Protocol: CTAP101-CL-4001

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
Study Number:	CTAP101-CL-4001
Short Title:	Repeated-dose safety, efficacy, PK and PD of CTAP101, IR Calcifediol, high-dose cholecalciferol, and paricalcitol plus low-dose cholecalciferol in patients with SHPT, CKD 3-4 and VDI
Study Phase:	4
Product Names:	CTAP101 Capsules, IR calcifediol, cholecalciferol, paricalcitol
Investigator(s):	Multi-Center

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

Version 7.0 16 August 2019

Confidentiality Statement

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

$1,25D_3$	1,25-dihydroxyvitamin D_3, calcitriol
CCI	
$25D_3$	25-hydroxyvitamin D_3, calcifediol, calcidiol
CCI	
AE	adverse event
AUC	area under the (concentration) curve
BA	bioavailability
BL	baseline
BMI	body mass index
CCI	
Ca	calcium
CFR	Code of Federal Regulations
CCI	
CKD	chronic kidney disease
CL/F	clearance
C_{max}	maximum concentration
Cr	creatinine
CRF	case report form
C_{ss}	steady-state concentration
CTCAE	Common Terminology Criteria for Adverse Events
CCI	
CV	coefficient of variation
DBP	vitamin D binding protein
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
EOS	end of study
ER	extended-release
ET	early termination
EU	European Union
FDA	Food and Drug Administration
FGF23	fibroblast growth factor 23
GCP	Good Clinical Practice
GCRC	General Clinical Research Center

GFR	glomerular filtration rate
HDPE	high-density polyethylene
HIV	human immunodeficiency virus
IB	Investigator Brochure
CCI	[redacted]
ICF	Informed Consent Form
ICH	International Council on Harmonisation
iPTH	intact parathyroid hormone
IR	immediate-release
IRB/EC	Institutional Review Board/Ethics Committee
ITT	intent-to-treat
IU	International Units
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
P	phosphorus
CCI	[redacted]
PD	pharmacodynamic(s)
PE	physical examinations
PK	pharmacokinetic(s)
PP	per-protocol
PTH	parathyroid hormone
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SHPT	secondary hyperparathyroidism
SOC	system organ class
SOP	standard operating procedure
$t_{1/2}$	terminal elimination half-life
CCI	[redacted]
TEAE	treatment-emergent adverse events
t_{max}	time to maximum concentration
t_{ss}	time to steady-state concentration

US	United States
Vd/F	volume of distribution
VDI	vitamin D insufficiency
VDR	vitamin D receptor
VS	vital signs

SYNOPSIS

Sponsor:

OPKO Ireland Global Holdings Ltd.

Name of Finished Products:

CTAP101 Capsules
Immediate-release (IR) calcifediol capsules
Cholecalciferol capsules
Paricalcitol capsules

Name of Active Ingredients:

Calcifediol, calcidiol, 25-hydroxyvitamin D_3
Cholecalciferol, vitamin D_3
Paricalcitol, 19-nor-1-alpha,25-dihydroxyvitamin D_2

Test Products, Dose, and Mode of Administration:

CTAP101 Capsules (30 mcg/capsule), 60 mcg, by the oral route
Calcifediol immediate-release (IR) (266 mcg/capsule), 266 mcg, by the oral route
Cholecalciferol (50,000 International Units (IU)/capsule), 300,000 IU, by the oral route
Paricalcitol (1 mcg/capsule) plus cholecalciferol (800 IU/capsule), 1 or 2 mcg plus 800 IU, by the oral route

Study Title:

An Open-Label, Repeated-Dose Safety, Efficacy, Pharmacokinetic and Pharmacodynamic Study of Oral CTAP101 Capsules, 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.

Study Number:

CTAP101-CL-4001

Study Phase: 4

Objectives:

The objectives of this study are to assess the repeated-dose safety, efficacy, pharmacokinetic (PK) CCI profiles of CTAP101 Capsules, 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).

Study Design:

This is a phase 4, multi-center, 4-arm, open-label study to gather comparative data evaluating the safety, efficacy and PK CCI profiles for CTAP101 Capsules, IR calcifediol, high-dose cholecalciferol, and paricalcitol plus low-dose cholecalciferol to treat SHPT in male and female subjects aged at least 18 years with stage 3 or 4 CKD and VDI. The study will be conducted at multiple sites within the United States (US). Approximately 160 subjects will be screened to

enroll approximately 80 eligible subjects who will be randomized 1:1:1:1 (approximately 20 per arm, balanced for body weight) to receive 8 weeks of treatment as follows: CTAP101 Capsules at a dose of 60 mcg per day; IR calcifediol at a dose of 266 mcg on Day 1 and Day 29; high-dose cholecalciferol at a dose of 300,000 IU on Day 1 and Day 29; and paricalcitol at a dose of 1 mcg per day (possibly increasing to 2 mcg per day at Day 29) plus low-dose cholecalciferol 800 IU per day. If a significant difference in average weight among subjects by treatment group emerges during the course of the study, subjects may be placed into specific treatment groups rather than randomly assigned, in order to try and achieve more balance in the treatment groups by body weight.

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 ($25D_3$) CCI [redacted] CCI [redacted] Blood samples for some of the PK/CC 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 outpatient visit, at 24 hours; during outpatient visit for 48 hours; and then weekly following the first dose and the Day 29 dose of each medication. CCI [redacted] Urine collections (24-hour) will be obtained at pre-treatment baseline (Visits 2 and 3), starting immediately after dosing on Day 1 (Visit 4) and Day 29 (Visit 10) and at the end of study (Visit 16) or early termination (ET). The schedule for collection of blood and urine samples is delineated in Section 7 (Study Activities) and in APPENDIX 1.

