review of concomitant medications
- AE assessment
- PE (including height, weight and BMI)
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Serum b-hCG pregnancy test (for females of child bearing potential; only for subjects in the PK sub-group receiving 900 mcg per week)

- Chemistry (full panel) and hematology
- Plasma iPTH and serum total 25-hydroxyvitamin D
- [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
- Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

- Subjects in the 900 mcg group will undergo the following tests:
  - [redacted]

- Subjects in the PK sub-group receiving 900 mcg per week of CTAP101 Capsules will terminate any further participation in the study.

7.2.3 Extension Treatment Period (26 weeks)

- Subjects who had been receiving CTAP101 Capsules at weekly doses of 300 or 600 mcg during the first 26 weeks of treatment will resume dosing with CTAP101 Capsules, as before, at a dose of 300 or 600 mcg per week starting at Visit 36.

7.2.3.1 Visits 36-42 (Days 267-407)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D

7.2.3.2 Visit 43 (Day 421)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- PE (including height, weight and BMI)
- VS assessment
- 12-Lead ECG
- Serum b-hCG pregnancy test (for females of child bearing potential)
- Blood samples will be drawn for the following analyses:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], total free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3

- [redacted]
- [redacted]
- [redacted]
- Subjects will not be dosed with study drug during hemodialysis and will discontinue further dosing with study drug.

7.2.4 Follow-up Period

7.2.4.1 Visit 44 (Day 449)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Clinical chemistry (partial panel)
  - Plasma iPTH and serum total 25-hydroxyvitamin D

7.2.4.2 Visit 45 (Day 463)

- Must be within ±3 days of scheduled visit
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples drawn for:
  - Chemistry (full panel) and hematology
  - Plasma iPTH and serum total 25-hydroxyvitamin D
  - [redacted], total 25-hydroxyvitamin D, free 25-hydroxyvitamin D, [redacted] and 24,25-dihydroxyvitamin D_3
  - Serum total 1,25-dihydroxyvitamin D and 1,25-dihydroxyvitamin D_3
- Subjects terminate further participation in the study

8 QUALITY CONTROL AND ASSURANCE

A quality assurance audit may be performed by the sponsor and/or its designee at selected sites to verify that the study is conducted in accordance with the protocol, ICH/GCP (International Conference on Harmonisation [ICH] and Good Clinical Practice [GCP]), and applicable SOPs and regulations, to ensure that the safety and welfare of subjects are addressed, and to confirm that problems reported by study monitors are resolved. Verification of study documents and 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. 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.

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 electronic data capture (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 PK 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.

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

A detailed description of the planned statistical methods can be found in the associated Statistical Analysis Plan. All analyses will be performed using appropriate statistical software. All data collected on eCRFs and from clinical laboratory evaluations will be grouped and listed by population sub-group, subject, visit, date and time as feasible. Summary tables will be presented by population sub-group as appropriate. Descriptive summaries of categorical outcomes will include the proportion of subjects. Descriptive summaries of quantitative measures will include the number of subjects, mean, standard deviation (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 1 decimal place.

Denominators of percentage of subject calculations will be based on the number of subjects in the sub-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, 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.

9.2 Determination of Sample Size

Formal power calculations have not been undertaken for Cohort 1. For Cohort 2, sample size has been calculated to provide power of 80% for a two-sided, alpha 0.05 level test of equal proportions comparing the numbers of subjects attaining both a mean serum total 25-hydroxyvitamin D level of ≥50 ng/mL and a mean decrease from pre-treatment baseline of at least 30% in plasma iPTH (averaged over the last 6 weeks of the 26-week treatment periods) on each of the three different weekly dosages of CTAP101 Capsules (active) versus placebo. Assuming response rates of at least 0.4 (CTAP101 Capsules) versus 0.1 (placebo), and using a 1:1 ratio of each dose of CTAP101 Capsules:placebo subjects with an estimated 30% dropout rate over the course of the study, a sample size of 53 subjects is required in each treatment arm of the study, allocated as 53 to CTAP101 Capsules at 300 mcg per week, 53 to CTAP101 Capsules at 600 mcg per week, 53 to CTAP101 Capsules at 900 mcg per week, and 53 to placebo.

9.3 Analysis Populations

Efficacy analyses will be conducted for the ITT and PP populations in Cohort 2, as indicated. The ITT populations will include all subjects who have been randomized to receive study drug.

The Safety population will include all subjects who have received at least one dose of study drug and will be used for assessing safety. Subjects who do not have at least one recorded value at baseline, defined in Section 9.10.1, for serum total 25-hydroxyvitamin D and for plasma iPTH will be excluded from all efficacy analyses. The PP population will be defined as all subjects for whom at least two serum total 25-hydroxyvitamin D and two plasma iPTH determinations are included in the calculated baseline value and in the EAP(s), and who do not have a major protocol deviation.

9.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized for the ITT and PP populations by sub-groups separately and combined. Baseline height, weight, body mass index (BMI), age, sex, race, ethnicity, tobacco and nicotine history, and alcohol history will be tabulated for the safety population. Age (years) will be calculated as (date of ICF - date of birth + 1)/365.

9.5 Subject Disposition and Withdrawal

Subject disposition will be tabulated and descriptively summarized for all randomized subjects by population sub-groups separately and combined. The primary reason for premature study termination will be detailed together with the proportion of subjects discontinuing for each reason. The primary reason for premature study termination will be collected from the ET eCRF page.

Medical history will be displayed in a data listing. 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.

9.6 Prior and Concomitant Medications

Prior medications are defined as any continuing or new medication used within 12 weeks and discontinued before Visit 1. Concomitant medications are defined as any continuing or new medication taken from Visit 1 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. World Health Organization Drug Dictionary Enhanced version September 2017, Format C, or later will be used to code concomitant and prior medications. Prior and concomitant medications will be tabulated by population sub-group using frequency counts and percentages for each anatomical/therapeutic/chemical Class Level 4 and drug trade 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.

9.7 Pharmacokinetic Analysis

Parameters to be calculated from observed and baseline-adjusted serum calcifediol (if data are sufficient for estimation) include, but may not be limited to the parameters listed in Table 5.

Table 5 Pharmacokinetic Parameters

Parameter	Definition
C_{max}	Maximum serum concentration.
C_{ss}	Steady state concentration
t_{max}	Time of maximum serum concentration.
AUC_{0-t}	Area under the serum concentration time curve from time zero to the last measurable time point, calculated by linear-log trapezoidal summation.
$AUC_{0-t'}$	Area under the serum concentration time curve from time zero to a fixed time point t, calculated by linear-log trapezoidal summation.
λ_z	Terminal rate constant (if estimable), determined by linear regression of the terminal points of the log-linear serum concentration-time curve.
t_{max}	Terminal elimination half-life (if estimable), determined as ln (2) / λ_z.

Non-compartmental method or PK modeling method will be used for the estimation.

Graphical presentation of the concentrations will be provided as needed.

[redacted]

9.8 Pharmacodynamic Analysis

Single-dose and repeated-dose PD profiles for serum DBP, total free 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3, and 24, 25-dihydroxvitamin D_3 from Visits 4 or 27 to Visits 9 or 35 will be will be presented as descriptive statistics and compared between the study arms.

T-test and mixed effect models or similar tests will be used to compare study arms for continuous variables at a single time point and multiple time points, respectively. Medians will be summarized descriptively with first and third quartiles and if feasible with a nonparametric rank sum test such as Mann-Whitney.

The categorical comparisons will be performed using Chi-square or Fisher's Exact as deemed appropriate. In addition, regression analysis and graphical presentations will be employed to explore the underlying dose-response relationships if feasible.

In an effort to characterize the dose-exposure-response relationships and to determine the impact of intrinsic and extrinsic factors on these relationships, population PK and PD models will be developed from pooled serum calcifediol data collected from subjects in both cohorts. PD markers to be considered in the population PD analysis include: plasma iPTH, and serum calcium (corrected), phosphorus and 1,25-dihydroxyvitamin D_3. The effect of the following covariates will be examined: body weight, age, gender, race, CKD stage, SHPT severity, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics.

9.9 Safety Analysis

All subjects in Safety population will be included in the safety analysis. Statistical summary analysis of safety data will be descriptive and performed by study arms. No inferential hypothesis testing will be performed on the safety variables with the exception of comparisons of serum calcium and serum phosphorus between treatment groups with different CTAP101 Capsules dosing regimens and the placebo group.

9.9.1 Primary Endpoints Analyses

9.9.1.1 Adverse Events

All AEs will be collected on the eCRF and coded via SOC and preferred term using MedDRA version 20.0 or higher. Additionally, the intensity of all AEs will be coded using CTCAE v. 5.0. AEs with missing onset date will be treated as TEAEs and missing onset date will be imputed as the date of Visit 1, unless the event end date indicates that the event resolved prior to Visit 1, 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. 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 is 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 the study drug. The incidence of the AEs will be summarized by population sub-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 population sub-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 Safety subjects in a particular population sub-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.

Diagnostic procedures will be collected separately in the eCRF and coded via SOC and preferred term using MedDRA version 20.0 or higher in a manner similar to AEs.

9.9.1.2 Vital Signs

Observed VS values will be summarized descriptively at baseline and changes from baseline will be descriptively summarized by study arms. Summaries will include n (%), mean, SD, median, minimum, and maximum. Vital sign values will be listed.

9.9.1.3 Physical Examination

Physical examination dates, whether a PE 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 20.0 or higher.

9.9.2 Secondary Endpoint Analyses

Secondary safety endpoints for Cohort 2 will include incidence of hypercalcemia and drug-related hyperphosphatemia. The number (n, %) of subjects with hypercalcemia (two consecutive visits with serum calcium >10.4 mg/dL) or hyperphosphatemia (two consecutive visits with serum phosphorus >6.5 mg/dL deemed to be related to the investigational study drug) will be compared between study arms using a Chi-square test statistic (alpha=0.05).

9.10 Efficacy Analyses

9.10.1 Primary Endpoint Analyses

There is no primary efficacy endpoint for Cohort 1, as efficacy in this part of the study is merely observational. Primary efficacy will be assessed in the ITT population for Cohort 2 by comparing each active treatment group to the placebo group with regard to the proportion of subjects achieving a mean serum total 25-hydroxyvitamin D ≥50 ng/mL and a mean ≥30% decrease in plasma iPTH from pre-treatment baseline in the first EAP, defined as the average of values obtained in the last 6 weeks of the first 26 weeks of treatment (Visits 24, 25 and 26). Baseline will be defined as the average of values obtained before receiving the first dose of study drug at screening Visit 1 (if an 8-week washout period is not required), pre-dose Visit 2, and Visit 3 (pre-dose). Visits are defined in Appendix 1 Schedule of Events.

