CLINICAL STUDY PROTOCOL: CTAP101-CL-4001

An Open-Label, Repeated-Dose Safety, Efficacy, Pharmacokinetic, and Pharmacodynamic Study of Oral CTAP101 Capsules, Immediate-Release (IR) Calcifediol, High-Dose Cholecalciferol, and Paricalcitol Plus Low-Dose Cholecalciferol in Patients with Secondary Hyperparathyroidism, Stage 3 or 4 Chronic Kidney Disease and Vitamin D Insufficiency

Statistical Analysis Plan

Version 1.0: 19 December 2018

Statistical Analysis Plan Signature Page

Study Title:	An Open-Label, Repeated-Dose Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of Oral CTAP101 Capsules, Immediate-Release (IR) Calcifediol, High-Dose Cholecalciferol, and Paricalcitol Plus Low-Dose Cholecalciferol in Patients with Secondary Hyperparathyroidism, Stage 3 or 4 Chronic Kidney Disease and Vitamin D Insufficiency
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Table of Contents

LIST OF ABBREVIATIONS

λ_z	terminal elimination rate constant
$1,25D_3$	1,25-dihydroxyvitamin D_3, calcitriol
$24,25D_3$	24,25-dihydroxyvitamin D_3
25D	25-hydroxyvitamin D
$25D_3$	25-hydroxyvitamin D_3, calcifediol, calcidiol
AE	adverse event
$Ae_{0\text{-}24h}$	amount excreted in urine over 24 hours
AUC	area under the concentration curve
$AUC_{0\text{-}24h}$	AUC from time 0 to 24 hours
$AUC_{0\text{-}28d}$	AUC from time 0 to 28 days
$AUC_{0\text{-}56d}$	AUC over the entire study period (56 days)
$AUC_{0\text{-}inf}$	AUC from time 0 extrapolated to infinity
$AUC_{0\text{-}t}$	AUC from time 0 to the last measurable time point
$AUC_{0\text{-}t'}$	AUC from time 0 to a fixed time point t
AUC_{ext}	percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation
AUC_{tau}	AUC during the dosing interval (tau)
BL	baseline
BLQ	below the limit of quantitation
BMI	body mass index
CCI [redacted]	
C_{avg}	average concentration over a dosing interval after multiple doses
$C_{avg,24h}$	C_{avg} over the 24-hour dosing interval
$C_{avg,28d}$	C_{avg} over the 28-day dosing interval
$C_{avg,56d}$	C_{avg} over the entire study period (56 days)
CCI [redacted]	
CKD	chronic kidney disease
C_{last}	last measurable concentration
CL/F	apparent clearance after extravascular administration
CL_{ss}/F	apparent clearance after multiple extravascular administrations
C_{max}	maximum concentration
$C_{max,0\text{-}24h}$	maximum concentration during a 24-hour interval
CCI [redacted]	
CV%	percent coefficient of variation
CCI [redacted]	

dL	deciliter
EAP	efficacy assessment period
eGFR	estimated glomerular filtration rate
EOS	end of study
ET	early termination
CCI [redacted]	
iPTH	intact parathyroid hormone
IR	immediate release
ITT	intent-to-treat
IU	international unit
LF	linearity factor
ln	natural log
MedDRA	Medical Dictionary for Regulatory Activities
mcg	microgram
mg	milligram
mL	milliliter
CCI [redacted]	
PD	pharmacodynamic
PK	pharmacokinetic
PP	per protocol
PT	preferred term
R^2-adj	adjusted coefficient of determination
RA,AUC	accumulation ratio based on AUC
RA,C_{max}	accumulation ratio based on C_{max}
SAP	statistical analysis plan
SD	standard deviation
SHPT	secondary hyperparathyroidism
SOC	system organ class
$t_{1/2}$	terminal elimination half-life
TEAE	treatment-emergent AE
T_{max}	time of maximum concentration
$T_{max,0-24h}$	time of maximum concentration during a 24-hour interval
CCI [redacted]	
T_{ss}	predicted time to steady state
V_d/F	apparent volume of distribution after extravascular administration
VDI	vitamin D insufficiency

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical analysis methods and data presentation to be used for the analysis and summarization of pharmacokinetic (PK), CCI and safety data from Protocol CTAP101-CL-4001.

The SAP will be finalized before database lock. Any changes made after finalization of the SAP will be documented, by either an amendment or addendum if prior to database lock; otherwise, changes made to the planned analyses after database lock will be documented in the clinical study report as post hoc analyses and any updates to the shell document will be made with changes documented in the revision history of that document. Related documents are the study protocol, study drug dispensing, protocol deviations, informed consent form, and electronic case report forms.

2 OBJECTIVES AND PARAMETERS

2.1 Objectives

The objectives of this study are to assess the repeated-dose safety, efficacy, PK, CCI profiles of CTAP101 Capsules, immediate-release (IR) calcifediol, high-dose cholecalciferol, and paricalcitol plus low-dose cholecalciferol in patients with secondary hyperparathyroidism (SHPT), stage 3 or 4 chronic kidney disease (CKD), and vitamin D insufficiency (VDI).

2.2 Endpoints

2.2.1 Efficacy Endpoints

This study is descriptive and no primary or secondary efficacy endpoints are defined.

2.2.2 Pharmacokinetic Endpoints

The following PK parameters will be calculated for observed and baseline (BL)-adjusted serum calcifediol (also known as 25-hydroxyvitamin D_3 [$25D_3$]) CCI concentrations using noncompartmental methods (data permitting), where additional parameters may be evaluated based on the concentration-time data:

1. C_{max} – maximum concentration (including C_{max} during a 24-hour interval [$C_{max,0\text{-}24h}$]);
2. T_{max} – time of maximum concentration (including T_{max} during a 24-hour interval [$T_{max,0\text{-}24h}$]);
3. $AUC_{0\text{-}t}$ – area under the concentration-time curve (AUC) from time 0 to the last measurable time point;
4. $AUC_{0\text{-}t'}$ – AUC from time 0 to a fixed time point t. This will include the AUC from time 0 to 24 hours ($AUC_{0\text{-}24h}$) for all dosing regimens and AUC from time 0 to 28 days ($AUC_{0\text{-}28d}$) for the monthly dosing regimens only;
5. $AUC_{0\text{-}56d}$ – AUC over the entire study period (56 days);
6. AUC_{tau} – AUC during the dosing interval (tau), where tau = 24 hours for the daily dosing regimens and tau = 28 days for the monthly dosing regimens. AUC_{tau} will only be calculated for the monthly dosing regimens if deemed appropriate;
7. $AUC_{0\text{-}inf}$ – AUC from time 0 extrapolated to infinity (paricalcitol only);
8. AUC_{ext} – percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation (a diagnostic parameter calculated and listed in the data listing, but not included in the descriptive statistics) (paricalcitol only);
9. C_{avg} – average concentration over a dosing interval after multiple doses. For the monthly dosing regimens, average exposure may be calculated over a 24-hour interval ($C_{avg,24h}$ = $AUC_{0\text{-}24h}$/24 hours), the entire dosing interval ($C_{avg,28d}$ = $AUC_{0\text{-}28d}$/28 days), and/or over the entire study period $C_{avg,56d}$ = $AUC_{0\text{-}56d}$/56 days);

10. T_{ss} – predicted time to steady state (paricalcitol only);
11. λ_z – terminal elimination rate constant (paricalcitol only);
12. $t_{1/2}$ –terminal elimination half-life (paricalcitol only);
13. CL/F – apparent clearance after extravascular administration (paricalcitol only);
14. CL_{ss}/F – apparent clearance after multiple extravascular administrations;
15. V_d/F – apparent volume of distribution after extravascular administration (paricalcitol only);
16. RA,C_{max} – accumulation ratio based on C_{max};
17. RA,AUC – accumulation ratio based on AUC;
18. LF – linearity factor (paricalcitol only).