Subjects receiving treatment with calcitriol or another 1α-hydroxylated vitamin D analog, must forgo treatment with these non-study agents and complete a 4-week washout period prior to baseline (BL) assessments and will remain off these non-study medications for the duration of the study. For subjects who are taking vitamin D supplementation (including multivitamins and fish oil), they must forgo treatment with these non-study agents for the duration of the study and undergo a 4 week washout. If at the end of the 4-week washout the serum total 25-hydroxyvitamin D level is still ≥30 ng/mL, washout may be extended by up to another four weeks for a maximum total of 8 weeks. Subjects will be excluded from enrollment if they have received calcimimetic therapy within 12 weeks preceding screening.

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 assessments. Key parameters to be analyzed in the collected samples include some or all of the following: serum calcifediol, CCI [redacted]

CCI [redacted] CCI [redacted]. Vital signs (VS) and adverse events (AEs) will be monitored at each study visit. Other parameters to be monitored less frequently include CCI [redacted] brief physical examinations (PEs) and clinical laboratory tests (hematology and routine clinical chemistries).

Subjects will maintain a dietary intake during the study of approximately 1,000-1,500 mg of elemental calcium per day by dietary counseling and, if necessary, a prescribed daily calcium supplement.

Dosing Plan:

Approximately 80 subjects will be randomized 1:1:1:1 (approximately 20 per arm) to receive one of the listed study medications with a sufficient quantity of a non-alcoholic beverage to enable swallowing of the capsules:

1) CTAP101 Capsules 60 mcg once daily outside of the phase 1 unit at bedtime, except on Days 1 and 29 when dosing will occur in the phase 1 unit in the morning before breakfast.
2) IR calcifediol 266 mcg in the phase 1 unit before breakfast on the mornings of Day 1 and Day 29.
3) Cholecalciferol 300,000 IU (high-dose) in the phase 1 unit before breakfast on the mornings of Day 1 and Day 29.
4) Paricalcitol 1 mcg plus cholecalciferol 800 IU (low-dose) once daily outside of the phase 1 unit in the morning before breakfast, except on the mornings of Days 1 and 29 when dosing will occur in the phase 1 unit before breakfast.

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 provided that (a) the plasma iPTH has not decreased by at least 30% from pretreatment BL and remains above 70 pg/mL, (b) corrected serum calcium is <9.8 mg/dL, and (c) 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 medication per the schedule below in the event that plasma iPTH is confirmed to be <30 pg/mL, corrected serum calcium is confirmed to be >10.3 mg/dL, or serum phosphorus is confirmed to be >5.5 mg/dL. Subjects will suspend dosing if plasma iPTH is confirmed to be <15 pg/mL or corrected serum calcium is confirmed to be >11.0 mg/dL, and will resume dosing when plasma iPTH is ≥30 pg/mL and corrected serum calcium is <9.8 mg/dL per the dose schedule below.

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

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 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

Duration of Treatment:

Subjects will participate in the study for up to approximately 14 weeks (1 week for screening, 4 weeks for washout (if required), 1 week for BL, and 8 weeks for treatment).

Primary Efficacy Endpoint:

This study is descriptive and no primary or secondary efficacy endpoints are defined. Descriptive analysis and plots will be created of serum calcifediol, CCI [redacted]

Primary Safety Endpoints:

Safety and tolerability of each medication will be evaluated in the Safety population by AEs, PEs, VS, and hematology and clinical chemistries.

Pharmacokinetic CCI [redacted] Endpoints:

The following PK parameters will be calculated using observed and BL-adjusted serum calcifediol CCI [redacted] 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 ($t_{½}$), clearance (CL/F), and volume of distribution (Vd/F), as feasible.

CCI [redacted]

Secondary Safety Endpoints:

The number (n, %) of subjects with hypercalcemia (two consecutive visits with serum calcium greater than 10.3 mg/dL) or hyperphosphatemia (two consecutive visits with serum phosphorus greater than 5.5 mg/dL) will be calculated.

Sample Size Estimation:

No formal sample size estimation has been performed for the study.

Statistical Analyses:

Descriptive statistical plan will be specified in an accompanying SAP.

Primary safety analyses will be conducted in the Safety population.

Secondary safety analyses will calculate the number and percentage of subjects in each treatment group with confirmed corrected serum calcium or serum phosphorus values above 10.3 mg/dL and 5.5 mg/dL, respectively.