9.10.2 Secondary Endpoint Analyses

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

Secondary efficacy endpoints for Cohorts 1 and 2 include the proportion of subjects in the per-protocol (PP) population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 30% from pre-treatment baseline during the first EAP. Additional secondary endpoints include the proportion of subjects in the PP population attaining both a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease in plasma iPTH of at least 10, 20 or 30% from pre-treatment baseline during the first and/or second EAP, as applicable, defined as the average of values obtained in the last 6 weeks of the second 26 weeks of treatment; the time courses of mean absolute changes from pre-treatment baseline in serum total 25-hydroxyvitamin D 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, DBP, [redacted] total free 25-hydroxyvitamin D, total 1,25-dihydroxyvitamin D, 1,25-dihydroxyvitamin D_3, and 24,25-dihydroxyvitamin D_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.

[redacted]

9.11 Statistical Analyses

Primary efficacy will be assessed in the ITT population of Cohort 2 by comparing the proportions of subjects in all three active groups versus those in the placebo group and, subsequently, each active dose group versus placebo (in the order of dose group bb, then cc, then aa versus dose group dd) attaining both a mean serum total 25-hydroxyvitamin D level of ≥50 ng/mL and a mean decrease from baseline in plasma iPTH of ≥30% in the first EAP using the Cochran-Mantel-Haenszel test statistic (alpha=0.05). Subjects who do not have at least two serum total 25-hydroxyvitamin D and plasma iPTH determinations in the EAP will be deemed non-responders. Dose groups will be defined for analysis of the first 26 weeks of treatment by the average weekly dose administered in the first EAP, as follows: dose group dd = 0 mcg; dose group aa = 1-300 mcg, dose group bb = 301-600 mcg and dose group cc = 601-900 mcg. Statistical comparisons will not be made between the active treatment groups receiving different average weekly dosages of CTAP101 Capsules.

Key secondary efficacy for Cohort 1 will be assessed in the ITT population by comparing the proportions of subjects in the active group versus those in the placebo group attaining both a mean serum total 25-hydroxyvitamin D level of ≥50 ng/mL and a mean decrease from baseline in plasma iPTH of ≥30% in the EAP using the Cochran-Mantel-Haenszel test statistic (alpha=0.05). Subjects who do not have at least two serum total 25-hydroxyvitamin D and plasma iPTH determinations in the EAP will be deemed non-responders. Dose groups will be defined for analysis of the 26 weeks of treatment by the average weekly dose administered in the EAP, as follows: dose group b = 0 mcg; dose group d = 1-300 mcg, dose group c = 301-600 mcg and dose group b = 601-900 mcg. Statistical comparisons will not be made between the active treatment groups receiving different average weekly dosages of CTAP101 Capsules.

Secondary efficacy will be assessed in the PP population of both cohorts by comparing the proportions of subjects in each active dose group versus those in the placebo group attaining a mean serum total 25-hydroxyvitamin D of ≥50 ng/mL and a mean decrease from baseline in plasma iPTH of ≥10, 20 and 30% in the first and/or second EAP, as applicable, using the Cochran-Mantel-Haenszel test statistic (alpha=0.05). Dose groups will be defined as described above. Statistical comparisons will not be made between the active treatment groups receiving different average weekly dosages of CTAP101 Capsules.

Primary safety analyses will be conducted in the Safety populations of both cohorts, and the statistical summary will be descriptive and performed by dose group (defined above). No

inferential hypothesis testing between each active group and the placebo group will be performed on the safety parameters with the exception of mean serum calcium and phosphorus.

Secondary safety analyses in both cohorts will compare the proportions of subjects with confirmed corrected serum calcium >10.4 mg/dL or confirmed serum phosphorus >6.5 mg/dL (deemed to be study drug related) between the CTAP101 Capsules and placebo dose groups using the Cochran-Mantel-Haenszel test statistic (alpha=0.05).

In addition to assessing the safety and efficacy evaluations for the full study population in Cohort 2, categorical comparisons (by dose group) will be conducted for sub-groups based on body weight, age, gender, race, dose and severity of SHPT and VDI, dialysis vintage, etiology of CKD and prior treatment with 1α-hydroxylated vitamin D analogs and/or calcimimetics. Also, mean plasma iPTH in the EAP of Cohort 1 and in the first EAP of Cohort 2 will be compared, by treatment group, to the mean pre-washout screening value for subjects who were previously treated with 1α-hydroxylated vitamin D analogs and/or calcimimetics.

An interim analysis of safety and efficacy will be completed for Cohort 2 after the last subject has completed the first 26 weeks of treatment.

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

Details of contract research organizations, central laboratories and other participating organizations will be provided in the laboratory manual supplied to each site.

10.2 Notification of Primary Care Physician

At Visit 1, the subject will be provided with a notification for his/her primary care physician and nephrologist that he/she is participating in this clinical study and that no further measurements of plasma iPTH, serum total 25-hydroxyvitamin D or serum calcifediol should be ordered.

10.3 Institutional Review Board/Ethics Committee Approval

Good Clinical Practice requires that the clinical protocol, any protocol amendments, the IB, the ICF, and all other forms of subject information related to the study and any other necessary documents be reviewed by an Independent Review Committee (eg, an IRB).

10.4 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. This study will be conducted in accordance with the protocol, all ICH and GCP regulations governing clinical study conduct, ethical principles that have their origin in the Declaration of Helsinki, and all applicable local laws and regulations. The investigator must assure that the study is conducted in accordance with prevailing local laws and customs.

It is the investigator's responsibility to ensure that this protocol is reviewed and approved by the appropriate IRB/EC. The IB must be provided to the IRB/EC.

The IRB/EC must also review and approve the site's ICF and any other written information provided to the subject and any advertisement that will be used for subject recruitment prior to its use.

10.5 Subject Information and Consent

The investigator or his/her qualified designee will explain the nature of the study to the subject, and answer all questions regarding this study, prior to obtaining informed consent.

The investigator or his/her qualified designee will obtain informed consent from each subject 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 or LAR has consented and has signed the ICF before any activity or treatment is undertaken which is not part of routine care. The subject and/or LAR 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/or LAR to participate in the study is entirely voluntary. The investigator or designate must emphasize to the subject and/or LAR 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).

10.6 Subject Confidentiality

Subject confidentiality will be strictly held in trust by the participating investigators, their staff, the 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.

10.7 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. The investigator will allocate adequate time for such monitoring activities. This monitoring will be in the form of site or remote visits and/or other monitoring surveillance approaches and communication and will include review of original source documents, eCRFs, 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 and managed under the Clinical Monitoring Plan.

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), and has adequate space to conduct the monitoring visit.

10.8 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 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 enrolled will be recorded in an individual, subject-specific eCRF as part of an EDC system. The sponsor or designee will provide training to the investigative site on the EDC system and eCRFs. All eCRFs will be completed in a timely manner as data are available in the source for each subject. As EDC 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.

A subject eCRF must be completed for each subject who signs a consent form and undergoes any procedure related to the study. All data generated from external sources, (eg, central laboratory results), will be integrated with the subject eCRF data through programming or other data integration techniques.

All eCRFs should be completed within 5 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. Queries also should be resolved in a timely manner.

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.

10.9 Protocol Deviations

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

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 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 enrolled and signed an ICF. Electronic data entry is accomplished through the 21CFR Part 11 compliant 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.

10.11 Retention of Data

In compliance with the ICH/GCP guidelines, the investigator/institution will maintain all eCRFs 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 years 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 or designee 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.

10.12 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.

10.13 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 trial 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.

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Appendix 1. Schedule of Events

1. Cohort 1 - Non-PK Sites

Subjects Randomized to Placebo (n=~4)		Screen	WO	Baseline							Dose Level = 0 mcg/week														
Subjects Randomized to Active (n=~12)		Screen	WO	Baseline							Dose Level = 300 mcg/week														
Study Visit		1		2	3		4	5	6	7-9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Treatment Week		**0**		**0**	**0**	**0**		**1**	**1**		**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	F		M	W		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	Sa		T	Th		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 dose)																									
SUBJECTS RANDOMIZED TO PLACEBO OR ACTIVE								No Study Procedures																	
CTAP101/Placebo Treatment Dose Number – TIW dose administration, once during each HD session						**1st HD Dose**		2	3		4	7	10	13	19	25	31	37	43	49	55	61	67	73[a]	**No Dose**
Study Week		-11 to -10		-2	-1	-1		1	1		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 adminstration during each HD during three weeks of the 6-week FU period																									
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 and nutritional status)		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] 25D3, 1,25D3 and 24,25D3				1	1													1							1

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

1. Cohort 1 Non-PK Sites (continued)

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	No Visit								
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

[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				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			No Visits			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 [c]																				
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
							(GCRC 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	6 e, g	f, 1	1	1	1	1															f
Adverse events						f	2 f, g	f, 1	1	1	1	1															f
Clinical chemistry (partial panel)						f	1f	f	1	1	1	1															f
Plasma iPTH and serum 25D												1															
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3						f	1f	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.

2. Cohort 1 PK Sites (continued)

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[b]	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] free 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,e]	1[d], 1	1	1	1				
Adverse events		2[c,f]	1[d], 1	1	1	1				
Clinical chemistry (partial panel)		1[1][d]	1[d]	1	1	1				
Plasma iPTH and serum 25D										
Serum DBP [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3		1[1][d]	1[d]	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; [h]Last dose administered on Day 209 for Placebo; [i]Last dose administered on Day 223 for Active.