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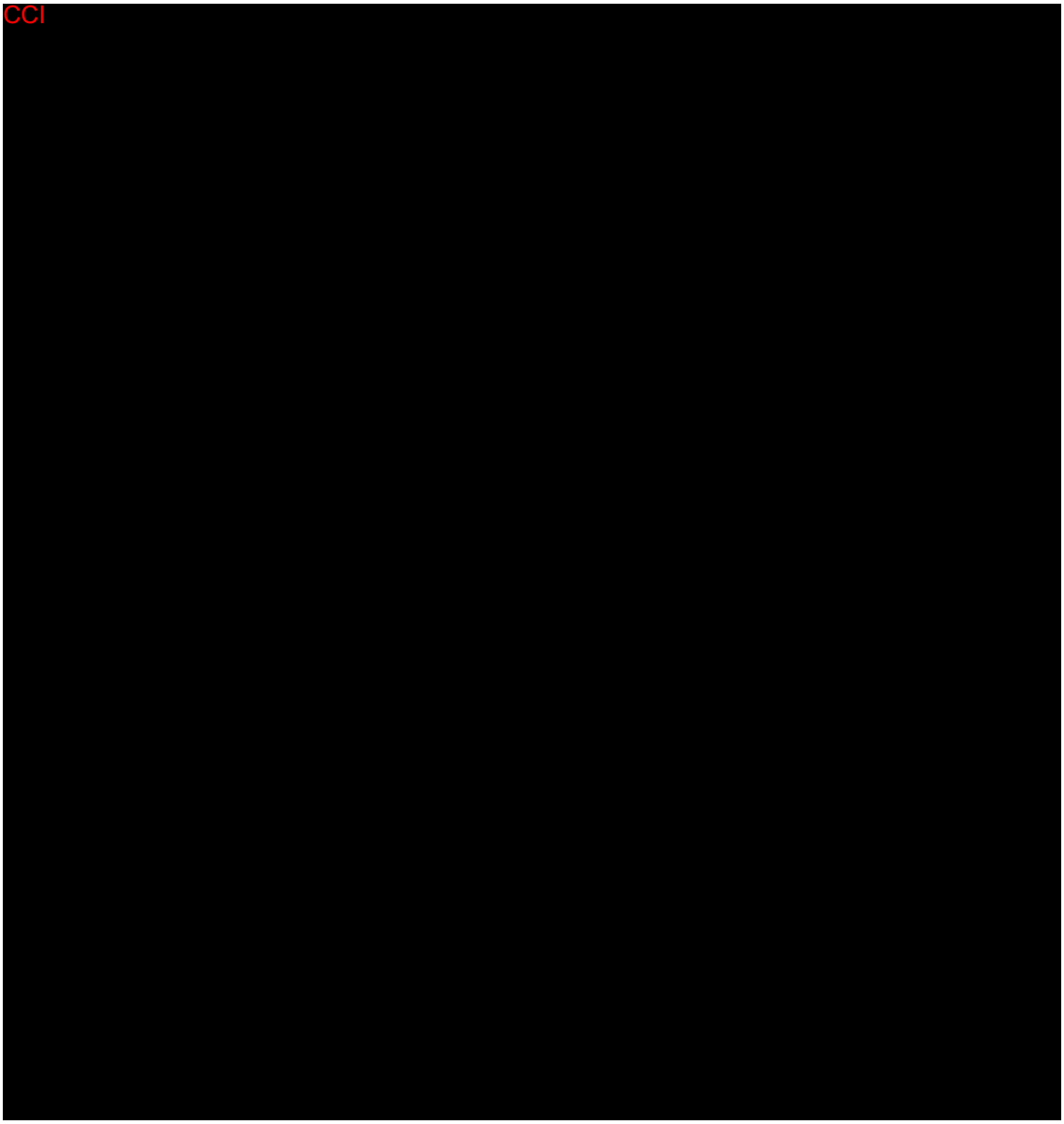

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2.2.4 Safety Endpoints

The safety and tolerability of each study drug will be evaluated using the following parameters:

1. Adverse events (AEs);
2. Physical examinations;
3. Vital signs;
4. Clinical laboratory test results (hematology and serum chemistry);
5. Incidence of hypercalcemia and drug-related hyperphosphatemia.

3 STUDY DESIGN

3.1 Number of Subjects

Approximately 160 subjects will be screened to enroll approximately 80 eligible subjects with approximately 20 subjects per treatment arm. After signing the informed consent form, prior to any study-related activities, each subject will be assigned a unique 7-digit subject identification number (SSSNNNN) which will be retained throughout the study and that will be unique across all sites. The number will consist of a 3-digit site number (SSS), followed by a 4-digit subject number (NNNN) at the applicable clinical site. Should a subject be withdrawn from the study, that subject's number will not be reassigned.

Randomization will be accomplished in blocks of 4 subjects in a 1:1:1:1 ratio, with subjects assigned to treatment with either CTAP101 Capsules, IR calcifediol, high-dose cholecalciferol, or paricalcitol plus low-dose cholecalciferol. Randomization will occur on Day 1 (Visit 4) provided that each subject is deemed eligible for enrollment based, in part, on laboratory assessments obtained at screening (Days –42 to –36, Visit 1). Laboratory assessments obtained at Days –7 to –1 (Visits 2-3) will not be considered in the determination of enrollment eligibility.

3.2 Sample Size Considerations

The total sample size of approximately 80 subjects was based on practical, clinical considerations and is typical for such studies. No formal sample size estimation was performed.

3.3 Study Design

This is a phase 4, single- or multi-center, open-label study to evaluate the comparative safety, efficacy, and PK and CCI profiles of CTAP101 Capsules, IR calcifediol, high-dose cholecalciferol, and paricalcitol plus low-dose cholecalciferol CCI [redacted] in male and female subjects at least 18 years of age with stage 3 or 4 CKD and VDI. The study will be conducted at up to 3 sites within the United States. Subjects (approximately 20 per arm) will receive the following treatments:

1) CTAP101 Capsules (30 mcg/capsule), 60 mcg by the oral route, once daily for 56 days;
2) Calcifediol IR (266 mcg/capsule), 266 mcg by the oral route, on Days 1 and 29;
3) Cholecalciferol (50,000 IU/capsule), 300,000 International Units (IU) by the oral route (6 capsules), on Days 1 and 29; and,
4) Paricalcitol (1 mcg/capsule) plus cholecalciferol (800 IU/capsule), 1 or 2 mcg plus 800 IU by the oral route, once daily for 56 days.

After 4 weeks of treatment, subjects who are receiving paricalcitol will double the dose to 2 mcg plus cholecalciferol 800 IU once daily in the morning before breakfast if all of the following conditions are met: the plasma iPTH has not decreased by at least 30% from

pretreatment BL and remains above 70 pg/mL, corrected serum total calcium is <9.8 mg/dL, and serum phosphorus is <5.5 mg/dL. Subjects who are receiving CTAP101 Capsules, IR calcifediol, or cholecalciferol (300,000 IU) will not undergo upward dose titration.