Inclusion Criteria

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

1. Be at least 18 years of age.
2. Have stage 3 or 4 CKD (estimated glomerular filtration rate (eGFR) of ≥15 to <60 mL/min/1.73m^2 using the Modification of Diet in Renal Disease equation).
3. Be without any disease state or physical condition that might impair evaluation or which, in the Investigator's opinion, would interfere with study participation, including:
   a. Serum albumin ≤ 3.0 g/dL;
   b. Serum transaminase (alanine transaminase, glutamic pyruvic transaminase, aspartate aminotransferase or glutamic oxaloacetic transaminase) > 2.5 times the upper limit of normal at screening; and,
   c. Urinary albumin excretion >3000 μg/mg creatinine.
4. Exhibit during the initial screening visit:
   a. Plasma iPTH ≥65 pg/mL and <400 pg/mL if receiving calcitriol or 1α-hydroxylated vitamin D analog (paricalcitol or doxercalciferol); or
   b. Plasma iPTH ≥85 pg/mL and <500 pg/mL if not receiving calcitriol or 1α-hydroxylated vitamin D analog; and,
   c. Serum total 25-hydroxyvitamin D <30 ng/mL, unless taking vitamin D supplementation (including multivitamins and fish oil); and,
   d. If taking calcitriol, or another 1α-hydroxylated vitamin D analog, subjects must forgo treatment with these non-study agents for the duration of the study and undergo a 4-week washout period and meet inclusion criterion 5.
   e. For subjects who are taking vitamin D supplementation (including multivitamins or fish oil), they must forgo treatment with these non-study agents for the duration of the study. If the serum 25-hydroxyvitamin D level is <30 ng/mL, there is no need for the subjects to complete a washout period as a result of vitamin D supplementation. If, however, serum 25-hydroxyvitamin D level is ≥30 ng/mL, the subjects must undergo a 4-week washout period and meet inclusion criterion 5. If at the end of 4 weeks of washout, the 25 hydroxyvitamin D level is still ≥30 ng/mL, the washout may be extended by up to another four weeks for a total of 8 weeks.

5. Exhibit after the washout period (if required):
   a. Plasma iPTH ≥85 pg/mL and <500 pg/mL;
   b. Corrected serum calcium <9.8 mg/dL; (corrected for serum albumin)
   c. Serum total 25-hydroxyvitamin D <30 ng/mL; and,
   d. Serum phosphorus <5.5 mg/dL.
6. If taking more than 1,500 mg/day of elemental calcium, reduce calcium use (to approximately 1,000 to ≤1,500 mg/day) for the duration of the study.
7. Willing and able to comply with study instructions and commit to all clinic visits for the duration of the study.
8. Female subjects of childbearing potential must be neither pregnant nor lactating and must have a negative blood pregnancy test at the first screening visit.
9. All female subjects of childbearing potential and male subjects with female partners of childbearing potential must agree to use effective contraception (implants, injectables, combined oral contraceptives, intrauterine device, sexual abstinence, vasectomy or vasectomized partner) for the duration of the study.
10. Be able to read, understand and sign the subject Informed Consent Form (ICF) or have a legal authorized representative (LAR) sign the ICF.

Exclusion Criteria

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

1. History of or planned kidney transplant or parathyroidectomy.
2. History (prior 3 months) of corrected serum calcium ≥9.8 mg/dL or serum phosphorus ≥5.5 mg/dL if not receiving calcitriol or other 1α-hydroxylated vitamin D analog.
3. Need for phosphate binders to maintain the serum phosphorus < 5.5 mg/dL or use of phosphate binders within 4 weeks prior to screening.
4. Use of calcimimetic therapy (cinacalcet or etelcalcetide) within 12 weeks of screening.
5. Receipt of bisphosphonate therapy or other bone modifying treatment within 1 year prior to enrollment.
6. 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.
7. 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.
8. Known or suspected hypersensitivity to any of the constituents of the study drugs.
9. Currently participating in, or has participated in, an interventional/investigational study within 30 days prior to study screening.

1 INTRODUCTION

1.1 Medications

1.1.1 CTAP101 Capsules

CTAP101 Capsules 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 stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency (VDI). Calcifediol is 25-hydroxyvitamin D_3, the physiological precursor to the vitamin D_3 hormone, 1,25-dihydroxyvitamin D_3 (calcitriol).

1.1.2 Calcifediol Capsules

Calcifediol capsules are available in the US and in certain countries of the European Union (EU) in immediate-release (IR) or ER formulations. Hidroferol is an IR oral formulation of calcifediol which Faes Farma is developing for the same indication. Hidroferol is on the market in Spain and will soon be marketed in certain other countries of the EU. Calcifediol is not approved in Japan.

1.1.3 Cholecalciferol Capsules

Cholecalciferol capsules are available in most countries of the world. None are available in ER oral formulations. They are used to treat VDI and are frequently used as a treatment for SHPT in patients with stage 3 or 4 CKD and VDI, although not formally approved for this use.

Published studies have reported the use of daily doses of vitamin D (either cholecalciferol or ergocalciferol) of 700 to 4,000 International Units (IU), weekly doses of 5,000 to 50,000 IU, and monthly doses of 50,000 to 300,000 IU. Irrespective of the treatment regimen used, no or inadequate reductions in parathyroid hormone (PTH) levels have been observed in randomized clinical trials and nutritional vitamin D remains unproven as an effective treatment for SHPT in patients with stage 3-4 CKD.

1.1.4 Paricalcitol Capsules

Paricalcitol capsules are available in the US and in the EU as a treatment for SHPT in patients with stage 3 or 4 CKD. Paricalcitol is a 1α-hydroxylated vitamin D analog which is active on administration and interacts with the vitamin D receptor (VDR) in the parathyroid gland to suppress the synthesis and secretion of PTH. Paricalcitol is frequently combined with cholecalciferol in order to both correct VDI and suppress elevated PTH in pre-dialysis patients, but the safety and efficacy of this combination of therapies has never been demonstrated in randomized clinical trials.

1.2 Metabolism of Calcifediol and Related Metabolites

Calcifediol 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.