3. Cohort 2 - All Sites

						Treatment Period													
	Screen	WO	Baseline			Single-dose PK Assessment						Initial Dose Level							
Visit	1	Washout (if applicable)	2	3		4	5	6	7	8	9	10	11	12	13	14	15	16	17
Week	-11 to -10		-2	-1	-1	1	1	1	1	2	2	3	4	5	6	8	10	12	14
Treatment Week	**0**		**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**1**	**2**	**3**	**4**	**6**	**8**	**10**	**12**
						(GCRC)													
Day	-83 to -69		-13 to -7	1	1	2-3	4	6	8	11	15	22	29	36	43	57	71	85	99
Hours				-24 to -12		-3 to 42	48												
Dose number																			
PK sub-groups																			
Active						1st PK Dose	No Dose	No Dose	No Dose	No Dose	1st HD dose	4	7	10	13	19	25	31	37
Placebo						1st PK Dose	No Dose	No Dose	No Dose	No Dose	1st HD dose	4	7	10	13	19	25	31	37
Non-PK sub-groups					1st HD dose	No visits required						4	7	10	13	19	25	31	37
Day of Week (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
Alternative Day of Week (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
ALL SUBJECTS																			
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
Adverse events	1		1	1								1	1	1	1	1	1	1	1
Physical exam (including height, weight and BMI)	1																		
Vital Signs (blood pressure and heart rate)	1		1	1								1	1	1	1	1	1	1	1
12-Lead ECG				1															
[redacted]				1															
Serum pregnancy test	1			1															1
Clinical chemistry (full panel)	1			1															1
Hematology	1			1															1
Plasma iPTH and serum 25D	1		1	1								1	1	1	1	1	1	1	1
Serum for biomarkers and CET			1	1															1
[redacted]				1															
NON-PK SUBJECTS ONLY																			
Clinical chemistry (partial panel) - non-PK subjects			1									1	1	1	1	1	1	1	
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3 - non-PK subjects			1	1															1
PK SUBJECTS ONLY																			
Concomitant medications					1[f]		1	1	1	1	1								
Vital Signs (blood pressure and heart rate)					1[f]	6[d,f]	1[f], 1	1	1	1	1								
Adverse events					1[f]	2[e,f]	1[f], 1	1	1	1	1								
Clinical chemistry (partial panel) - PK subjects			1	1	1[f]	1[f]	1[f]	1	1	1	1	1	1	1	1	1	1	1	
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3 - PK subjects				1	1[f]	1[f]	1[f]	1	1	1	1								1

[a]Visit may be skipped in the absence of upward dose titration at the start of week 13; [b]Visit required only for subjects in the PK subgroup receiving CTAP101 at 900 mcg per week; [c]Required only for subjects in the PK subgroup receiving CTAP101 at 900 mcg/week or ET; [d]Vital Signs taken three times per day on Days 2 and 3; [e]Adverse Events assessed daily at Days 2 and 3; [f]Activity performed at Phase 1 unit or equivalent.

3. Cohort 2 - All Sites (continued)

		Treatment period																		
		Initial or Titrated Dose Level									Repeated-dose PK Assessment									
Visit		18[a]	19	20[a]	21	22	23	24	25	26	27	28	29	30	31	32[b]	33[b]	34[b]	35[b]
Week		15	16	17	18	20	22	24	26	28	29	29	29	29	30	30	31	32	34
Treatment Week		**13**	**14**	**15**	**16**	**18**	**20**	**22**	**24**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**	**26**
											(GCRC)								
Day		106	113	120	127	141	155	169	183	197	198-199	200	202	204	207	211	218	225	239
Hours										-12	0-42	48							
Dose number																			
PK sub-groups																			
Active		40	43	46	49	55	61	67	73	79	2nd PK Dose	No Dose	No Dose	No Dose	No Dose	No Dose	No Dose	No Dose	No Dose
Placebo		40	43	46	49	55	61	67	73	79	No visits required								
Non-PK sub-groups		40	43	46	49	55	61	67	73	79	No visits required								
Day of Week (W is acceptable for all visits shaded in blue)		F	F	F	F	F	F	F	F	F	Sa-S	M	W	F	M	F	F	F	F
Alternative Day of Week (Th is acceptable for all visits shaded in blue)		Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	S-M	T	Th	Sa	T	Sa	Sa	Sa	Sa
	Vol (mL)																		
ALL SUBJECTS																			
Sign ICF																			
Review/confirm inclusion/exclusion criteria																			
Medical history and demographics																			
Prior/concomitant medications		1	1	1	1	1	1	1	1	1			1	1	1	1	1	1	†[e]
Adverse events		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	†[e]
Physical exam (including height, weight, BMI)										1									†[e]
Vital Signs (blood pressure and heart rate)		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	†[e]
12-Lead ECG										1[d]									†[e]
[redacted]										1									†[e]
Serum pregnancy test	2									1									†[e]
Clinical chemistry (full panel)	3									1									†[e]
Hematology	2									1									†[e]
Plasma iPTH and serum 25D	5	1	1	1	1	1	1	1	1	1									†[e]
Serum for biomarkers and CFT	10									1									
[redacted]										1									
NON-PK SUBJECTS ONLY (n=140)																			
Clinical chemistry (partial panel) - non-PK subjects	3	1	1	1	1	1	1	1	1										
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3 - non-PK subjects	8									1									
PK SUBJECTS ONLY (n=72)																			
Clinical chemistry (partial panel) - PK subjects	3	1	1	1	1	1	1	1	1		11	1	1	1	1	1	1	1	
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3 - PK subjects	8									2	11	1	1	1	1	1	1	1	†[e]

[a]Visit may be skipped in the absence of upward dose titration at the start of week 13; [b]Visit required only for subjects in the PK subgroup receiving CTAP101 at 900 mcg per week; [c]Required only for subjects in the PK subgroup receiving CTAP101 at 900 mcg/week or ET; [d]Vital Signs taken three times per day on Days 2 and 3; [e]Adverse Events assessed daily at Days 2 and 3; [f]Activity performed at Phase 1 unit or equivalent.

3. Cohort 2 - All Sites (continued)

	Treatment Period								Follow-up		ET
	Continuation of Titrated Dose Level										
Visit	36	37	38	39	40	41	42	43	44	45	
Week	38	42	46	50	54	56	58	60	64	66	
Treatment Week	**30**	**34**	**38**	**42**	**46**	**48**	**50**	**52**	**52**	**52**	
Day	267	295	323	351	379	393	407	421	449	463	
Hours											
Dose number											
PK sub-groups											
Active	91	103	115	127	139	145	151	**No Dose**	**No Dose**	**No Dose**	
Placebo	91	103	115	127	139	145	151	**No Dose**	**No Dose**	**No Dose**	
Non-PK sub-groups	91	103	115	127	139	145	151	**No Dose**	**No Dose**	**No Dose**	
Day of Week (W is acceptable for all visits shaded in blue)	F	F	F	F	F	F	F	F	F	F	
Alternative Day of Week (Th is acceptable for all visits shaded in blue)	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	Sa	
ALL SUBJECTS											
Sign ICF											
Review/confirm inclusion/exclusion criteria											
Medical history and demographics											
Prior/concomitant medications	1	1	1	1	1	1	1	1	1	1	1
Adverse events	1	1	1	1	1	1	1	1	1	1	1
Physical exam (including height, weight and BMI)								1			1
Vital Signs (blood pressure and heart rate)	1	1	1	1	1	1	1	1	1		1
12-Lead ECG								1			1
[redacted]								1			1
Serum pregnancy test								1			1
Clinical chemistry (full panel)								1		1	1
Hematology								1		1	1
Plasma iPTH and serum 25D	1	1	1	1	1	1	1	1	1	1	1
Serum for biomarkers and CFT								1			1
[redacted]								1		1	1
NON-PK SUBJECTS ONLY											
Clinical chemistry (partial panel) - non-PK subjects	1	1	1	1	1	1	1		1		
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3 - non-PK subjects								1			1
PK SUBJECTS ONLY											
Concomitant medications											
Vital Signs (blood pressure and heart rate)											
Adverse events											
Clinical chemistry (partial panel) - PK subjects	1	1	1	1	1	1	1		1		
Serum DBP, [redacted] free 25D, 25D3, 125D, 1,25D3, 24,25D3 - PK subjects								1		1	1

[a]Visit may be skipped in the absence of upward dose titration at the start of week 13; [b]Visit required only for subjects in the PK subgroup receiving CTAP101 at 900 mcg per week; [c]Required only for subjects in the PK subgroup receiving CTAP101 at 900 mcg/week or ET; [d]Vital Signs taken three times per day on Days 2 and 3; [e]Adverse Events assessed daily at Days 2 and 3; [f]Activity performed at Phase 1 unit or equivalent.

Appendix 2. Cinacalcet (Cipla) April 2019 Label

CINACALCET- cinacalcet tablet
Cipla USA Inc.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use CINACALCET HYDROCHLORIDE TABLETS safely and effectively. See full prescribing information for CINACALCET HYDROCHLORIDE TABLETS.

CINACALCET HYDROCHLORIDE tablets, for oral use
Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Dosage and Administration (2.4) 4/2019

INDICATIONS AND USAGE

Cinacalcet hydrochloride is a calcium-sensing receptor agonist indicated for:

- Secondary Hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis. (1.1)

Limitations of Use: Cinacalcet hydrochloride tablets are not indicated for use in patients with CKD who are not on dialysis.

- Hypercalcemia in adult patients with Parathyroid Carcinoma (PC). (1.2)
- Severe hypercalcemia in adult patients with primary HPT who are unable to undergo parathyroidectomy. (1.3)

DOSAGE AND ADMINISTRATION

- Cinacalcet hydrochloride tablets should be taken with food or shortly after a meal (2.1).
- Tablets should always be taken whole and not divided (2.1)

- Secondary HPT in patients with CKD on dialysis (2.2):
  - Starting dose is 30 mg once daily.
  - Titrate dose no more frequently than every 2 to 4 weeks through sequential doses of 30, 60, 90, 120, and 180 mg once daily as necessary to achieve targeted intact parathyroid hormone (iPTH) levels.
  - iPTH levels should be measured no earlier than 12 hours after most recent dose.

- Hypercalcemia in patients with PC or severe hypercalcemia in patients with primary HPT (2.3):
  - Starting dose is 30 mg twice daily.
  - Titrate dose every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, 90 mg twice daily, and 90 mg three or four times daily as necessary to normalize serum calcium levels.

- Once the maintenance dose has been established, monitor serum calcium approximately monthly for patients with secondary HPT and every 2 months for patients with PC or primary HPT (2.4)

DOSAGE FORMS AND STRENGTHS

Tablets: 30mg, 60mg, and 90 mg tablets (3)

CONTRAINDICATIONS

Cinacalcet tablets treatment initiation is contraindicated if serum calcium is less than the lower limit of the normal range. (4, 5.1)

WARNINGS AND PRECAUTIONS

- *Hypocalcemia:* Life threatening events and fatal outcomes were reported. Hypocalcemia can prolong QT interval, lower the threshold for seizures, and cause hypotension, worsening heart failure, and/or arrhythmia. Monitor serum calcium carefully for the occurrence of hypocalcemia during treatment. (2.4, 5.1)

Upper Gastrointestinal (GI) Bleeding: Patients with risk factors for upper GI bleeding may be at increased risk. Monitor patients and promptly evaluate and treat any suspected GI bleeding. (5.2)

Hypotension, Worsening Heart Failure and/or Arrhythmias : In postmarketing safety surveillance, isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia have been reported in patients with impaired cardiac function. (5.3)

Adynamic Bone Disease : May develop if iPTH levels are suppressed below 100 pg/mL. (5.4)

ADVERSE REACTIONS

The most common adverse reactions (i.e., ≥ 25%) associated with cinacalcet hydrochloride were nausea and vomiting. (6)
To report SUSPECTED ADVERSE REACTIONS, contact Cipla Ltd., at 1-866-604-3268 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Co-administration with a strong CYP3A4 inhibitor may increase serum levels of cinacalcet. Dose adjustment and

monitoring of iPTH serum phosphorus and serum calcium may be required. (7.1)
- Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments may be required for concomitant medications that are predominantly metabolized by CYP2D6. (7.2)

USE IN SPECIFIC POPULATIONS
- Pediatric Use: A fatal outcome was reported in a pediatric clinical trial patient with severe hypocalcemia. Cinacalcet tablets is not indicated for use in pediatric patients. (8.4).