Subjects will reduce the dose of study drug per the following schedule if any of the following conditions are met: plasma iPTH is confirmed to be <30 pg/mL, corrected serum total calcium is confirmed to be >10.3 mg/dL, or serum phosphorus is confirmed to be >5.5 mg/dL.

Dose reduction (if needed):

CTAP101: decrease to 30 mcg per day (from 60 mcg per day)

IR calcifediol: hold Day 29 dose

Cholecalciferol 300,000 IU: hold Day 29 dose

Paricalcitol: decrease dose to 1 mcg per day (from 2 mcg per day)

Cholecalciferol 800 IU will not be adjusted

Subjects will suspend dosing if plasma iPTH is confirmed to be <15 pg/mL or corrected serum total calcium is confirmed to be >11.0 mg/dL, and will resume dosing when plasma iPTH is ≥30 pg/mL and corrected serum total calcium is <9.8 mg/dL per the following schedule. In the event that a dose reduction is required for a subject receiving the minimum dosage of CTAP101 Capsules (30 mcg per day) or paricalcitol (1 mcg per day), the subject will suspend dosing and resume when iPTH is ≥30 pg/mL and corrected serum total calcium is <9.8 mg/dL at the same minimum dosage.

Dose resumption (if needed):

CTAP101: 30 mcg per day

Paricalcitol 1 mcg per day

The subjects will be housed in a phase 1 unit for approximately 14 to 26 hours at the beginning of the study and on study Day 29 to provide the blood samples required for a detailed determination of the PK profiles for serum calcifediol CCI [redacted] Blood samples for some of the PK and CCI assessments will be collected in the phase 1 unit at –2, 0, 2, 4, 6, and 12 hours, either in the phase 1 unit or during an outpatient visit at 24 hours, during the outpatient visit at 48 hours, and then weekly following the first dose and the Day 29 dose of study drug. Blood samples for other CCI assessments will be collected at less frequent intervals. Urine collections (over 24 hours) will be obtained at pretreatment BL (Visits 2 and 3), starting immediately after dosing on Day 1 (Visit 4) and Day 29 (Visit 10), and at the end of study (EOS) visit

(Visit 16) or at early termination (ET). The full schedule of assessments is provided in Table 1.

Subjects receiving treatment with calcitriol or another 1α-hydroxylated vitamin D analog, or if serum total 25D >30 ng/mL when taking vitamin D supplementation (including multivitamins and fish oil), will complete a 4-week washout period before BL assessments. Subjects will forgo further dosing with these nonstudy drugs for the duration of the study. Subjects receiving calcimimetic therapy within the 12 weeks preceding Screening will be ineligible for enrollment.

Blood samples will be collected from all subjects at weekly intervals during the screening and BL periods, during the 8-week treatment period, and at the specified times during the PK/CCI assessment. Key parameters to be analyzed in the collected samples include some or all of the following: serum calcifediol, CCI [redacted] serum 24,25D_3, CCI [redacted]

Vitals signs and AEs will be monitored at each study visit. Other safety parameters to be monitored less frequently include CCI [redacted] brief physical examinations, and clinical laboratory tests (hematology and serum chemistry). The number and percentage of subjects with hypercalcemia (defined as 2 consecutive visits with serum total calcium >10.3 mg/dL) or hyperphosphatemia (defined as 2 consecutive visits with serum phosphorus >5.5 mg/dL) will be calculated as a secondary safety endpoint.

Subjects will maintain a dietary intake during the study of approximately 1,000 to 1,500 mg of elemental calcium per day with dietary counseling and, as necessary, administration of a daily calcium supplement.

Table 1. Schedule of Assessments

	Screening	Washout	Baseline		Treatment												EOS/ ET
Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Week	–5		–1	–1	1	1	1	2	3	4	5	5	5	6	7	8	9
Day(s)	–42 to –36	–35 to –8	–7 to –2	–1	1	2	3	8	15	22	29	30	31	36	43	50	57
					(GCRC)						(GCRC)						
Hour(s)					–2, 0, 2, 4, 6, 12	24	48				–2, 0, 2, 4, 6, 12	24	48				
Study drug dispensed					1[a,b]						1[a,b]						
Dosing compliance and dosing diary assessed								1	1	1	1			1	1	1	1
Sign informed consent form	1																
Review inclusion/exclusion criteria	1		1	1													
Medical history and demographics	1	Washout															
Diet history and counseling for (as needed) calcium intake	1																
Prior medications review	1																
Concomitant medications review	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Adverse events			1	1	6	1	1	1	1	1	6	1	1	1	1	1	1
Physical exam (including weight, height, and BMI)	1																1
Vital signs assessment	1		1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Blood pregnancy test (for females of childbearing potential)	1		1														1
Serum hepatitis B, hepatitis C, and HIV screen	1																
eGFR	1																
Urinary albumin excretion	1																
Clinical chemistry (full panel)	1		1	1							1						1
Hematology	1		1	1							1						1
Clinical chemistry (partial panel)[d]					6	1	1	1	1	1	6	1	1	1	1	1	
Urine drugs of abuse screen	1																
CCI [redacted]																	

	Screening	Washout	Baseline		Treatment												EOS/ ET
Visit	1		2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Week	–5		–1	–1	1	1	1	2	3	4	5	5	5	6	7	8	9
Day(s)	–42 to –36	–35 to –8	–7 to –2	–1	1	2	3	8	15	22	29	30	31	36	43	50	57
					(GCRC)						(GCRC)						
Hour(s)					–2, 0, 2, 4, 6, 12	24	48				–2, 0, 2, 4, 6, 12	24	48				
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Abbreviations: $1,25D_3$, 1,25-dihydroxyvitamin D_3; $24,25D_3$, 24,25-dihydroxyvitamin D_3; CCI, 25-hydroxyvitamin D; $25D_3$, calcifediol; BMI, body mass index; CCI eGFR, estimated glomerular filtration rate; EOS, end of study; ET, early termination; CCI GCRC, general clinical research center; HIV, human immunodeficiency virus; CCI ionized calcium; iPTH, intact parathyroid hormone; CCI

NOTE: The number listed under each respective event reflects the number of occurrences for that specific type of event on the specific visit designations; absence of number designation indicates that no occurrence of such event is required.

a Study drug dispensing for subjects assigned to CTAP101 Capsules and paricalcitol capsules plus low-dose cholecalciferol.

b Study drug dispensed for t = 0 dose on Days 1 and 29 from monthly study drug supply.

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d Partial chemistry panel includes serum calcium, calcium (corrected), phosphorus, and albumin.

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4 GENERAL STATISTICAL CONSIDERATIONS

All analyses described in this plan are considered a priori analyses in that they have been defined before locking the database. All other analyses, if any, designed subsequent to locking the database will be considered post hoc analyses and will be applied as exploratory methodology. All post hoc analyses will be identified as such in the clinical study report.

All statistical tests will be tested at $\alpha = 0.05$, 2-sided significance level, unless otherwise stated. Descriptive statistics for continuous variables will include number of subjects, mean, standard deviation (SD), median, minimum, and maximum, unless otherwise noted. In descriptive summary tables of PK CCI data, if needed, the geometric mean, geometric percent coefficient of variation (CV%), and arithmetic CV% will be included, where the geometric mean will be calculated using the exponential function (exp) of the mean of the natural log (ln)-transformed data, the geometric CV% will be calculated as $[\exp(SD^2)-1]^{1/2} \times 100$, where SD is the standard devation for ln-transformed data, and the CV% will be calculated as 100×(SD/[arithmetic mean]). Descriptive statistics for categorical variables will consist of counts and percentages.