The two vitamin D prohormones are activated by healthy kidneys into hormones by CYP27B1, located in the proximal kidney tubule [DeLuca 2004]. Activation occurs under tight regulation by PTH, which is secreted by the parathyroid glands. The prohormones (25-hydroxyvitamin D_2 and 25-hydroxyvitamin D_3) are metabolized directly to 1α,25-dihydroxyvitamin D_2 (ercalcitriol) and 1α,25-dihydroxyvitamin D_3 (calcitriol), respectively. These two vitamin D hormones, collectively referred to as "1,25-dihydroxyvitamin D", are secreted by the kidneys into the blood for systemic delivery.

The two vitamin D prohormones are also activated extra-renally by CYP27B1 in parathyroid and many other cells [Adams et al 2014] to provide a local supply of hormones that may prove critical to cell growth regulation and the prevention of cancer, autoimmune disorders (such as psoriasis) and certain types of infection. Adequate local hormone production depends entirely on sufficient levels of circulating 25-hydroxyvitamin D.

1.3 Vitamin D Insufficiency

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 considered adequate in CKD patients while levels of <30 ng/mL are considered "insufficient" [Holick et al 2011]. The normal 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 intact parathyroid hormone (iPTH) targets [Ennis 2016]. 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.

1.4 Chronic Kidney Disease

CKD is a steadily-increasing health problem 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, including urinary loss of vitamin D binding protein (DBP), decreased hepatic

synthesis of calcifediol and excessive expression of the vitamin D catabolic enzyme, CYP24A1 [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 PTH by the parathyroid glands and, ultimately, SHPT.

1.5 Secondary Hyperparathyroidism

SHPT is a condition commonly associated with CKD in which the parathyroid glands secrete excessive amounts of PTH. SHPT affects 40% to 82% of patients with stage 3 or 4 CKD [Levin et al 2007] and frequently arises as a result of either VDI or impaired kidney function, both of which can prevent sufficient production of vitamin D hormone to properly regulate calcium and phosphorus metabolism and PTH secretion. Impaired kidney function can also cause elevated serum phosphorus and fibroblast growth factor 23 (FGF23) which exacerbate SHPT. SHPT requires prompt and effective treatment, as prolonged elevation of PTH causes excessive calcium and phosphorus to be released from bone, leading to metabolic bone disease and calcification of cardiovascular and renal tissues. In the absence of effective treatment, SHPT becomes progressively more severe and unresponsive to treatment [Nigwekar et al 2014].

1.6 Clinical Practice Guidelines

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.

1.7 The Current Unmet Medical Need

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 et al: *"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 et al 2009]. A more recent review of the published randomized clinical trials concluded that vitamin

D had no efficacy in lowering iPTH levels in patients with stage 3 to 5 CKD [Agarwal 2016]. Hence, there is a need for effective treatment to increase serum total 25-hydroxyvitamin D and control elevated iPTH in this patient population.

1.8 Nonclinical Experience with Study Medications

1.8.1 CTAP101 Capsules

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 (e.g., kidney, stomach, aorta and heart) and death. Severe adverse reactions to CTAP101 Capsules were observed in dogs treated with 500 or 1,000 mcg/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 mcg/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 mcg/kg. Toxicities included an increased incidence of nephrocalcinosis and uroliths. Oral administration of calcifediol to dogs at ≤2 mcg/kg/day resulted in no compound-related findings.

Results from in vitro drug release and nonclinical PK studies in male Yucatan swine 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 IR 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 IR formulation (t_{max} ~4 hours).

1.8.2 Cholecalciferol, Calcifediol and Paricalcitol

Toxicity associated with cholecalciferol, calcifediol and paricalcitol is well understood in the medical literature. 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 urine calcium levels;
- 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.

1.9 Previous Clinical Experience with CTAP101

CTAP101 Capsules (30 mcg) have been approved as Rayaldee® 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, CTAP-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 maximum serum concentration (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 pre-treatment baseline (BL) and compared to placebo during 6 weeks of treatment. The mean % decrease in iPTH from BL 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.

Efficacy was confirmed in the phase 3 program with nearly all subjects (97%) treated with CTAP101 Capsules 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 BL of at least 30%. Fewer than 9% of placebo subjects achieved a 30% reduction in iPTH or achieved a normal 25-hydroxyvitamin D level.

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

1.10 Previous Clinical Experience with IR Calcifediol Capsules

IR formulations of calcifediol have been available for decades in the EU for indications such as rickets, prevention of calcium disorders secondary to corticosteroid or anticonvulsant therapy and treatment of osteomalacia, renal osteodystrophy, hypoparathyroidism, familial hypophosphatemia and vitamin D malabsorption. In the US, IR calcifediol was marketed from 1980 to 2002 as Calderol® for the treatment of metabolic bone disease in dialysis patients and was withdrawn from the market in 2002 for commercial reasons not associated with safety or efficacy.

Published clinical studies have clearly shown that IR calcifediol increased serum 25-hydroxyvitamin D far more quickly and effectively than vitamin D supplements but failed to produce clinically meaningful reductions in PTH (≥30% from pre-treatment levels) in many patients with stage 3 or 4 CKD at doses considered to be safe [Bordier 1975; Letteri 1977; Fournier 1988].

1.11 Previous Clinical Experience with Cholecalciferol Capsules

Oral formulations of cholecalciferol have been available for decades in many countries of the world, frequently evaluated in clinical studies and used (frequently in the absence of regulatory approval) for indications such as rickets, prevention of calcium disorders secondary to corticosteroid or anticonvulsant therapy and treatment of osteomalacia, renal osteodystrophy, hypoparathyroidism, familial hypophosphatemia and vitamin D malabsorption.