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 4/2019

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Secondary Hyperparathyroidism

Cinacalcet hydrochloride tablets are indicated for the treatment of secondary hyperparathyroidism (HPT) in adult patients with chronic kidney disease (CKD) on dialysis *[see Clinical Studies (14.1)]*.

Limitations of Use:

Cinacalcet hydrochloride tablets are not indicated for use in patients with CKD who are not on dialysis because of an increased risk of hypocalcemia *[see Warnings and Precautions (5.1)]*.

1.2 Parathyroid Carcinoma

Cinacalcet tablets are indicated for the treatment of hypercalcemia in adult patients with Parathyroid Carcinoma *[see Clinical Studies (14.2)]*.

1.3 Primary Hyperparathyroidism

Cinacalcet hydrochloride tablets are indicated for the treatment of severe hypercalcemia in adult patients with primary HPT who are unable to undergo parathyroidectomy *[see Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Administration

Cinacalcet hydrochloride tablets should be taken with food or shortly after a meal.

Cinacalcet hydrochloride tablets are administered orally and should always be taken whole and not chewed, crushed, or divided.

2.2 Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease on Dialysis

The recommended starting oral dose of cinacalcet hydrochloride tablets is 30 mg once daily. Serum calcium and serum phosphorus should be measured within 1 week and intact parathyroid hormone (iPTH) should be measured 1 to 4 weeks after initiation or dose adjustment of cinacalcet hydrochloride tablets *[see Dosage and Administration (2.3)]*. Cinacalcet hydrochloride tablets should be titrated no more frequently than every 2 to 4 weeks through sequential doses of 30, 60, 90, 120, and 180 mg once daily to target iPTH levels of 150 to 300 pg/mL. Serum iPTH levels should be assessed no earlier than 12 hours after dosing with cinacalcet hydrochloride tablets.

Cinacalcet hydrochloride tablets can be used alone or in combination with vitamin D sterols and/or phosphate binders.

During dose titration, serum calcium levels should be monitored frequently and if levels decrease below the normal range, appropriate steps should be taken to increase serum calcium levels, such as by

providing supplemental calcium, initiating or increasing the dose of calcium-based phosphate binder, initiating or increasing the dose of vitamin D sterols, or temporarily withholding treatment with cinacalcet hydrochloride tablets *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1)]*.

2.3 Patients with Parathyroid Carcinoma and Primary Hyperparathyroidism

The recommended starting oral dose of cinacalcet hydrochloride tablet is 30 mg twice daily.

The dose of cinacalcet hydrochloride tablets should be titrated every 2 to 4 weeks through sequential doses of 30 mg twice daily, 60 mg twice daily, and 90 mg twice daily, and 90 mg 3 or 4 times daily as necessary to normalize serum calcium levels. Serum calcium should be measured within 1 week after initiation or dose adjustment of cinacalcet hydrochloride tablets *[see Dosage and Administration (2.4) and Warnings and Precautions (5.1)]*.

2.4 Switching from Parsabiv (etelcalcetide) to Cinacalcet

Discontinue etelcalcetide for at least 4 weeks prior to starting Cinacalcet. Ensure corrected serum calcium is at or above the lower limit of normal prior to Cincalcetinitiation *[see Warnings and Precautions (5.1)]*. Initiate Cinacalcet treatment at a starting dose of 30 mg once daily.

2.5 Monitoring for Hypocalcemia

Once the maintenance dose has been established, serum calcium should be measured approximately monthly for patients with secondary hyperparathyroidism with CKD on dialysis, and every 2 months for patients with parathyroid carcinoma or primary hyperparathyroidism *[see Dosage and Administration (2.2, 2.3)]*.

For secondary hyperparathyroidism patients with CKD on dialysis, if serum calcium falls below 8.4 mg/dL but remains above 7.5 mg/dL, or if symptoms of hypocalcemia occur, calcium-containing phosphate binders and/or vitamin D sterols can be used to raise serum calcium. If serum calcium falls below 7.5 mg/dL, or if symptoms of hypocalcemia persist and the dose of vitamin D cannot be increased, withhold administration of cinacalcet hydrochloride tablets until serum calcium levels reach 8.0 mg/dL and/or symptoms of hypocalcemia have resolved. Treatment should be reinitiated using the next lowest dose of cinacalcet hydrochloride tablets *[see Dosage and Administration (2.2)]*.

3 DOSAGE FORMS AND STRENGTHS

Cinacalcet Hydrochloride Tablets 30 mg:

Light green colored, oval shaped, biconvex film coated tablets debossed with 'CL' on one side and '410' on other side.

Cinacalcet Hydrochloride Tablets 60 mg:

Light green colored, oval shaped, biconvex film coated tablets debossed with 'CL' on one side and '411' on other side.

Cinacalcet Hydrochloride Tablets 90 mg:

Light green colored, oval shaped, biconvex film coated tablets debossed with 'CL' on one side and '412' on other side.

4 CONTRAINDICATIONS

Cinacalcet hydrochloride tablets treatment initiation is contraindicated if serum calcium is less than the lower limit of the normal range *[see Warnings and Precautions (5.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hypocalcemia

Cinacalcet hydrochloride tablets lowers serum calcium and can lead to hypocalcemia *[see Adverse Reactions (6.1)]*. Significant lowering of serum calcium can cause paresthesias, myalgias, muscle spasms, tetany, seizures, QT interval prolongation and ventricular arrhythmia. Life threatening events and fatal outcomes associated with hypocalcemia have been reported in patients treated with cinacalcet hydrochloride tablets, including in pediatric patients. The safety and effectiveness of cinacalcet hydrochloride tablets have not been established in pediatric patients *[see Pediatric Use (8.4)]*.

Cinacalcet hydrochloride tablets are not indicated for patients with CKD not on dialysis *[see Indications and Usage (1)]*. In patients with secondary HPT and CKD not on dialysis, the long term safety and efficacy of cinacalcet hydrochloride tablets have not been established. Clinical studies indicate that cinacalcet-treated patients with CKD not on dialysis have an increased risk for hypocalcemia compared with cinacalcet-treated patients with CKD on dialysis, which may be due to lower baseline calcium levels. In a phase 3 study of 32 weeks duration and including 404 patients with CKD not on dialysis (302 cinacalcet, 102 placebo), in which the median dose for cinacalcet was 60 mg per day at the completion of the study, 80% of cinacalcet-treated patients experienced at least one serum calcium value < 8.4 mg/dL compared with 5% of patients receiving placebo.

QT Interval Prolongation and Ventricular Arrhythmia

Decreases in serum calcium can also prolong the QT interval, potentially resulting in ventricular arrhythmia. Cases of QT prolongation and ventricular arrhythmia have been reported in patients treated with cinacalcet hydrochloride tablets.

Patients with congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia may be at increased risk for QT interval prolongation and ventricular arrhythmias if they develop hypocalcemia due to cinacalcet hydrochloride. Closely monitor corrected serum calcium and QT interval in patients at risk receiving cinacalcet hydrochloride.

Seizures

In clinical studies, seizures (primarily generalized or tonic-clonic) were observed in 1.4% (43/3049) of cinacalcet-treated patients and 0.7% (5/687) of placebo-treated patients. While the basis for the reported difference in seizure rate is not clear, the threshold for seizures is lowered by significant reductions in serum calcium levels. Monitor serum calcium levels in patients with seizure disorder receiving cinacalcet hydrochloride tablets.

Concurrent Administration with Other Calcium-Lowering Drug Products

Concurrent administration of cinacalcet hydrochloride with calcium-lowering drugs including other calcium-sensing receptor agonists could result in severe hypocalcemia. Closely monitor serum calcium in patients receiving cinacalcet hydrochloride and concomitant therapies known to lower serum calcium levels.

Patient Education and Hypocalcemia Treatment

Educate patients on the symptoms of hypocalcemia and advise them to contact a healthcare provider if they occur.

If corrected serum calcium falls below the lower limit of normal or symptoms of hypocalcemia develop, start or increase calcium supplementation (including calcium, calcium-containing phosphate binders, and/or vitamin D sterols or increases in dialysate calcium concentration). Cinacalcet hydrochloride tablets dose reduction or discontinuation of cinacalcet hydrochloride tablets may be necessary *[see Dosage and Administration (2.2)]*.

5.2 Upper Gastrointestinal Bleeding

Cases of gastrointestinal bleeding, mostly upper gastrointestinal bleeding, have occurred in patients using calcimimetics, including cinacalcet hydrochloride, from postmarketing and clinical trial sources. The exact cause of GI bleeding in these patients is unknown.

Patients with risk factors for upper GI bleeding (such as known gastritis, esophagitis, ulcers or severe vomiting) may be at increased risk for GI bleeding when receiving cinacalcet hydrochloride treatment. Monitor patients for worsening of common GI adverse reactions of nausea and vomiting associated with cinacalcet hydrochloride *[see Adverse Reactions (6.1)]* and for signs and symptoms of GI bleeding and ulcerations during cinacalcet hydrochloride tablets therapy. Promptly evaluate and treat any suspected GI bleeding.

5.3 Hypotension, Worsening Heart Failure and/or Arrhythmias

In postmarketing safety surveillance, isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia have been reported in patients with impaired cardiac function, in which a causal relationship to cinacalcet hydrochloride tablets could not be completely excluded and which may be mediated by reductions in serum calcium levels *[see Adverse Reactions (6.2)]*.