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% and geometric CV% will be rounded to 1 decimal place.

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

All analyses will be conducted with SAS® version 9.4 or later using procedures appropriate for the particular analysis.

5 ANALYSIS POPULATIONS

5.1 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who are randomly assigned to treatment. If actual treatment differs from the randomized treatment, the randomized treatment will be used.

5.2 Per-Protocol Population

CCI [redacted] If actual treatment differs from the randomized treatment, additional analyses using the actual treatment may be provided.

5.3 Safety Population

The safety population will include all subjects who are randomly assigned to treatment and receive at least 1 dose of study drug. The safety population will be used for all safety assessments.

5.4 Pharmacokinetic Population

The PK population will include all subjects who are randomly assigned to treatment, receive at least 1 dose of study drug, have no major protocol deviations, have at least 1 PK data point at BL, and sufficient measureable serum calcifediol or paricalcitrol concentrations to facilitate the calculation of at least 1 postdose PK parameter using validated methods. Presentation of data will use the actual treatment. In cases where a subject's dosing compliance is found to be an issue, PK parameters may not be calculated for that subject.

5.5 Handling of Missing Data

Missing data will not be imputed with the exception of incomplete medication start and stop dates and missing onset dates for AEs. Data that are excluded from the descriptive or inferential analyses will be included in the data listings. This will include those measurements from excluded subjects or measurements from unscheduled visits/collections. In calculation of the concentration summaries and displays in graphs, if values are below the limit of quantitation (BLQ) predose they will be set to zero and postdose they will be set to 'missing'; however, they will be presented as BLQ in data listings. If all concentrations at a given time point predose are BLQ, the mean will be presented as zero and the SD and CV% will be reported as not applicable.

For the calculation of PK parameters, BLQ values will be treated as follows:

- BLQ values in samples collected before administration or before the first measurable concentration will be set to zero.

- BLQ values that occur after the first measurable concentration will be set to 'missing.'
- BLQ values that occur at the end of the concentration-time profile will be set to 'missing.'

If both values of the predose average (–2 and 0 hour samples) on Day 29 are missing or BLQ, the minimum concentration for the dosing interval will be used for the calculation of AUC and associated PK parameters, as deemed appropriate. For BL-adjusted profiles, the negative values will be retained for calculation of PK parameters.

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5.6 Key Definitions

In the event that there are multiple results at a given visit or time point, the following logic will be applied for purposes of summarization by visit or time point:

Baseline value for safety endpoints is defined as the most recent nonmissing result before the time of the first dose for all treatments. Baseline value for PK CCI endpoints is defined as the average of all predose Day 1 samples excluding data collected on Days –42 to –36 (Visit 1).

Predose value for the PK CCI endpoints in calculation of the PK CCI parameters is defined as the average of the –2 and 0 hour samples predose on Day 1 for calculations following the first dose (Day 1) and the average of the –2 and 0 hour samples predose on Day 29 for the calculations following the last dose (Day 29).

Relative study day is defined as the number of days from the first dose date (Day 1) and will be presented in all data listings where a complete date is presented. Dates before the first dose date are decreased by 2 so there is no study Day 0, where the day before dosing is considered study Day –1.

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6 SUBJECT DISPOSITION AND BASELINE CHARACTERISTICS

6.1 Subject Discontinuation

The number of subjects who enroll in the study and the number and percentage of subjects who complete treatment and complete the study will be presented by treatment and overall for all enrolled subjects. A summary of the number of subjects within each population, along with the frequency and percentage of subjects who withdraw or discontinue from the study and the primary reason for withdrawal or discontinuation, will be summarized for each treatment and overall.

A data listing of subject disposition, including treatment and study completion status and reason for study discontinuation, will be provided. In addition, subject populations and reasons for exclusion from the population will be provided in a data listing.

6.2 Protocol Deviations

Major protocol deviations will be captured as a log by the clinical research coordinator, exported into a clinical dataset, and presented in a data listing.

6.3 Demographics and Baseline Characteristics

Descriptive statistics (ie, number of subjects, mean, SD, median, minimum, and maximum) will be calculated for continuous demographic and BL characteristic variables (age at Screening, weight at BL, height at Screening, and body mass index [BMI] at BL) and counts and percentages will be tabulated for categorical demographic variables (sex, race, and ethnicity) for each analysis population by treatment and overall.

A data listing will be provided for all demographic data. In addition, the BL characteristics of weight, height, and BMI will be included in the vital sign data listing.

6.4 Medical History

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 documented. Medical history data will be mapped using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.0 or higher to system organ class (SOC) and preferred term (PT) and will be listed by subject identification, medical condition reported term, onset date, and ongoing status/resolution date for all enrolled subjects and summarized by SOC and PT by treatment and overall for the safety population.

6.5 Inclusion and Exclusion Criteria

Inclusion and exclusion criteria not met by randomized subjects will be provided in a data listing.

6.6 Substance Use

Substance use history, including historical use of tobacco, nicotine, and alcohol, will be provided in a data listing by subject.

7 PHARMACOKINETIC ANALYSES

7.1 Serum and Plasma Concentrations

Blood samples will be collected from all subjects to determine the observed serum calcifediol CCI concentrations. Baseline-adjusted serum calcifediol concentrations will be calculated by subtracting the average of the BL concentrations. Negative BL-adjusted values will be retained in the analysis.

For each analyte, observed and BL-adjusted serum calcifediol CCI concentrations will be summarized using descriptive statistics (number of subjects, mean, SD, CV%, median, minimum, maximum, geometric mean, and geometric CV%) by visit, time point, and treatment for the PK population. Concentrations that are BLQ will be treated as outlined in Section 5.5. Mean serum and plasma concentration-time profiles will be plotted by treatment on linear (both calcifediol and paricalcitol) and semilogarithmic scales (only paricalcitol) using nominal times for the PK population. Individual concentration-time plots and spaghetti plots with subject concentration-time profiles overlaid by treatments will be included in the appendices using linear (both calcifediol and paricalcitol) and semilogarithmic scales (only paricalcitol).

Subgroups will also be presented for subjects who received the full dose of study drug versus those who received dose adjustments (ie, summaries provided for paricalcitol 1 mcg and 2 mcg on Day 29, where further categorization will be determined once the study is complete).

7.2 Serum and Plasma Pharmacokinetic Parameters

All PK analyses will be performed, as feasible, according to applicable standard operating procedures and protocol specifications. Pharmacokinetic parameters will be calculated using Phoenix® WinNonlin® Version 8.0 or later (Certara, Princeton, NJ, USA) and actual sampling times. If actual times are missing, nominal times may be used and will be noted in the appropriate data listing.

The PK parameters for observed and BL-adjusted serum calcifediol CCI will be calculated as follows (data permitting):

Pharmacokinetic Parameters Following the First Dose (Day 1):

Note: The following parameters will be calculated using the data through 24 hours (once daily dosing regimens) or 28 days (monthly dosing regimens) after the first dose on Day 1 for each of the analytes, as indicated.	
C_{max}:	Maximum concentration, observed by inspection of individual study participant concentration-time profiles.
$C_{max,0-24h}$:	Maximum concentration over a 24-hour interval, observed by inspection of individual study participant concentration-time profiles. Presented for the monthly dosing regimens only. (For the daily dosing regimens, C_{max} will be equivalent to $C_{max,0-24h}$.)