1.12 Previous Clinical Experience with Paricalcitol Capsules

Oral paricalcitol has been demonstrated in randomized clinical trials to be effective in controlling elevated PTH which characterizes SHPT but it frequently causes hypercalcemia in pre-dialysis patients. In the PRIMO trial [Thadhani 2012], paricalcitol, administered orally at 2 mcg per day, lowered mean PTH from a BL level of approximately 130 pg/mL to the normal range within 8 weeks, and maintained it normal for another 40 weeks of treatment. No PTH reduction was observed in the parallel placebo group. Mean serum calcium and phosphorus rose with paricalcitol treatment by 0.57 mg/dL (P<0.001) and 0.19 mg/dL (P=0.05), respectively, versus placebo. Nearly 23% of subjects experienced hypercalcemia, defined as 2 consecutive measurements above 10.5 mg/dL, on paricalcitol versus 0.9% on placebo (P<0.001). In the OPERA Trial [Wang 2014], paricalcitol, administered orally at 1 mcg per day, reduced median PTH by 86 pg/mL (55%) from a BL level of 156 pg/mL while placebo treatment increased PTH by 21 pg/mL (16%) from a BL level of 129 pg/mL. Mean serum calcium rose with paricalcitol treatment but not with placebo, and 43% of subjects on paricalcitol experienced hypercalcemia, defined as serum calcium above 10.2 mg/dL, versus 3% on placebo (P<0.001). In US phase 3 trials, paricalcitol produced a mean decrease of 45% in PTH after 24 weeks compared with a mean increase of 14% with placebo, and raised serum calcium and phosphorus by 0.2 and 0.1 mg/dL, respectively [Coyne 2006]. Hypercalcemia, defined as two consecutive serum calcium determinations above 10.5 mg/dL, was observed in 2% of subjects receiving paricalcitol versus 0 % on placebo.

As mentioned above, oral paricalcitol is often used in combination with oral cholecalciferol to control elevated PTH and correct VDI in patients with stage 3 or 4 CKD, although this

combination of therapies has not been shown in randomized clinical trials to be either safe or effective for this purpose.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

The objectives of this study are to assess the repeated-dose safety, efficacy, pharmacokinetic (PK) and CCI [redacted] profiles of CTAP101 Capsules, IR calcifediol, high-dose cholecalciferol, and paricalcitol plus low-dose cholecalciferol in patients with SHPT, stage 3 or 4 CKD and VDI.

2.2 Study Endpoints

2.2.1 Pharmacokinetic Endpoints

The following PK parameters will be calculated using observed and BL-adjusted serum calcifediol CCI [redacted] concentrations: AUC, C_{max}, t_{max}, steady-state concentration (C_{ss}), time to steady-state concentration (t_{ss}), terminal elimination half-life ($t_{½}$), clearance (CL/F), and volume of distribution (Vd/F), as feasible.

CCI [redacted]

2.2.3 Primary Safety Endpoints

Safety and tolerability of each medication will be evaluated in the Safety population by AEs, physical examinations (PEs), vital signs (VS), hematology and clinical chemistries.

2.2.4 Secondary Safety Endpoints

Secondary safety endpoints will include incidence of hypercalcemia and drug-related hyperphosphatemia. The number (n, %) of subjects with hypercalcemia (two consecutive visits with serum calcium greater than 10.3 mg/dL) or hyperphosphatemia (two consecutive visits with serum phosphorus greater than 5.5 mg/dL) will be calculated.

2.2.5 Efficacy Endpoints

This study is descriptive and no primary or secondary efficacy endpoints are defined. Descriptive analysis and plots for the ITT and PP populations will be created of serum calcifediol, CCI [redacted] which will be specified in an accompanying statistical analysis plan (SAP).

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a phase 4, 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 to treat SHPT in male and female subjects aged at least 18 years with stage 3 or 4 CKD and VDI. The study will be conducted at multiple sites within the US. Approximately 160 subjects will be screened to enroll approximately 80 eligible subjects who will be randomized 1:1:1:1 (approximately 20 per arm, balanced for body weight) to receive the following medications:

Test Products, Dose, and Mode of Administration:

CTAP101 Capsules (30 mcg/capsule), 60 mcg, by the oral route

Calcifediol immediate-release (IR) (266 mcg/capsule), 266 mcg, by the oral route

Cholecalciferol (50,000 IU/capsule), 300,000 IU, by the oral route

Paricalcitol (1 mcg/capsule) plus cholecalciferol (800 IU/capsule), 1 or 2 mcg plus 800 IU, by the oral route.

If a significant difference in average weight among subjects by treatment group emerges during the course of the study, subjects may be placed into specific treatment groups rather than randomly assigned, in order to try and achieve more balance in the treatment groups by body weight.

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 and CCI [redacted] Blood samples for some of the PK/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 outpatient visit, at 24 hours; during outpatient visit for 48 hours; and then weekly following the first dose and the Day 29 dose of each medication. Blood samples for other CCI assessments will be collected at less frequent intervals. Urine collections (24-hour) will be obtained at pre-treatment baseline (Visits 2 and 3), starting immediately after dosing on Day 1 (Visit 4) and Day 29 (Visit 10) and at the end of study (Visit 16) or early termination (ET). The schedule for blood and urine sample collections is delineated in Section 7 (Study Activities) and in APPENDIX 1.