5.4 Adynamic Bone Disease

Adynamic bone disease may develop if iPTH levels are suppressed below 100 pg/mL. One clinical study evaluated bone histomorphometry in patients treated with cinacalcet tablets for 1 year. Three patients with mild hyperparathyroid bone disease at the beginning of the study developed adynamic bone disease during treatment with cinacalcet tablets. Two of these patients had iPTH levels below 100 pg/mL at multiple time points during the study. In three 6-month, phase 3 studies conducted in patients with CKD on dialysis, 11% of patients treated with cinacalcet tablets had mean iPTH values below 100 pg/mL during the efficacy-assessment phase. If iPTH levels decrease below 150 pg/mL in patients treated with cinacalcet tablets, the dose of cinacalcet tablets and/or vitamin D sterols should be reduced or therapy discontinued.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of labeling:

- Hypocalcemia *[see Warnings and Precautions (5.1)]*
- Upper Gastrointestinal Bleeding *[see Warnings and Precautions (5.2)]*
- Hypotension, Worsening Heart Failure and/or Arrhythmias [*see Warnings and Precautions (5.3)]*
- Adynamic Bone Disease *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease on Dialysis

In three double-blind, placebo-controlled clinical trials, 1126 patients with CKD on dialysis received study drug (656 cinacalcet, 470 placebo) for up to 6 months. The most frequently reported adverse reactions are listed in Table 1.

Seizures were observed in 1.4% (13/910) of cinacalcet-treated patients and 0.7% (5/641) of placebo-treated patients across all completed placebo-controlled trials.

Table 1. Adverse Reactions with Frequency ≥ 5% in Patients on Dialysis in Short-Term Studies for up to 6 Months

Event*	Placebo (n = 470) (%)	Cinacalcet (n = 656) (%)
Nausea	19	31
Vomiting	15	27
Diarrhea	20	21
Myalgia	14	15
Dizziness	8	10
Hypertension	5	7
Asthenia	4	7
Anorexia	4	6
Pain Chest, Non-Cardiac	4	6
Dialysis Access Site Infection	4	5

* Included are events that were reported at a greater incidence in the cinacalcet group than in the placebo group

In a randomized, double-blind placebo-controlled study of 3-883 patients with secondary HPT and CKD receiving dialysis in which patients were treated for up to 64 months (mean duration of treatment was 21 months in the cinacalcet group), the most frequently reported adverse reactions (incidence of ≥ 5% in the cinacalcet group and a difference ≥ 1% compared to placebo) are listed in Table 2.

Table 2. Frequency of Adverse Reactions in Dialysis Patients Treated for up to 64 Months in a Long-Term Study*

	Placebo (n=1923)	Cinacalcet (n=1938)
	3699 subject-years	4044 subject-years
Percent of subjects reporting Adverse Reactions (%)	90.9	93.2
Nausea	15.5	29.1
Vomiting	13.7	25.6
Diarrhea	18.7	20.5
Dyspnea	11.5	13.4
Cough	9.8	11.7
Hypotension	10.5	11.6
Headache	9.6	11.5
Hypocalcemia	1.4	11.2
Muscle spasms	9.2	11.1
Abdominal pain	9.6	10.9
Abdominal pain upper	6.3	8.2
Hyperkalemia	6.1	8.1
Upper respiratory tract infection	6.3	7.6
Dyspepsia	4.6	7.4
Dizziness	4.7	7.3
Decreased appetite	3.5	5.9

Asthenia	3.8	5.4
Constipation	3.8	5.0

Crude incidence rate = 100 * Total number of subjects with event/ n

n=Number of subjects receiving at least one dose of study drug

* Adverse reactions that occurred in ≥ 5% frequency in the cinacalcet group and a difference ≥1% compared to the placebo group (Safety Analysis Set)

Additional adverse reaction rates from the long-term, randomized, double-blind placebo-controlled study for cinacalcet tablets versus placebo are as follows: seizure (2.5%, 1.6%), rash (2.2%, 1.9%), hypersensitivity reactions (9.4%, 8.3%).

Patients with Parathyroid Carcinoma and Primary Hyperparathyroidism

The safety profile of cinacalcet hydrochloride tablets in these patient populations is generally consistent with that seen in patients with CKD on dialysis. Forty six patients were treated with cinacalcet hydrochloride tablets in a single-arm study, 29 with Parathyroid Carcinoma and 17 with intractable pHPT. Nine (20%) of the patients withdrew from the study due to adverse events. The most frequent adverse reactions and the most frequent cause of withdrawal in these patient populations were nausea and vomiting. Severe or prolonged cases of nausea and vomiting can lead to dehydration and worsening hypercalcemia so careful monitoring of electrolytes is recommended in patients with these symptoms.

Eight patients died during treatment with cinacalcet hydrochloride tablets in this study, 7 with Parathyroid Carcinoma (24%) and 1 (6%) with intractable pHPT. Causes of death were cardiovascular (5 patients), multi-organ failure (1 patient), gastrointestinal hemorrhage (1 patient) and metastatic carcinoma (1 patient). Adverse events of hypocalcemia were reported in three patients (7%).

Seizures were observed in 0.7% (1/140) of cinacalcet-treated patients and 0.0% (0/46) of placebo-treated patients in all clinical studies.

Hypocalcemia

In 26-week studies of patients with secondary HPT and CKD on dialysis 66% of patients receiving cinacalcet hydrochloride tablets compared with 25% of patients receiving placebo developed at least one serum calcium value less than 8.4 mg/dL, whereas, 29% of patients receiving cinacalcet hydrochloride tablets compared with 11% of patients receiving placebo developed at least one serum calcium value less than 7.5 mg/dL. Less than 1% of patients in each group permanently discontinued study drug due to hypocalcemia.

In a randomized, double-blind, placebo-controlled study in patients with secondary HPT and CKD receiving dialysis in which patients were treated for up to 64 months (mean duration of treatment was 21 months in the cinacalcet group), 75% of patients receiving cinacalcet hydrochloride tablets compared with 29% of patients receiving placebo developed at least one serum calcium value less than 8.4 mg/dL and 33% of cinacalcet patients compared with 12% of patients receiving placebo had at least one serum calcium value less than 7.5 mg/dL. Most of the cases of severe hypocalcemia less than 7.5 mg/dL (21/33=64%) occurred during the first 6 months. In this trial, 1.1% of patients receiving cinacalcet hydrochloride tablets and 0.1% of patients receiving placebo permanently discontinued study drug due to hypocalcemia.

Table 3. Adverse Reactions with Frequency ≥ 10% in a Single-Arm, Open-Label Study in Patients with Primary Hyperparathyroidism or Parathyroid Carcinoma

	Cinacalcet Hydrochloride Tablets		
	Parathyroid Carcinoma	Intractable pHPT (n=17)	Total (n=46)

	(n=29) n (%)	n (%)	n (%)
Number of Subjects Reporting Adverse Reaction	28 (97)	17 (100)	45 (98)
Nausea	19 (66)	10 (59)	29 (63)
Vomiting	15 (52)	6 (35)	21 (46)
Paresthesia	4 (14)	5 (29)	9 (20)
Fatigue	6 (21)	2 (12)	8 (17)
Fracture	6 (21)	2 (12)	8 (17)
Hypercalcemia	6 (21)	2 (12)	8 (17)
Anorexia	6 (21)	1 (6)	7 (15)
Asthenia	5 (17)	2 (12)	7 (15)
Dehydration	7 (24)	0 (0)	7 (15)
Anemia	5 (17)	1 (6)	6 (13)
Arthralgia	5 (17)	1 (6)	6 (13)
Constipation	3 (10)	3 (18)	6 (13)
Depression	3 (10)	3 (18)	6 (13)
Headache	6 (21)	0 (0)	6 (13)
Infection Upper Respiratory	3 (10)	2 (12)	5 (11)
Pain Limb	3 (10)	2 (12)	5 (11)

n=Number of subjects receiving at least one dose of study drug.
pHPT=primary hyperparathyroidism

Hypocalcemia

In 26-week studies of patients with secondary HPT and CKD on dialysis 66% of patients receiving cinacalcet hydrochloride tablets compared with 25% of patients receiving placebo developed at least one serum calcium value less than 8.4 mg/dL, whereas, 29 % of patients receiving cinacalcet hydrochloride tablets compared with 11% of patients receiving placebo developed at least one serum calcium value less than 7.5 mg/dL. Less than 1% of patients in each group permanently discontinued study drug due to hypocalcemia.

In a randomized, double-blind, placebo-controlled study in patients with secondary HPT and CKD receiving dialysis in which patients were treated for up to 64 months (mean duration of treatment was 21 months in the cinacalcet group), 75% of patients receiving cinacalcet hydrochloride tablets compared with 29% of patients receiving placebo developed at least one serum calcium value less than 8.4 mg/dL and 33% of cinacalcet patients compared with 12% of patients receiving placebo had at least one serum calcium value less than 7.5 mg/dL. Most of the cases of severe hypocalcemia less than 7.5mg/dL (21/33=64%) occurred during the first 6 months. In this trial, 1.1% of patients receiving cinacalcet hydrochloride tablets and 0.1% of patients receiving placebo permanently discontinued study drug due to hypocalcemia.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of cinacalcet tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Rash and hypersensitivity reactions (including angioedema, and urticaria), and myalgia have been identified as adverse reactions during post approval use of cinacalcet tablets. Isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia have been reported in cinacalcet-treated patients with impaired cardiac function in postmarketing safety surveillance *[see Warnings and Precautions (5.1)]*.

- Rash and hypersensitivity reactions (including angioedema and urticaria), and myalgia
- Isolated, idiosyncratic cases of hypotension, worsening heart failure, and/or arrhythmia have been reported in patients with impaired cardiac function
- Gastrointestinal bleeding

7 DRUG INTERACTIONS

7.1 Strong CYP3A4 Inhibitors

Cinacalcet is partially metabolized by CYP3A4. Dose adjustment of cinacalcet hydrochloride tablets may be required if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor (e.g., ketoconazole, itraconazole). The iPTH and serum calcium concentrations should be closely monitored in these patients *[see Clinical Pharmacology (12.3)]*.

7.2 CYP2D6 Substrates

Cinacalcet is a strong inhibitor of CYP2D6. Dose adjustments may be required for concomitant medications that are predominantly metabolized by CYP2D6 (e.g., desipramine, metoprolol, and carvedilol) and particularly those with a narrow therapeutic index (e.g., flecainide and most tricyclic antidepressants) *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited case reports of cinacalcet hydrochloride use in pregnant women are insufficient to inform a drug associated risk of adverse developmental outcomes. In animal reproduction studies, when female rats were exposed to cinacalcet during the period of organogenesis through to weaning at 2-3 times the systemic drug levels (based on AUC) at the maximum recommended human dose (MRHD) of 180 mg/day, peripartum and early postnatal pup loss and reduced pup body weight gain were observed in the presence of maternal hypocalcemia *[see Data]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In pregnant female rats given oral gavage doses of 2, 25, 50 mg/kg/day cinacalcet during gestation, no teratogenicity was observed at doses up to 50 mg/kg/day (exposure 4 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). Decreased fetal body weights were observed at all doses (less than 1 to 4 times a human oral dose of 180 mg/day based on AUC comparison) in conjunction with maternal toxicity (decreased food consumption and body weight gain).