T_{max}:	Time of maximum concentration, obtained directly from the observed concentration-time data.
$T_{max,0\text{-}24h}$:	Time of maximum concentration over a 24-hour interval, obtained directly from the observed concentration-time data. Presented for the monthly dosing regimens only. (For the daily dosing regimens, T_{max} will be equivalent to $T_{max,0\text{-}24h}$.)
$AUC_{0\text{-}t}$:	AUC from time 0 to the last measurable time point, calculated by linear-log trapezoidal summation.
$AUC_{0\text{-}t'}$:	AUC from time 0 to a fixed time point t, calculated by linear-log trapezoidal summation. This will include the AUC from time 0 to 24 hours ($AUC_{0\text{-}24h}$) for all dosing regimens and AUC from time 0 to 28 days ($AUC_{0\text{-}28d}$) for the monthly dosing regimens only.
$AUC_{0\text{-}inf}$:	AUC from time 0 extrapolated to infinity, calculated as $AUC_{0\text{-}t} + C_{last}/\lambda_z$, where C_{last} is the last measurable concentration (paricalcitol only). The reliability of $AUC_{0\text{-}inf}$ values is contingent upon the percentage obtained by extrapolation (AUC_{ext}), where AUC_{ext} is >40%, $AUC_{0\text{-}inf}$ values are considered unreliable.
AUC_{ext}:	Percentage of $AUC_{0\text{-}inf}$ obtained by extrapolation, calculated as $[(AUC_{0\text{-}inf} - AUC_{0\text{-}t})/AUC_{0\text{-}inf}] \times 100$; (a diagnostic parameter calculated and listed in the data listing, but not included in the descriptive statistics; paricalcitol only).
λ_z:	Terminal elimination rate constant (if estimable), determined by linear regression of the terminal points of the log-linear concentration-time profile (paricalcitol only). Calculation of λ_z requires a minimum of 3 data points after (and not including) C_{max}. The adjusted coefficient of determination (R^2-adj) for the linear regression must be at least 0.80.
$t_{1/2}$:	Terminal elimination half-life (if estimable), determined as $[\ln(2)/\lambda_z]$ (paricalcitol only).
CL/F:	Apparent clearance after extravascular administration, calculated as $Dose/AUC_{0\text{-}inf}$ (paricalcitol only).
V_d/F:	Apparent volume of distribution after extravascular administration, calculated as $Dose/(\lambda_z \times AUC_{0\text{-}inf})$ (paricalcitol only).
T_{ss}:	Predicted time to steady state, calculated as $(t_{1/2} \times 5)$ (paricalcitol only).

Pharmacokinetic Parameters Following the Last Dose (Day 29):

Note: The following parameters will be calculated using the data through 24 hours for the once daily dosing regimens or through the EOS/ET sample on Day 57 (ie, 28 days post Day 29 dose) for the monthly dosing regimens, where possible.	
C_{max}:	Maximum concentration during the dosing interval (24 hours for once daily and 28 days for monthly), observed by inspection of individual study participant concentration-time profiles.
$C_{max,0-24h}$:	Maximum concentration over a 24-hour interval, observed by inspection of individual study participant concentration-time profiles. Presented for the monthly dosing regimens only. (For the daily dosing regimens, C_{max} will be equivalent to $C_{max,0-24h}$.)
T_{max}:	Time of maximum concentration during the dosing interval (24 hours for once daily and 28 days for monthly), obtained directly from the observed concentration-time data.
$T_{max,0-24h}$:	Time of maximum concentration over a 24-hour interval, obtained directly from the observed concentration-time data. Presented for the monthly dosing regimens only. (For the daily dosing regimens, T_{max} will be equivalent to $T_{max,0-24h}$.)
AUC_{0-t}:	AUC from time 0 to the last measurable time point, calculated by linear-log trapezoidal summation.
AUC_{tau}:	AUC during the dosing interval (tau), where tau = 24 hours for the daily dosing regimens and tau = 28 days for the monthly dosing regimens.
$AUC_{0-t'}$:	AUC from time 0 to a fixed time point t, calculated by linear-log trapezoidal summation. This will include the AUC_{0-24h} for the monthly dosing regimens (equivalent to AUC_{tau} for the daily dosing regimens).
C_{avg}:	Average concentration over a dosing interval after multiple doses, calculated as AUC_{tau}/tau. For the monthly dosing regimens, average exposure over a 24-hour interval ($C_{avg,24h}$ = AUC_{0-24h}/24 hours) and/or over the entire dosing interval ($C_{avg,28d}$ = AUC_{0-28d}/28 days).
RA,C_{max}	Accumulation ratio based on C_{max}, calculated as (C_{max}, Day 29)/(C_{max}, Day 1).
RA,AUC	Accumulation ratio based on AUC. For once daily dosing regimens, calculated as (AUC_{tau}, Day 29)/(AUC_{0-24h}, Day 1). For monthly dosing regimens, AUCs from 0 to 24 hours or 28 days may be used, as deemed appropriate.
LF	Linearity factor, calculated as (AUC_{tau}, Day 29)/(AUC_{0-inf}, Day 1) (paricalcitol only).

λ_z:	Terminal elimination rate constant (if estimable), determined by linear regression of the terminal points of the log-linear concentration-time profile (paricalcitol only). Calculation of λ_z requires a minimum of 3 data points after (and not including) C_{max}. The R^2-adj for the linear regression must be at least 0.80.
$t_{1/2}$:	Terminal elimination half-life (if estimable), determined as [ln(2)/λ_z] (paricalcitol only).
CL_{ss}/F:	Apparent clearance after multiple extravascular administrations, calculated as Dose/AUC_{tau} (calculated for paricalcitol and for BL-adjusted calcifediol following the calcifediol treatments only, where possible).

In addition to the above parameters, measures of exposure over the entire 56-day study period will be determined for calcifediol (for the monthly dosing regimens only), according to the following calculations:

- $AUC_{0\text{-}56d}$: AUC over the entire study period (56 days), calculated as ($AUC_{0\text{-}28d}$, Day 1) + (AUC_{tau}, Day 29);
- $C_{avg,56d}$: Average concentration over the entire study period (56 days), calculated as $AUC_{0\text{-}56d}$/56 days.

All subjects in the PK population will be included in the descriptive statistics for the PK parameters. No value for λ_z, $AUC_{0\text{-}inf}$, AUC_{ext}, CL/F, V_d/F, T_{ss}, or $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile. No PK parameters will be calculated for subjects with insufficient data following BLQ imputation, see Section 5.5 (eg, fewer than 3 quantifiable postdose concentrations for AUC, λ_z, and associated parameters; C_{max} and T_{max} parameters may be presented for subjects with fewer quantifiable concentrations, if deemed appropriate).

Descriptive statistics of PK parameters for calcifediol and paracalcitol will be provided for the PK population by visit and treatment and will include number of subjects, mean, SD, CV%, median, minimum, maximum, geometric mean and geometric CV%.

Subgroups will also be presented for subjects who received the full dose of study drug versus those who received dose adjustments (ie, summaries provided for paricalcitol 1 mcg and 2 mcg on Day 29, where categories will be determined once the study is complete).

All calculated PK parameters will be presented in a data listing.

7.3 Statistical Analysis of Pharmacokinetic Parameters

As an exploratory analysis, PK parameters for observed and BL-adjusted serum calcifediol will be compared between treatments using a mixed-effects model for the PK population. The dependent variable will be the value of the PK parameter. The model will include a term for treatment and BL calcifediol as a covariate. The PK parameters

compared may include C_{max} and AUC_{0-24h} for Day 1 and C_{max}, AUC_{0-24h} (ie, AUC_{tau} for daily dosing regimen), and C_{avg} for Day 29. Additional parameters (eg, alternative AUC_{0-t}, parameters) may be compared (and/or substituted) as deemed appropriate.