Subjects receiving treatment with calcitriol or another 1α-hydroxylated vitamin D analog, or if serum total 25-hydroxyvitamin D ≥30 ng/mL when taking vitamin D supplementation (including multivitamins and fish oil), will complete a 4-week washout period prior to BL assessments. Subjects will forgo further dosing with these none study medications for the duration of the study. Subjects receiving calcimimetic therapy within 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] CCI [redacted] VS and AEs will be monitored at each study visit. Other parameters to be monitored less frequently include CCI [redacted] brief PEs and clinical laboratory tests (hematology and routine clinical chemistries).

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

3.2 Rationale for Study Design

OPKO is developing CTAP101 Capsules for the treatment of SHPT in patients with stage 3 or 4 CKD and VDI. 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 CYP24A1 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, iPTH, calcium and phosphorus [Petkovich et al 2015].

The principal aims of the present study are to compare the safety and efficacy of CTAP101 Capsules, IR calcifediol, high-dose cholecalciferol, and paricalcitol plus low-dose cholecalciferol for up to 8 weeks to treat SHPT in subjects aged 18 years or older with stage 3 or 4 CKD and VDI and to better characterize the repeated-dose PK profiles for serum calcifediol CCI [redacted].

The starting dose of CTAP101 Capsules of 30 mcg/day is the lowest dose approved for marketing in the US. This dose is based on the results from prior repeat-dose, placebo-

controlled, double-blind studies with CTAP101 Capsules in patients with VDI and stage 3-4 CKD. These studies demonstrated that 30 mcg/day of CTAP101 Capsules safely and effectively decreased mean plasma iPTH by clinically meaningful amounts and increased mean serum total 25-hydroxyvitamin D within the currently accepted target range of 30-100 ng/mL.

A phase 2b dose ranging study in which CTAP101 Capsules were administered at daily doses of 30, 60 and 90 mcg (or 210, 420 and 630 mcg/week) for six weeks showed that mean plasma iPTH decreased from pre-treatment BL in a dose-proportional manner by 20.9, 32.8 and 39.3%, respectively, and that serum total 25-hydroxyvitamin D rose to levels ≥30 ng/mL in almost all subjects (CTAP101-CL-2008). The daily doses of 30 and 60 mcg increased serum 25-hydroxyvitamin D to a mean levels of 37 and 67 ng/mL, respectively, well within the range of 30 to 100 ng/mL. The daily dose of 90 mcg raised mean serum 25-hydroxyvitamin D at EOT to 85 ng/mL causing levels to exceed 100 ng/mL in a substantial proportion of subjects. This dose was considered too high for further evaluation in the phase 3 studies. 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 was determined in phase 3 studies to be attained after 12 weeks of treatment (CTAP101-CL-3001 and CTAP101-CL-3002).

3.3 Study Duration

This study is expected to be conducted in approximately 26 weeks from time of initial subject enrollment (first subject consented) to study completion for the last subject (last subject out/last visit complete). Subjects will participate in the study for up to approximately 14 weeks (1 week for screening, 4 weeks for washout (if required), 1 week for BL, and 8 weeks for treatment).

4 STUDY POPULATION SELECTION

4.1 Study Population

The target population for this study is subjects at least 18 years old diagnosed with SHPT, stage 3 or 4 CKD and VDI (serum total 25-hydroxyvitamin D <30 ng/mL).

Approximately 160 patients will be screened to enroll approximately 80 eligible subjects, approximately 20 per treatment arm.

4.2 Inclusion Criteria

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

1. Be at least 18 years of age.
2. Have stage 3 or 4 CKD (eGFR of ≥15 to <60 mL/min/1.73m^2 using the Modification of Diet in Renal Disease equation).
3. Be without any disease state or physical condition that might impair evaluation of safety and efficacy or which, in the Investigator's opinion, would interfere with study participation, including:
   a. Serum albumin ≤ 3.0 g/dL;
   b. Serum transaminase (alanine transaminase, glutamic pyruvic transaminase, aspartate aminotransferase or glutamic oxaloacetic transaminase) > 2.5 times the upper limit of normal at screening; and,
   c. Urinary albumin excretion >3000 µg/mg creatinine.
4. Exhibit during the initial Screening Visit:
   a. Plasma iPTH ≥65 pg/mL and <400 pg/mL if receiving calcitriol or other 1α-hydroxylated vitamin D analog (paricalcitol or doxercalciferol); or
   b. Plasma iPTH ≥85 pg/mL and <500 pg/mL if not receiving calcitriol or other 1α-hydroxylated vitamin D analog;
   c. Serum total 25-hydroxyvitamin D <30 ng/mL, unless taking vitamin D supplementation (including multivitamins and fish oil); and,
   d. If taking calcitriol or another 1α-hydroxylated vitamin D analog, subjects must forgo treatment with these non-study agents for the duration of the study and undergo a 4-week washout period and meet inclusion criterion 5.
   e. For subjects who are taking vitamin D supplementation (including multivitamins or fish oil), they must forgo treatment with these non-study agents for the duration of the study. If the serum 25-hydroxyvitamin D level is <30 ng/mL, there is no need for the subjects to complete a washout period as a result of vitamin D supplementation. If, however, serum 25-hydroxyvitamin D level is ≥30 ng/mL, the subjects must undergo a 4-week washout period and meet inclusion criterion 5. If at the end of 4 weeks of washout, the 25 hydroxyvitamin D level is still ≥30 ng/mL, the washout may be extended by up to another four weeks for a total of 8 weeks.
5. Exhibit after the washout period (if required):
   a. Plasma iPTH ≥85 pg/mL and <500 pg/mL;

b. Corrected serum calcium <9.8 mg/dL; (corrected for serum albumin)
c. Serum total 25-hydroxyvitamin D <30 ng/mL; and,
d. Serum phosphorus <5.5 mg/dL.