In pregnant female rabbits given oral gavage doses of 2, 12, 25 mg/kg/day cinacalcet during gestation, no adverse fetal effects were observed (exposures less than with a human oral dose of 180 mg/day based on AUC comparisons). Reductions in maternal food consumption and body weight gain were seen at doses of 12 and 25 mg/kg/day. Cinacalcet has been shown to cross the placental barrier in rabbits.

In pregnant rats given oral gavage doses of 5, 15, 25 mg/kg/day cinacalcet during gestation through lactation, no adverse fetal or pup (post-weaning) effects were observed at 5 mg/kg/day (exposures less than with a human therapeutic dose of 180 mg/day based on AUC comparisons). Higher doses of 15 and 25 mg/kg/day cinacalcet (exposures 2 to 3 times a human oral dose of 180 mg/day based on AUC comparisons) were accompanied by maternal signs of hypocalcemia (periparturient mortality and early

postnatal pup loss), and reductions in postnatal maternal and pup body weight gain.

8.2 Lactation

Risk Summary

There are no data regarding the presence of cinacalcet hydrochloride in human milk or effects on the breastfed infant or on milk production. Studies in rats showed that cinacalcet was excreted in the milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for cinacalcet hydrochloride tablets and any potential adverse effects on the breastfed infant from cinacalcet hydrochloride or from the underlying maternal condition.

8.4 Pediatric Use

The safety and efficacy of cinacalcet hydrochloride tablets have not been established in pediatric patients.

Dosing with cinacalcet hydrochloride in a pediatric study was stopped because of a fatality in a cinacalcet hydrochloride-treated individual. The individual was noted to be severely hypocalcemic at the time of death. The cause of death was multifactorial and a contribution of cinacalcet hydrochloride to the death could not be excluded *[see Warnings and Precautions (5.1)]*.

Additional information describing clinical studies in which efficacy was not demonstrated in pediatric patients is approved for Amgen Inc.'s SENSIPAR® (cinacalcet hydrochloride). However, due to Amgen Inc.'s marketing exclusivity rights, this drug product is not labeled with that pediatric information.

8.5 Geriatric Use

Of the total number of subjects (n=1136) in clinical studies of cinacalcet hydrochloride tablets, 26 percent were 65 and over, and 9 percent were 75 and over. No overall differences in the safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger subjects, but greater sensitivity of some older individuals cannot be ruled out *[see Clinical Studies (14) and Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

No dosage adjustment is necessary for renal impairment *[see Clinical Pharmacology (12.3)]*.

8.7 Hepatic Impairment

Patients with moderate and severe hepatic impairment should have serum calcium, serum phosphorus, and iPTH levels monitored closely throughout treatment with cinacalcet hydrochloride tablets because cinacalcet exposure ($AUC_{0\text{-infinite}}$) is increased by 2.4 and 4.2 fold, respectively, in these patients *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

Overdosage of cinacalcet hydrochloride may lead to hypocalcemia. In the event of overdosage, patients should be monitored for signs and symptoms of hypocalcemia and appropriate measures taken to correct serum calcium levels *[see Warnings and Precautions (5.1)]*.

Since cinacalcet hydrochloride is highly protein bound, hemodialysis is not an effective treatment for overdosage of cinacalcet hydrochloride tablets.

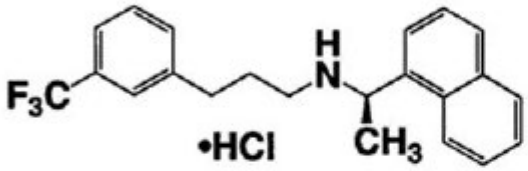
11 DESCRIPTION

Cinacalcet is a calcimimetic agent that increases the sensitivity of the calcium-sensing receptor to activation by extracellular calcium. Cinacalcet tablets contain the hydrochloride salt of cinacalcet. Its empirical formula is $C_{22}H_{22}F_3N \cdot HCl$ with a molecular weight of 393.9 g/mol (hydrochloride salt) and 357.4 g/mol (free base). It has one chiral center having an R-absolute configuration. The R-enantiomer is the more potent enantiomer and has been shown to be responsible for pharmacodynamic activity.

The hydrochloride salt of cinacalcet is a white to off-white, crystalline solid that is soluble in methanol or 95% ethanol and slightly soluble in water.

Cinacalcet tablets are formulated as light-green, film-coated, oval-shaped tablets for oral administration in strengths of 30 mg, 60 mg, and 90 mg of cinacalcet as the free base equivalent (33 mg, 66 mg, and 99 mg as the hydrochloride salt, respectively).

The hydrochloride salt of cinacalcet is described chemically as N-[1-(R)-(-)-(1-naphthyl)ethyl]-3-[3-(trifluoromethyl)phenyl]-1-aminopropane hydrochloride and has the following structural formula:



Inactive Ingredients

The following are the inactive ingredients in cinacalcet hydrochloride tablets: pre-gelatinized starch (botanical source is maize starch), microcrystalline cellulose, povidone, crospovidone, magnesium stearate and isopropyl alcohol. Tablets are coated with Opadry II Green (hypromellose, lactose monohydrate, titanium dioxide, triacetin, FD&C blue #2/indigo carmine AL, iron oxide yellow).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The calcium-sensing receptor on the surface of the chief cell of the parathyroid gland is the principal regulator of PTH synthesis and secretion. Cinacalcet, the active ingredient in cinacalcet hydrochloride tablets, directly lowers PTH levels by increasing the sensitivity of the calcium-sensing receptor to extracellular calcium. The reduction in PTH is associated with a concomitant decrease in serum calcium levels.

12.2 Pharmacodynamics

Reduction in iPTH levels correlated with the plasma cinacalcet concentrations in patients with CKD. The nadir in iPTH level occurs approximately 2 to 6 hours post dose, corresponding with the maximum plasma concentration (C_{max}) of cinacalcet. After steady-state cinacalcet concentrations are reached (which occurs within 7 days of dose change), serum calcium concentrations remain constant over the dosing interval in patients with CKD.

Reductions in PTH are associated with a decrease in bone turnover and bone fibrosis in patients with CKD on dialysis and uncontrolled secondary HPT.

12.3 Pharmacokinetics

After oral administration of cinacalcet, C_{max} is achieved in approximately 2 to 6 hours. Cinacalcet C_{max} and $AUC_{(0\text{-infinite})}$ were increased by 82% and 68%, respectively, following administration with a high-fat meal compared with fasting in healthy volunteers. The C_{max} and $AUC_{(0\text{-infinite})}$ of cinacalcet were increased by 65% and 50%, respectively, when cinacalcet was administered with a low-fat meal compared with fasting.

After absorption, cinacalcet concentrations decline in a biphasic fashion with an initial half-life of approximately 6 hours and terminal half-life of 30 to 40 hours. Steady-state drug levels are achieved within 7 days, and the mean accumulation ratio is approximately 2 with once daily oral administration. The median accumulation ratio is approximately 2 to 5 with twice daily oral administration. The AUC and C_{max} of cinacalcet increase proportionally over the dose range of 30 to 180 mg once daily. The pharmacokinetic profile of cinacalcet does not change over time with once daily dosing of 30 to 180 mg. The volume of distribution is approximately 1000 L, indicating extensive distribution. Cinacalcet is approximately 93% to 97% bound to plasma protein(s). The ratio of blood cinacalcet concentration to plasma cinacalcet concentration is 0.80 at a blood cinacalcet concentration of 10 ng/mL.

Metabolism and Excretion

Cinacalcet is metabolized by multiple enzymes, primarily CYP3A4, CYP2D6, and CYP1A2. After administration of a 75 mg radiolabeled dose to healthy volunteers, cinacalcet was metabolized via: 1) oxidative N-dealkylation to hydrocinnamic acid and hydroxy-hydrocinnamic acid, which are further metabolized via β-oxidation and glycine conjugation; the oxidative N-dealkylation process also generates metabolites that contain the naphthalene ring; and 2) oxidation of the naphthalene ring on the parent drug forming dihydrodiols, which are further conjugated with glucuronic acid. The plasma concentrations of the major circulating metabolites, including the cinnamic acid derivatives and glucuronidated dihydrodiols, markedly exceed the parent drug concentrations. The hydrocinnamic acid metabolite and glucuronide conjugates have minimal or no calcimimetic activity. Renal excretion of metabolites was the primary route of elimination of radioactivity. Approximately 80% of the dose was recovered in the urine and 15% in the feces.

Specific Populations

Age: Geriatric Population

The pharmacokinetic profile of cinacalcet in geriatric patients (age ≥ 65 years, n = 12) is similar to that for patients who are < 65 years of age (n = 268) *[see Use in Specific Populations (8.5)]*.

Hepatic Impairment

The disposition of a 50 mg cinacalcet hydrochloride tablets single dose was compared between patients with hepatic impairment and patients with normal hepatic function. Cinacalcet exposure ($AUC_{(0\text{-infinite})}$) was comparable between healthy volunteers and patients with mild hepatic impairment. However, in patients with moderate and severe hepatic impairment (as indicated by the Child-Pugh method), cinacalcet exposures ($AUC_{(0\text{-infinite})}$) were 2.4 and 4.2 fold higher, respectively, than that in healthy volunteers. The mean half-life of cinacalcet increased from 49 hours in healthy volunteers to 65 hours and 84 hours in patients with moderate and severe hepatic impairment, respectively. Protein binding of cinacalcet is not affected by impaired hepatic function *[see Use in Specific Populations (8.7)]*.

Renal Impairment

The pharmacokinetic profile of a 75 mg cinacalcet hydrochloride tablets single dose in patients with mild, moderate, and severe renal impairment, and those on hemodialysis or peritoneal dialysis is comparable with that in healthy volunteers *[see Use in Specific Populations (8.6)]*.

Drug Interactions

In vitro studies indicate that cinacalcet is a strong inhibitor of CYP2D6, but not an inhibitor of CYP1A2, CYP2C9, CYP2C19, and CYP3A4. In vitro induction studies indicate that cinacalcet is not an inducer of

CYP450 enzymes. Tables 5 and 6 list the findings from in vivo drug-drug interaction studies.