Treatment least-squares means and least-squares differences and 95% confidence intervals for the difference will be constructed for the values of each parameter. In addition, the *P* values will be presented for treatment and BL in the analysis table.

The SAS Proc Mixed code is as follows:

```
PROC MIXED DATA = adpc;
  BY paramn paramcd param;
  CLASS trtp;
  MODEL aval = trtp base_calcifediol;
  ESTIMATE ‘CTAP101 Capsules vs. Calcifediol IR' trtp 1 –1 0 0 / cl;
  ESTIMATE ‘CTAP101 Capsules vs. Cholecalciferol' trtp 1 0 –1 0 / cl;
  ESTIMATE ‘CTAP101 Capsules vs. Paracalcitol plus cholecalciferol' trtp 1 0 0 –1 / cl;
RUN;
```

Alternative statistical analyses may be provided if insufficient data or issues with the model are found.

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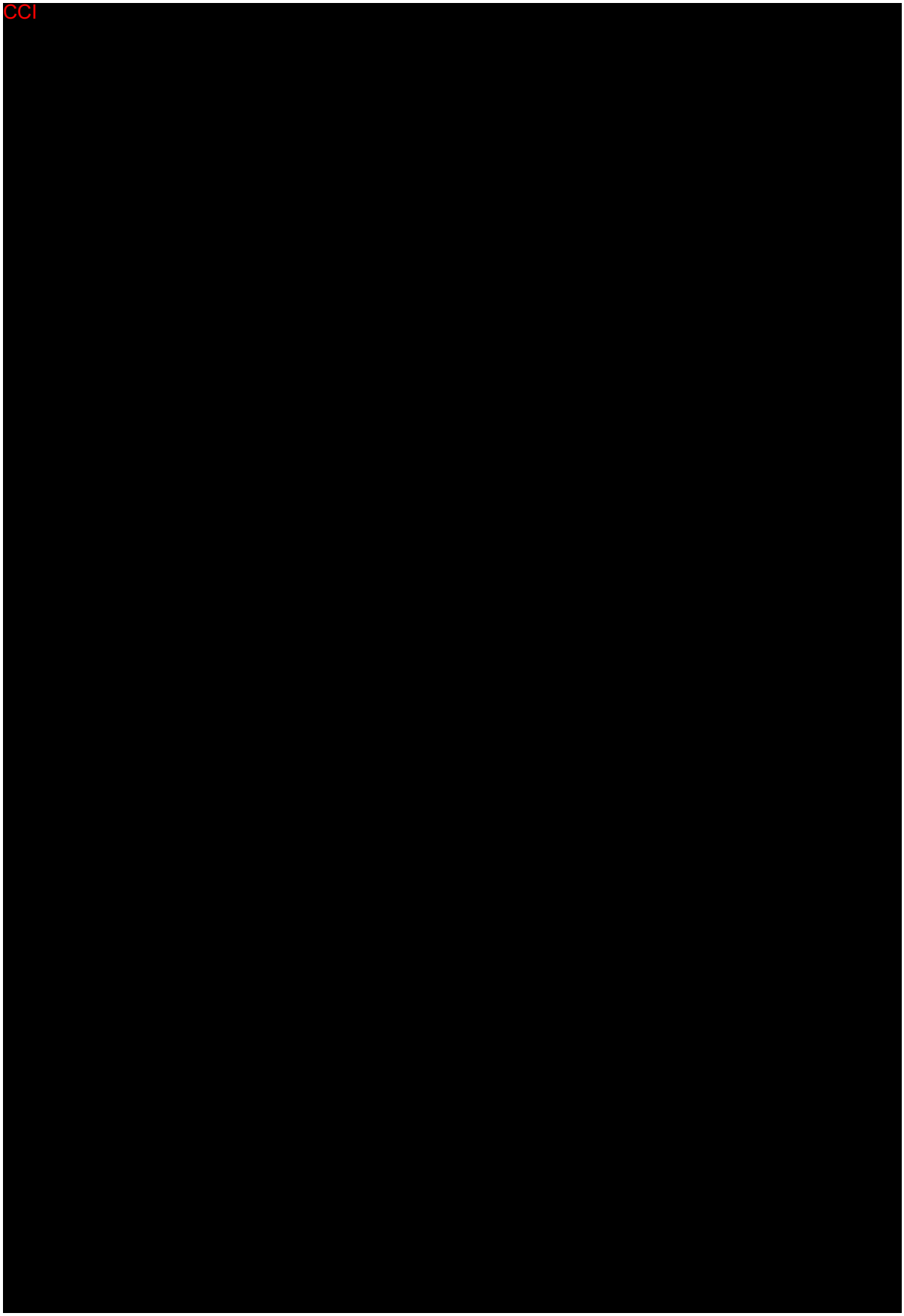

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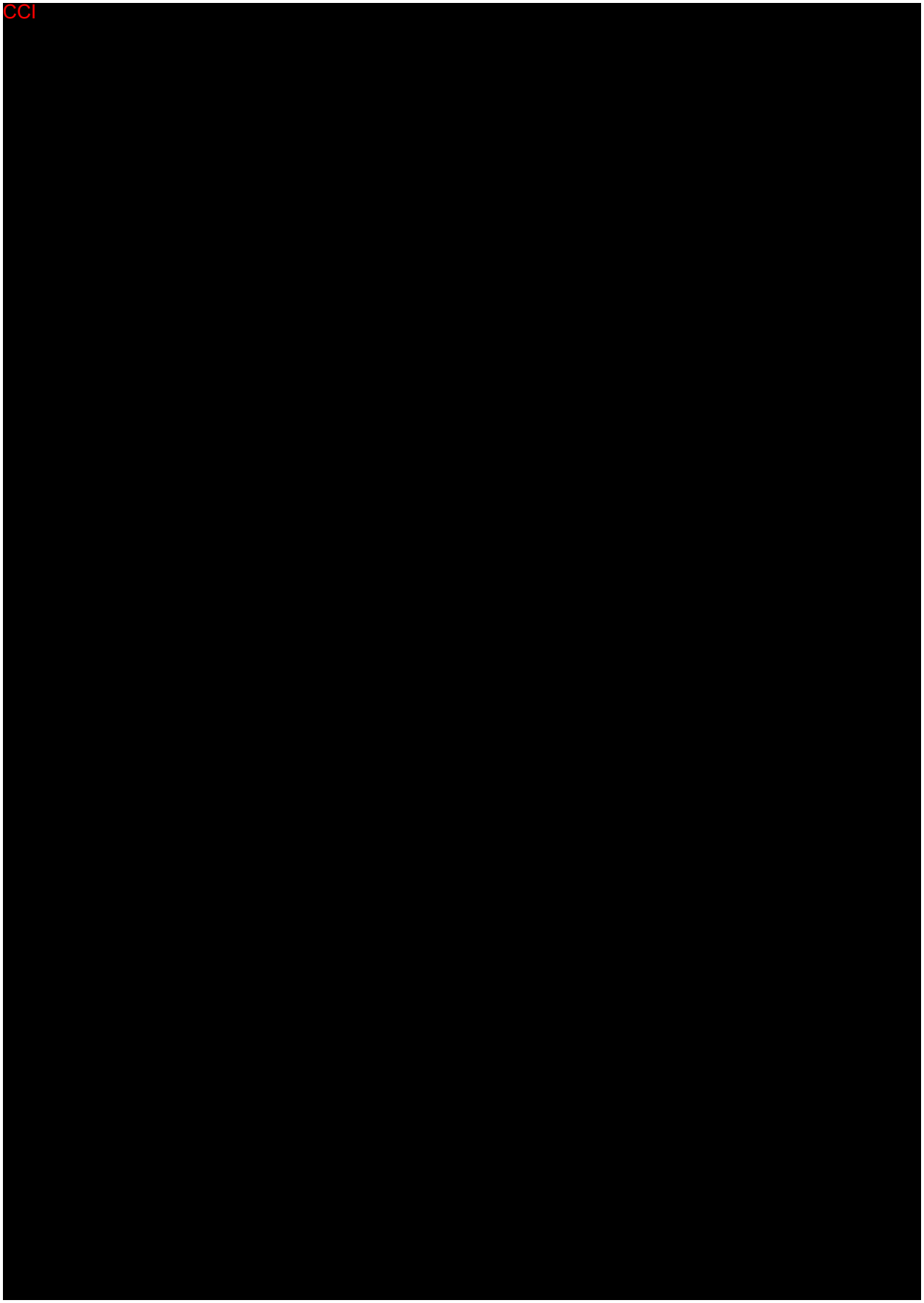