6. If taking more than 1,500 mg/day of elemental calcium, reduce calcium use (to approximately 1,000 to ≤1,500 mg/day) for the duration of the study.
7. Willing and able to comply with study instructions and commit to all clinic visits for the duration of the study.
8. Female subjects of childbearing potential must be neither pregnant nor lactating and must have negative blood pregnancy tests at the first screening visit.
9. All female subjects of childbearing potential and male subjects with female partners of childbearing potential must agree to use effective contraception (implants, injectables, combined oral contraceptives, intrauterine device, sexual abstinence, vasectomy or vasectomized partner) for the duration of the study.
10. Be able to read, understand and sign the subject Informed Consent Form (ICF) or have a legal authorized representative (LAR) sign the ICF.

4.3 Exclusion Criteria

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

1. History of or planned kidney transplant or parathyroidectomy.
2. History (prior 3 months) of corrected serum calcium ≥9.8 mg/dL or serum phosphorus ≥5.5 mg/dL if not receiving calcitriol or other 1α-hydroxylated vitamin D analog.
3. Need for phosphate binders to maintain the serum phosphate < 5.5 mg/dL or use of phosphate binders within 4 weeks prior to screening.
4. Use of calcimimetic therapy (cinacalcet or etelcalcetide) within 12 weeks of screening.
5. Receipt of bisphosphonate therapy or other bone modifying treatment within 6 months prior to enrollment.
6. 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.
7. 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.
8. Known or suspected hypersensitivity to any of the constituents of the study drugs.
9. 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 Study Medications

Five study medications will be used in the execution of this protocol which are described in sections 5.1.1 through 5.1.5. All study medications will be securely stored for light and heat protection and in accordance to USP Controlled Room Temperature, defined as 20°C to 25°C (68°F to 77°F) with excursions permitted between 15°C to 30°C (59°F to 86°F).

5.1.1 Description of CTAP101 Capsules

Dosage form:	Soft gel capsule
Dose strength:	30 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)

5.1.2 Description of Calcifediol IR Capsules

Dosage form:	Soft gel capsule
Dose strength:	266 mcg calcifediol IR capsule
Product description:	Orange capsule. Each Al-Al blister or PVC/PVDC-Al blister pack carton contains 10 capsules.
Active component:	Calcifediol
Non-active components:	Absolute anhydrous ethanol, medium chain triglycerides, gelatin, vegetable glycerin, sorbitol (70%) (E-420), titanium dioxide (E-171), yellow-orange dye S (E-110) and purified water.

For product information, refer to APPENDIX 2.

5.1.3 Description of High-Dose Cholecalciferol Capsules

Dosage form:	Soft gel capsule
Dose strength:	50,000 IU cholecalciferol capsule
Product description:	Red, oval-shaped capsule with “50” printed in white ink. Each PVDC/aluminum foil blister pack with cardboard carton contains 3 capsules.

Active component:	Cholecalciferol
Non-active components:	All-rac-α-tocopherol (E307), medium chain triglycerides, glycerol, gelatin, Allura Red AC (E129), Opacode® white imprinting ink, shellac (E904), titanium dioxide (E171) and simethicone.

For product information, refer to APPENDIX 3.

5.1.4 Description of Low-Dose Cholecalciferol Capsules

Dosage form:	Soft gel capsule
Dose strength:	800 IU cholecalciferol capsule
Product description:	Pink, oval-shaped capsule with "0.8" printed in white ink. Each PVDC/aluminum foil blister with cardboard carton contains 28 capsules.
Active component:	Cholecalciferol
Non-active components:	All-rac-α-tocopherol (E307), medium chain triglycerides, glycerol, gelatin, Allura Red AC (E129), Opacode® white imprinting ink, shellac (E904), titanium dioxide (E171) and simethicone.

For product information, refer to APPENDIX 4.

5.1.5 Description of Paricalcitol Capsules

Dosage form:	Soft gel capsule
Dose strength:	1 mcg paricalcitol capsule
Product description:	The 1 mcg capsule is an oval, gray, soft gelatin capsule imprinted with Abbott "a" logo and ZA, and is packaged in bottles of 30 (NDC 0074-4317-30), or an equivalent, U.S. approved generic alternate source.
Active component:	Paricalcitol
Non-active components:	Medium chain triglycerides, alcohol and butylated hydroxytoluene, gelatin, glycerin, titanium dioxide, iron oxide black and water.

5.2 Dosing Plan

Approximately 80 subjects will be randomized 1:1:1:1 (approximately 20 per arm) to receive one of the listed study medications with a sufficient quantity of a non-alcoholic beverage to enable swallowing of the capsules:

1) CTAP101 Capsules 60 mcg once daily outside of the phase 1 unit at bedtime, except on Days 1 and 29 when dosing will occur in the phase 1 unit in the morning before breakfast.
2) IR calcifediol 266 mcg in the phase 1 unit before breakfast on the mornings of Day 1 and Day 29.
3) Cholecalciferol 300,000 IU (high-dose) in the phase 1 unit before breakfast on the mornings of Day 1 and Day 29.