Table 5. Effect of co-administered drugs on cinacalcet

Co-administered drug and dosing regimen	Cinacalcet		
	Dose*	Mean change in $AUC_{(0\text{-inf})}$	Mean change in C_{max}
200 mg ketoconazole twice daily for 7 days	90 mg on day 5	↑127%	↑116%
1500 mg calcium carbonate, single dose	100 mg	↓6%	↓5%
80 mg pantoprazole daily for 3 days	90 mg on day 3	↑1%	↓3%
2400 mg sevelamer HCl three times a day for 2 days	90 mg on day 1 with first dose of sevelamer	↓4%	↓7%

* Single dose.

Table 6. Effect of cinacalcet co-administration on other drugs

Cinacalcet dosing regimen	Co-administered drug		
	Name and Dose	Mean change in $AUC_{(0\text{-inf})}$	Mean change in C_{max}
30 mg twice daily for 8 days	25 mg warfarin* tablet†	↑1 % for R-warfarin ↓1% for S-warfarin	↓10 % for R-warfarin ↓12 % for S-warfarin
90 mg daily for 7 days to CYP2D6 extensive metabolizers	50 mg desipramine†	↑264%	↑75%
90 mg daily for 5 days	2 mg midazolam†	↑5%	↓5%
25 or 100 mg single dose to CYP2D6 extensive metabolizers	50 mg amitriptyline single dose	↑21-22% for amitriptyline ↑17-23% for nortriptyline‡	↑13-21% for amitriptyline ↑11-15% for nortriptyline‡

* No significant change in prothrombin time.
† Single dose on day 5.
‡ Nortriptyline is an active metabolite of amitriptyline.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Standard lifetime dietary carcinogenicity bioassays were conducted in mice and rats. Mice were given cinacalcet at dietary doses of 15, 50, and 125 mg/kg/day in males and 30, 70, and 200 mg/kg/day in females (exposures up to 2 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). Rats were given dietary doses of 5, 15, and 35 mg/kg/day in males and 5, 20, and 35 mg/kg/day in females (exposures up to 2 times those resulting with a human oral dose of 180 mg/day

based on AUC comparison). No increased incidence of tumors was observed following treatment with cinacalcet.

Mutagenicity

Cinacalcet was not genotoxic in the Ames bacterial mutagenicity assay, nor in the Chinese Hamster Ovary (CHO) cell HGPRT forward mutation assay and CHO cell chromosomal aberration assay, with and without metabolic activation, nor in the in vivo mouse micronucleus assay.

Impairment of Fertility

Female rats were given oral gavage doses of 5, 25, and 75 mg/kg/day cinacalcet beginning 2 weeks before mating and continuing through gestation day 7. Male rats were given oral doses 4 weeks prior to mating, during mating (3 weeks) and 2 weeks postmating. No effects were observed in male or female fertility at 5 and 25 mg/kg/day (exposures up to 3 times those resulting with a human oral dose of 180 mg/day based on AUC comparison). At 75 mg/kg/day, there were slight adverse effects (slight decreases in body weight and food consumption) in males and females.

14 CLINICAL STUDIES

14.1 Secondary Hyperparathyroidism in Patients with Chronic Kidney Disease on Dialysis

Three 6-month, multicenter, randomized, double-blind, placebo-controlled clinical studies of similar design were conducted in patients with CKD on dialysis. A total of 665 patients were randomized to cinacalcet hydrochloride tablets and 471 patients to placebo. The mean age of the patients was 54 years, 62% were male, and 52% were Caucasian. The average baseline iPTH level by the Nichols IRMA was 712 pg/mL, with 26% of the patients having a baseline iPTH level > 800 pg/mL. The mean baseline Ca x P product was 61 mg^2/dL^2. The average duration of dialysis prior to study enrollment was 67 months. Ninety-six percent of patients were on hemodialysis and 4% on peritoneal dialysis. At study entry, 66% of the patients were receiving vitamin D sterols and 93% were receiving phosphate binders. Cinacalcet hydrochloride tablets (or placebo) was initiated at a dose of 30 mg once daily and titrated every 3 or 4 weeks to a maximum dose of 180 mg once daily to achieve an iPTH of ≤ 250 pg/mL. The dose was not increased if a patient had any of the following: iPTH ≤ 200 pg/mL, serum calcium < 7.8 mg/dL, or any symptoms of hypocalcemia. If a patient experienced symptoms of hypocalcemia or had a serum calcium < 8.4 mg/dL, calcium supplements and/or calcium-based phosphate binders could be increased. If these measures were insufficient, the vitamin D dose could be increased. Approximately 70% of patients in the cinacalcet hydrochloride arm and 80% of the patients in the placebo arm completed the 6-month studies. In the primary efficacy analysis, 40% of the patients on cinacalcet hydrochloride tablets and 5% of placebo-treated patients achieved an iPTH ≤ 250 pg/mL ($p < 0.001$) (Table 7, Figure 1). These studies showed that cinacalcet hydrochloride tablets reduced iPTH while lowering Ca x P, calcium, and phosphorus levels (Table 7, Figure 2). The median dose of cinacalcet hydrochloride tablets at the completion of the studies was 90 mg. Patients with milder disease typically required lower doses.

Similar results were observed when either the iPTH or biointact PTH (biPTH) assay was used to measure PTH levels in CKD patients on dialysis; treatment with cinacalcet did not alter the relationship between iPTH and biPTH.

Table 7. Effects of Cinacalcet Hydrochloride Tablets on iPTH, Ca x P, Serum Calcium, and Serum Phosphorus in 6-month Phase 3 Studies (Patients on Dialysis)

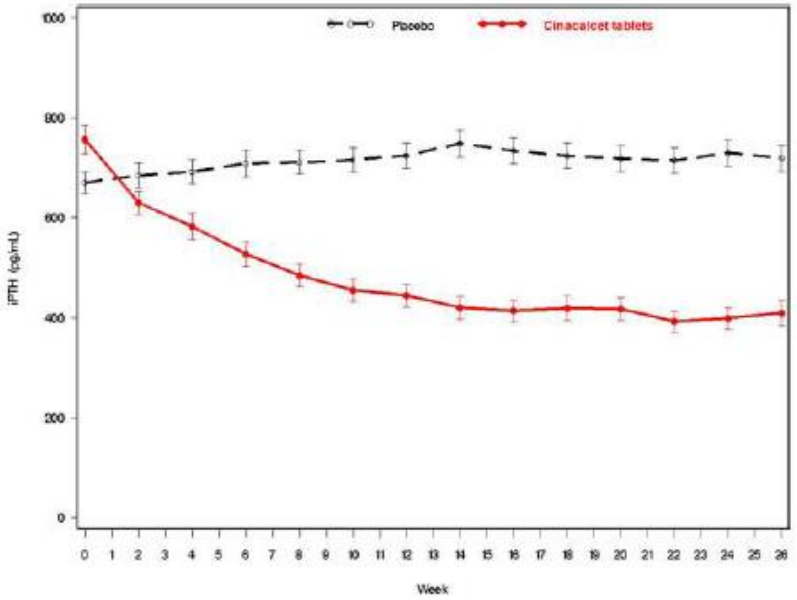
	Study 1		Study 2		Study 3	
	Placebo (n = 205)	Cinacalcet hydrochloride tablets (n = 205)	Placebo (n =165)	Cinacalcet hydrochloride tablets (n =166)	Placebo (n =101)	Cinacalcet hydrochloride tablets (n =294)
iPTH						

Baseline (pg/mL):	535	537	556	547	670	703
Median	651 (398)	636 (341)	630 (317)	652 (372)	832 (486)	848 (685)
Mean (SD)						
Evaluation Phase	563	275	592	238	737	339
(pg/mL)	+3.8	-48.3	+8.4	-54.1	+2.3	-48.2
Median Percent Change	4%	41%†	7%	46%†	6%	35%†
Patients Achieving Primary Endpoint (iPTH ≤ 250 pg/mL) (%)*						
Patients Achieving ≥	11%	61%	12%	68%	10%	59%
30% Reduction in iPTH	1%	32%		35%	5%	
(%)a			5%			28%
Patients Achieving iPTH ≤ 250 pg/mL and Ca x P < 55 mg2/dL2 (%)						
Ca x P						
Baseline (mg2/dL2)	62	61	61	61	61	59
Evaluation Phase	59	52	59	47	57	48
(mg2/dL2)	-2.0	-14.9	-3.1	-19.7	-4.8	-15.7
Median Percent Change						
Calcium						
Baseline (mg/dL)	9.8	9.8	9.9	10.0	9.9	9.8
Evaluation Phase	9.9	9.1	9.9	9.1	10.0	9.1
(mg/dL)	+0.5	-5.5	+0.1	-7.4	+0.3	-6.0
Median Percent Change						
Phosphorus						
Baseline (mg/dL)	6.3	6.1	6.1	6.0	6.1	6.0
Evaluation Phase	6.0	5.6	5.9	5.1	5.6	5.3
(mg/dL)	-1.0	-9.0	-2.4	-12.4	-5.6	-8.6
Median Percent Change						

* $p < 0.001$ compared with placebo; p-values presented for primary endpoint only.

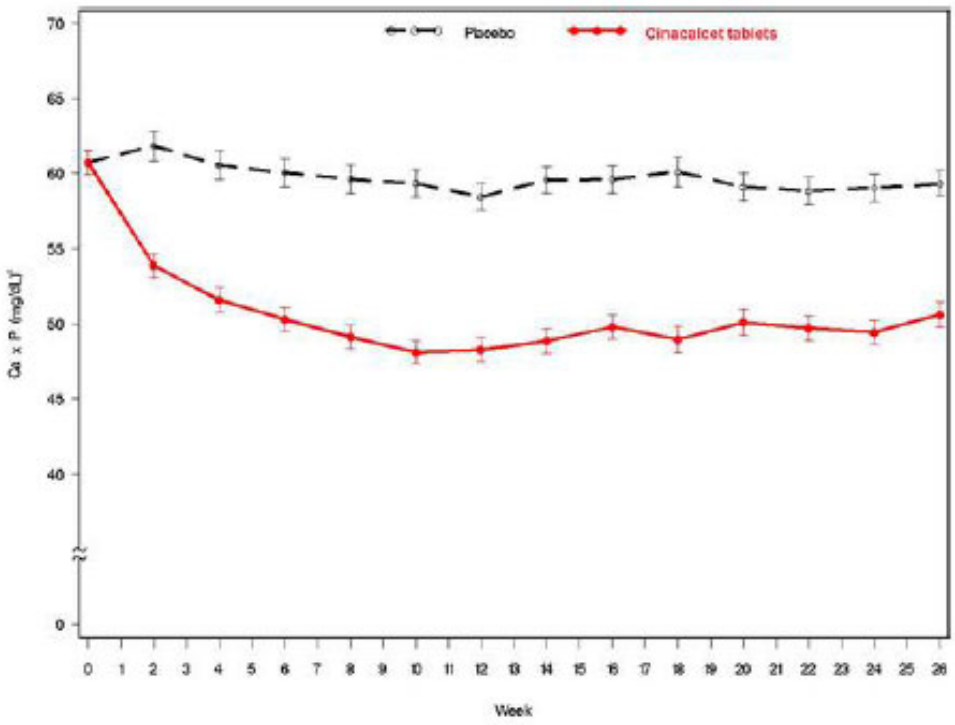
† iPTH value based on averaging over the evaluation phase (defined as weeks 13 to 26 in studies 1 and 2 and weeks 17 to 26 in study 3). Values shown are medians unless indicated otherwise.