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9 SAFETY ANALYSIS

9.1 Adverse Events

Adverse events will be coded using MedDRA (Version 21.0 or higher). Each verbatim term will be mapped to a SOC and PT. Severity grades for safety parameters will be assigned using the Common Terminology Criteria for Adverse Events (Version 5.0). When changes in the severity of an AE occur more frequently than once a day, the maximum severity for the experience that day will be noted.

Treatment-emergent AEs (TEAE) are events with onset dates and times on or after the administration of the first dose of study drug and within 30 days after the last dose of study drug, or a continuing AE diagnosed before the date of the first dose of study drug, which increases in frequency, severity, or character during the course of the study.

An overall summary of TEAEs will be provided for the safety population summarizing subjects with at least 1: TEAE, related TEAE, grade 3, 4, or 5 TEAE, serious TEAE, related serious TEAE, TEAE leading to study discontinuation, or related TEAE leading to study discontinuation as well as the number of events within each of the previously mentioned categories by treatment.

In addition, summaries of unique TEAEs will be presented for the safety population by SOC, PT, and by treatment and overall, and will include the number and percentage of subjects who experience the unique event for:

1. All TEAEs,
2. All TEAEs by relationship,
3. All TEAEs by severity grade,
4. All TEAEs leading to study discontinuation,
5. All serious TEAEs, if more than 1 serious TEAE is recorded.

Related TEAEs include all those classified by the investigator as possibly related or related. Unrelated TEAEs are those events classified as not related or unlikely related.

For summaries by relationship, the most related event will be selected. For summaries by severity, the most severe grade will be selected.

Multiple events will be counted only once per subject and treatment in each of the previously mentioned summaries by treatment and overall. In the presentation, SOC and PT will be sorted in alphabetical order.

All AEs captured in the database will be presented in by-subject data listings; however, only TEAEs will be summarized.

MedDRA version will be provided in a footnote in both tables and data listings.

9.2 Clinical Laboratory Evaluations (Hematology and Serum Chemistry)

Clinical laboratory evaluations of hematology and serum chemistry will be performed. Results and change from BL will be summarized by treatment and scheduled visit and time point for the safety population, using descriptive statistics for numeric parameters and using counts and percentages for categorical parameters. Baseline is defined as stated in Section 5.6. Values reported with a '<' or '>' sign will be converted to numeric values and summarized.

Shifts from BL to values outside of the normal range will be presented for the safety population by parameter and summarized using the number and percentage of subjects with clinical laboratory test results below, within, and above normal ranges for numeric parameters, and normal or abnormal for categorical parameters, and will be tabulated by treatment and scheduled visit/time point. The denominators for calculating the percentages will be based on the number of subjects with nonmissing assessments for each parameter.

Clinically significant laboratory values (as determined by the investigator) will be provided in a data listing including all values for a given parameter for subjects who had at least 1 postbaseline clinically significant value.

All clinical laboratory data will also be presented in data listings in chronological order by date if unscheduled or repeated values.

9.3 Hypercalcemia and Hyperphosphatemia

A summary will be provided for the safety population indicating the number and percentage of subjects with hypercalcemia (1 and 2 consecutive visits with serum corrected total calcium >10.3 mg/dL) or drug-related hyperphosphatemia (1 and 2 consecutive visits with serum phosphorus >5.5 mg/dL) by treatment.

9.4 Vital Signs

Descriptive statistics for vital sign measurements, obtained at BL and each scheduled postbaseline visit, will be summarized for the safety population by treatment. In addition, change from BL will be calculated, where BL is defined as stated in Section 5.6. If a parameter is repeated for a visit, the first value reported will be used in the summary.

Vital sign measurements will also be presented in a data listing.

9.5 Concomitant Medications

Prior and concomitant medications will be classified according to the World Health Organization Drug dictionary (WHO-DDE March 2018 Version, format C or higher) and summarized by treatment using frequency counts and percentages for each Anatomical Therapeutic Chemical Class Level 2 and 4, and generic drug name for the safety population. Prior and concomitant medications, including start and stop (or ongoing as of) dates, AE number (if applicable), indication, dose, unit, route, and frequency will be presented in a data listing.

Prior medications are defined as any continuing or new medication used within 12 weeks and discontinued before Screening (Days –42 to –36; Visit 1). Concomitant medications are defined as any continuing or new medication taken from Screening (Days –42 to –36; Visit 1) or anytime thereafter until the end of the study.

9.6 Extent of Exposure

The extent of exposure will be summarized in terms of the number of doses using counts and percentages. Study drug administration dates and times will be presented in a data listing.

9.7 Dosing Compliance

Dosing compliance information for subjects assigned to CTAP101 Capsules and paricalcitol capsules plus low-dose cholecalciferol, including the number of capsules returned, the actual number of capsules taken, the number that should have been taken, and the calculated dosing compliance value will be provided for Visits 7 through 10 (Days 8, 15, 22, and 29) and 13 through 16 (Days 36, 43, 50, and EOS/ET) and presented in a data listing. Dose dispensing information will be provided for these same treatments, along with dose diary (reduction, suspension, and resumption) and dosing plan (type of change to treatment, reason, and the actual dose change) information for all treatments, in the data listings.

Summaries of the number of capsules returned, the actual number of capsules taken, the number that should have been taken, and the calculated dosing compliance will be provided by visit and overall for each treatment for the safety, ITT, and PP populations.

9.8 Ancillary Data

Dietary counseling information, including whether or not a subject required calcium supplementation as a concomitant medication, will be presented in a data listing.

9.9 Other Safety Assessments

The physical examination findings, unscheduled electrocardiogram safety assessments, and all other clincial laboratory parameters will be presented in data listings.

10 REFERENCES

Not applicable.

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Shells of the PK, CCI and safety tables, listings, and figures will be provided as a separate document and titles may change slightly from what is presented here in this appendix, where this appendix is designed to give the reader an understanding of what is intended to be presented. In creating the shells, the tables may need to be presented differently to adhere to the actual data collected.