Figure 1. Mean (SE) iPTH Values (Pooled Phase 3 Studies)



Data are presented for patients who completed the studies; Placebo (n = 342), cinacalcet hydrochloride tablets (n = 439).

Figure 2. Mean (SE) Ca x P Values (Pooled Phase 3 Studies)



Data are presented for patients who completed the studies; Placebo (n = 342), cinacalcet hydrochloride tablets (n = 439).

Reductions in iPTH and Ca x P were maintained for up to 12 months of treatment.

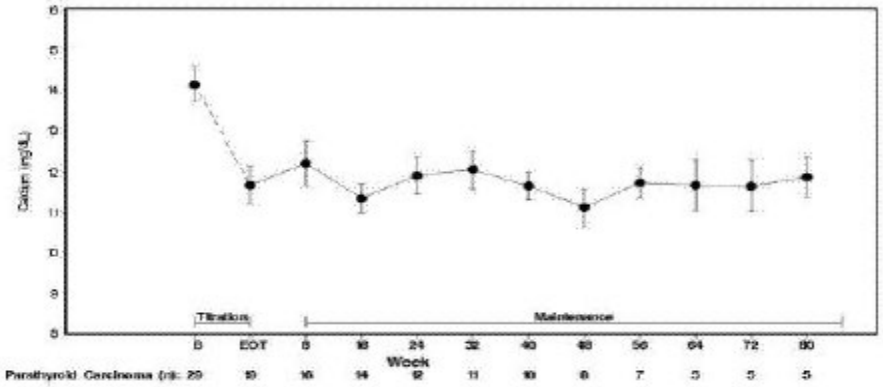
Cinacalcet hydrochloride tablets decreased iPTH and Ca x P levels regardless of disease severity (i.e., baseline iPTH value), duration of dialysis, and whether or not vitamin D sterols were administered. Approximately 60% of patients with mild (iPTH ≥ 300 to ≤ 500 pg/mL), 41% with moderate (iPTH > 500 to 800 pg/mL), and 11% with severe (iPTH > 800 pg/mL) secondary HPT achieved a mean iPTH value of ≤ 250 pg/mL. Plasma iPTH levels were measured using the Nichols IRMA.

14.2 Parathyroid Carcinoma

Twenty-nine patients with Parathyroid Carcinoma were enrolled in a single-arm, open-label study. The study consisted of two phases, a dose-titration phase and a maintenance phase. Patients initially received 30 mg cinacalcet twice daily and then were titrated every 2 weeks to a maximum dose of 90 mg four times daily. Dosage escalation during the variable-length (2 to 16 weeks) titration phase continued until the serum calcium concentration was ≤ 10 mg/dL (2.5 mmol/L), the patient reached the highest possible dosage, or adverse events precluded further dosage increases.

Twenty-nine patients entered the study. The median exposure to cinacalcet was 229 days (range: 1 to 1051). At baseline the mean (SE) serum calcium was 14.1 (0.4) mg/dL. At the end of the titration phase, the mean (SE) serum calcium was 12.4 (0.5) mg/dL, which is a mean reduction of 1.7 (0.6) mg/dL from baseline. Figure 3 illustrates mean serum calcium (mg/dL) over time for all patients still on study at each time point from the beginning of titration to study visit week 80. Daily dose during the study ranged from 30 mg twice daily to 90 mg four times daily.

Figure 3. Serum Calcium Values in Patients with Parathyroid Carcinoma Receiving Cinacalcet Tablets at Baseline, Titration, and Maintenance Phase



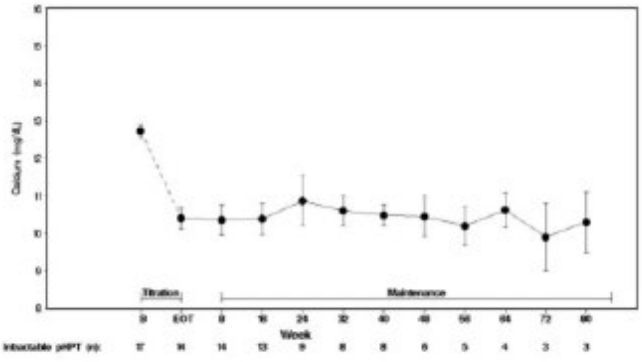
n = Number of patients with non-missing values at the timepoint. End of Titration (EOT) phase could occur at any visit from week 2 to 16. Patients at EOT are those who completed titration.

14.3 Patients with Hypercalcemia Due to Primary Hyperparathyroidism

Seventeen patients with severe hypercalcemia due to primary HPT, who had failed or had contraindications to parathyroidectomy, participated in an open-label, single-arm study. The study consisted of two phases, a dose-titration phase and a maintenance phase. In this trial, severe hypercalcemia was defined as a screening serum calcium level of > 12.5 mg/dL. Patients initially received 30 mg cinacalcet twice daily and then were titrated every 2 weeks to a maximum dose of 90 mg 4 times daily. Dosage escalation during the variable-length (2 to 16 weeks) titration phase continued until the serum calcium concentration was ≤ 10 mg/dL (2.5 mmol/L), the patient reached the highest possible dosage, or adverse events precluded further dosage increases.

Seventeen patients entered the study. The median exposure to cinacalcet was 270 days (range: 32 to 1,105). At baseline the mean (SE) serum calcium was 12.7 (0.2) mg/dL. At the end of the titration phase the mean (SE) serum calcium was 10.4 (0.3) mg/dL, which is a mean reduction of 2.3 (0.3) mg/dL from baseline. Figure 4 illustrates mean serum calcium (mg/dL) over time for all patients still on study at each time point from the beginning of titration to study visit week 80. Daily dose during the study ranged from 30 mg twice a day to 90 mg four times a day.

Figure 4.Mean SerumCalcium(SE) at Baseline, End of Titration, and Scheduled Maintenance Visits (Patients with Severe intractable primary HPT)



n = Number of patients with non-missing values at the timepoint.

End of Titration (EOT) phase could occur at any visit from week 2 to 16. Patients at EOT are those who completed titration.

16 HOW SUPPLIED/STORAGE AND HANDLING

Cinacalcet hydrochloride 30 mg tablets are formulated as light-green, film-coated, oval-shaped, biconvex tablets debossed with "CL" on one side and "410" on the opposite side, packaged in bottles of 30 tablets. (NDC 69097-410-02).

Cinacalcet hydrochloride 60 mg tablets are formulated as light-green, film-coated, oval-shaped, biconvex tablets debossed with "CL" on one side and "411" on the opposite side, packaged in bottles of 30 tablets. (NDC 69097-411-02).

Cinacalcet hydrochloride 90 mg tablets are formulated as light-green, film-coated, oval-shaped, biconvex tablets debossed with "CL" on one side and "412" on the opposite side, packaged in bottles of 30 tablets. (NDC 69097-412-02).

Storage

Store at 25 °C (77 °F), excursions permitted from 15to 30 °C (59 to 86 °F). [See USP controlled room temperature.]

17 PATIENT COUNSELING INFORMATION

- *Hypocalcemia:* Advise patients to report symptoms of hypocalcemia, including paresthesias, myalgias, muscle spasms, and seizures, to their healthcare provider [see Warnings and Precautions (5.1)].
- *Upper Gastrointestinal Bleeding* : Advise patients to report any symptoms of upper gastrointestinal bleeding to their health care provider [see Warnings and Precautions (5.2)].
- *Heart Failure:* Advise patients with heart failure that use of cinacalcet hydrochloride tablets may worsen their heart failure and additional monitoring may be required *[seeWarnings and Precautions (5.3)]*.
- Advise patients to report nausea and vomiting to their health care provider *[see Adverse Reactions (6.1)]* .
- Advise patients to take cinacalcet hydrochloride tablets with food or shortly after a meal and to take the tablets whole and not divide them *[see Dosage and Administration (2.1)]* .
- Inform patients of the importance of regular blood tests, in order to monitor the safety and efficacy of cinacalcet hydrochloride tablets therapy.

Manufactured by:

Cipla Limited,

Patalganga, District Raigad

Maharashtra, Pin code: 410 220.

India

Manufactured for:

Cipla USA, Inc.

1560 Sawgrass Corporate Parkway,

Suite 130, Sunrise, FL 33323

Revised: 04/2019

Appendix 3. Investigator's Signature

Study Title:	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.
Study Number:	CTAP101-CL-2010
Final Date:	05 May 2020

I agree:

To assume responsibility for the proper conduct of the study at this site.

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 OPKO Ireland Global Holdings Ltd. or its designee(s).

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/EC, 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).

That I am thoroughly familiar with the appropriate use of the investigational drugs, 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 OPKO Ireland Global Holdings Ltd. or its designee(s).

To ensure that all persons assisting me with the study are adequately informed about the investigational drugs and of their study-related duties and functions as described in the protocol.

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. OPKO Ireland Global Holdings Ltd. will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply OPKO Ireland Global Holdings 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 OPKO Ireland Global Holdings Ltd. may disclose this information about such ownership interests and financial ties to regulatory authorities.

Signed:_____ Date:_____

Printed Name:_____

Signature Page for CTAP101-CL-2010 Protocol v14.0

Approval	[redacted] 06-May-2020 15:19:16 GMT+0000

Approval	[redacted]ger 06-May-2020 15:50:25 GMT+0000

Approval	[redacted] 06-May-2020 15:55:54 GMT+0000

Signature Page for RIM-CLIN-000472 v14.0