14 TABLES, LISTINGS, AND FIGURES REFERRED TO BUT NOT PRESENTED IN THE TEXT

14.1 Disposition and Demographic Data Summary Tables

Table 14.1.1 Subject Disposition (Enrolled Subjects)
Table 14.1.2 Demographic and Baseline Characteristics (Safety Population)
Table 14.1.3 Demographic and Baseline Characteristics (ITT Population)
Table 14.1.4 Demographic and Baseline Characteristics (PP Population)
Table 14.1.5 Demographic and Baseline Characteristics (PK Population)
Table 14.1.6 Summary of Medical History (Safety Population)
Table 14.1.7 Summary of Prior Medications (Safety Population)
Table 14.1.8 Summary of Concomitant Medications (Safety Population)

14.2 Pharmacokinetic CCI [redacted] Summary Tables, Figures, and Analyses

14.2.1 Serum and Plasma Concentration and Pharmacokinetic Summaries, Figures, and Analyses

Table 14.2.1.1 Summary of Concentrations (PK Population)
Table 14.2.1.2 Summary of Pharmacokinetic Parameters (PK Population)
Table 14.2.1.3 Summary of Statistical Analyses of the Pharmacokinetic Parameters (PK Population)
Figure 14.2.1.1 Mean ±SD Serum Calcifediol Concentration (ng/mL)-Time Profile, Linear Scale (PK Population)

CCI [redacted]

CCI [redacted]

CCI

[redacted]

14.2.3 Urine Concentration and Pharmacodynamic Parameter Summaries

Table 14.2.3.1 Summary of Urinary Excretion (ITT Population)
Table 14.2.3.2 Summary of Urinary Excretion (PP Population)

14.2.4 Pharmacokinetic/CCI [redacted] Figures

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[redacted]

Figure 14.2.4.2 Plot of Time-Matched Serum 1,25-dihydroxyvitamin D_3 ($1,25D_3$) Change From Baseline Concentration Versus Serum Calcifediol Concentrations (PK Population)

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[redacted]

14.3 Safety Data Summary Tables

14.3.1 Adverse Events

Table 14.3.1.1 Overall Summary of Treatment-Emergent Adverse Events (Safety Population)
Table 14.3.1.2 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.3 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Relationship to Study Drug (Safety Population)
Table 14.3.1.4 Treatment-Emergent Adverse Events by System Organ Class, Preferred Term, and Maximum Severity (Safety Population)
Table 14.3.1.5 Treatment-Emergent Adverse Events Leading to Study Discontinuation by System Organ Class, Preferred Term, and Relationship to Study Drug (Safety Population)
Add Table 14.3.1.6 Serious TEAEs by System Organ Class and Preferred Term (Safety Population) and Table 14.3.1.7 Serious Related TEAEs by System Organ Class and Preferred Term (Safety Population), if more than 1 SAE is reported. Follow the same format as the 14.3.1.2 table.

14.3.2 Listing of Deaths, Other Serious and Significant Adverse Events

Listing 14.3.2.1 Serious Adverse Events and Deaths (Safety Population)

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Provided by Clinical, if applicable.

14.3.4 Abnormal Laboratory Value Listings

Listing 14.3.4.1 Clinically Significant Laboratory Results (Safety Population)

14.3.5 Other Observations Related to Safety

Table 14.3.5.1 Extent of Exposure (Safety Population)
Table 14.3.5.2 Dosing Plan Summary (Safety Population)
Table 14.3.5.3 Dosing Compliance (Safety Population)
Table 14.3.5.4 Vital Sign Results and Change From Baseline (Safety Population)
Table 14.3.5.5 Hematology Parameter Results and Change From Baseline (Safety Population)
Table 14.3.5.6 Hematology Parameter Shifts From Baseline (Safety Population)
Table 14.3.5.7 Serum Chemistry Parameter Results and Change From Baseline (Safety Population)

16.1 Study Information

Appendix 16.1.7.1 Randomization Schedule
Appendix 16.1.10.1 Clinical Laboratory Reference Ranges

16.2 Subject Data Listings

16.2.1 Subject Discontinuation

Appendix 16.2.1.1 Subject Disposition

16.2.2 Protocol Deviations

Appendix 16.2.2.1 Protocol Deviations

16.2.3 Subject Populations and Excluded Reasons

Appendix 16.2.3.1 Subjects in the Safety, ITT, PP, and PK Populations and Excluded Reasons

16.2.4 Demographic Data

Appendix 16.2.4.1 Demographics and Baseline Characteristics
Appendix 16.2.4.2 Inclusion/Exclusion Criteria Not Met
Appendix 16.2.4.3 Medical History
Appendix 16.2.4.4 Substance Use

16.2.5 Compliance and Drug Concentration Data

Appendix 16.2.5.1 Study Drug Administration at the Clinic
Appendix 16.2.5.2 Dosing Compliance Information
Appendix 16.2.5.3 Dose Dispensed Information
Appendix 16.2.5.4 Dose Diary and Dosing Plan
Appendix 16.2.5.5 Dietary Counseling Information
Appendix 16.2.5.6 Pharmacokinetic Concentrations and Sampling Times
CCI [redacted]
Appendix 16.2.5.8 Urine Concentrations, Amount Excreted, Volume, and Sampling Times

16.2.6 Pharmacokinetic CCI [redacted] Data

Appendix 16.2.6.1 Pharmacokinetic Parameters
CCI [redacted]
Appendix 16.2.6.3 Figures for Serum Calcifediol Individual Concentration (ng/mL)-Time Profiles, Linear Scale
Appendix 16.2.6.4 Spaghetti Plots for Serum Calcifediol Individual Concentration (ng/mL)-Time Profiles, Linear Scale
Appendix 16.2.6.5 Figures for Baseline-Adjusted Serum Calcifediol Individual Concentration (ng/mL)-Time Profiles, Linear Scale
Appendix 16.2.6.6 Spaghetti Plots for Baseline-Adjusted Serum Calcifediol Individual Concentration (ng/mL)-Time Profiles, Linear Scale

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Appendix 16.2.6.31 Figures for Serum 1,25-dihydroxyvitamin D_3 ($1,25D_3$) Individual Concentration (ng/mL)-Time Profiles, Linear Scale

Appendix 16.2.6.32 Spaghetti Plots for Serum 1,25-dihydroxyvitamin D_3 ($1,25D_3$) Individual Concentration (ng/mL)-Time Profiles, Linear Scale

Appendix 16.2.6.33 Figures for Baseline-Adjusted Serum 1,25-dihydroxyvitamin D_3 ($1,25D_3$) Individual Concentration (ng/mL)-Time Profiles, Linear Scale

Appendix 16.2.6.34 Spaghetti Plots for Baseline-Adjusted Serum 1,25 dihydroxyvitamin D_3 ($1,25D_3$) Individual Concentration (ng/mL)-Time Profiles, Linear Scale

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16.2.7 Adverse Events and Other Safety Data

Appendix 16.2.7.1 Adverse Events

Appendix 16.2.7.2 Adverse Events Leading to Study Discontinuation

Appendix 16.2.7.3 Prior and Concomitant Medications

Appendix 16.2.7.4 Vital Sign Measurements

Appendix 16.2.7.5 Unscheduled Safety 12-Lead Electrocardiogram

Appendix 16.2.7.6 Physical Examination
Appendix 16.2.7.7 Meal Information
Appendix 16.2.7.8 Calcium Assessment

16.2.8 Individual Laboratory Safety Response Data

Appendix 16.2.8.1 Clinical Laboratory Results for Hematology
Appendix 16.2.8.2 Clinical Laboratory Results for Serum Chemistry
Appendix 16.2.8.3 Urine Drug and Alcohol Screen Results
Appendix 16.2.8.4 HIV and Hepatitis Screen Results
Appendix 16.2.8.5 Serum Pregnancy Test Results (Female Subjects Only)