4) Paricalcitol 1 mcg plus cholecalciferol 800 IU (low-dose) once daily outside of the phase 1 unit in the morning before breakfast, except on Days 1 and 29 when dosing will occur in the phase 1 unit before breakfast.

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 provided that (a) the plasma iPTH has not decreased by at least 30% from pretreatment BL and remains above 70 pg/mL, (b) corrected serum calcium is <9.8 mg/dL, and (c) 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.

5.3 Dose Reduction Criteria

Subjects will reduce the dose of medication at any time by the schedule below in the event that plasma iPTH is confirmed to be <30 pg/mL, corrected serum calcium is confirmed to be >10.3 mg/dL, or serum phosphorus is confirmed to be >5.5 mg/dL. Subjects will suspend dosing if plasma iPTH is confirmed to be <15 pg/mL or corrected serum calcium is confirmed to be >11.0 mg/dL, and will resume when plasma iPTH is ≥30 pg/mL and corrected serum calcium is <9.8 mg/dL per the dose schedule below.

Dose reduction:

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 during the study period

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 calcium is <9.8 mg/dL at the same minimum dosage.

Dose resumption:

CTAP101: 30 mcg per day

Paricalcitol: 1 mcg per day

5.3.1 Overdose and Toxicity

Excessive administration of calcifediol, cholecalciferol, or paricalcitol can cause hypercalciuria, 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, cholecalciferol, or paricalcitol 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 and

urine 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.

5.4 Method of Assigning Subjects to Treatment Groups

After signing the ICF, prior to any study-related activities, each subject will be assigned a unique 7 digit subject identification number which will be retained throughout the study and that will be unique across all sites. The 7 digit subject identification number (SSSNNNN) will consist of a 3-digit site number (SSS) and a 4-digit subject number (NNNN) at the applicable clinical site. Should a subject be withdrawn from the study, that subject's 7 digit identification number will not be reassigned.

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

In the event that a significant difference in mean baseline body weight among subjects by treatment group emerges as enrollment progresses, the randomization scheme (described immediately above) will be suspended and subjects will be assigned to a specific treatment group using the following alternative procedure:

Step 1: Calculate the mean body weight for subjects who have been previously entered into the treatment period, in aggregate and by treatment group.

Step 2: Compare the subject's body weight (measured at Visit 1) with the current mean body weight of all subjects who have previously been entered into the treatment period. If the subject's weight is equal to or higher than the current mean body weight of all previously treated subjects, then assign the subject to a treatment group (which still has less than 20 subjects) having the lowest mean body weight. If the subject's weight is lower than the current mean body weight of all previously treated subjects, then assign the subject to a treatment group (which still has less than 20 subjects) having the highest mean body weight.

Step 3 (if needed): If a subject cannot be assigned to a treatment group according to Step 2 (above) and there are fewer than 80 subjects assigned to treatment, then assign the subject to a treatment group (which still has less than 20 subjects) with the most similar mean body weight.

5.5 Prior and Concomitant Therapy

Subjects should not take any vitamin D and/or bone metabolism therapy other than the study drug. Excluded therapies include any non-study prescribed dose of 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 concomitant medication usage from Visit 1 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.

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. Phenobarbital or other anticonvulsants or other compounds that stimulate microsomal hydroxylation reduce the half-life of calcifediol.

5.5.1 Phosphate Binder and Elemental Calcium Therapy

Use of phosphate binders is prohibited throughout the study. Elemental calcium may be prescribed during the screening visit to ensure the dietary intake is within the range of 1,000-1,500 mg per day. The overall dose of elemental calcium intake should remain stable throughout the study.

5.5.2 Diet Restrictions

There are no study specific dietary restrictions. Subjects should follow their dietary plan if one has been prescribed. Changes in prescribed dietary phosphorus or calcium therapy are discouraged and any changes during the study should be captured in the electronic case report form (eCRF).

Subjects will maintain a dietary intake during the study of approximately 1,000-1,500 mg per day of elemental calcium per dietary counseling and, as necessary, administration of a daily calcium supplement. Subjects will complete a dietary questionnaire on Visit 1 and receive counseling from a dietician on their dietary calcium intakes, if needed.

Subjects will report to the phase 1 unit on the mornings of Day 1 and Day 29 after an overnight fast. They will receive standardized meals while housed in the phase 1 unit. These meals will contain 400 mg of elemental calcium and will be administered at approximately 2, 6, and 10 hours post-dose.

5.5.3 Subject Activity Restrictions

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

5.6 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, subject dosing diaries, 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 protocol deviation.

5.7 Labeling

All study drug labels will include the protocol number, sponsor identification and address, study drug container contents, unique container number, area for subject and Investigator identification as applicable, investigational use statements, storage conditions, expiry date and instructions for use.

5.8 Storage and Accountability

All medications will be shipped to sites using standardized shipment and temperature monitoring procedures. While at the study site, all study drug will be stored in an area with light and heat protection and in accordance to USP Controlled Room Temperature (20-25°C or 68-77°F) and 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, and verify that the supplies were maintained within an appropriate temperature range during shipment. 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.

5.9 Investigational Product Retention at Study Site

At the conclusion of the study, a final accountability 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 ICF.

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 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 for ongoing subjects).

6.2 Medical History and Concomitant Medications

A detailed medical history, including demographics, will be recorded at Visit 1/screening. Concomitant medications will be reviewed with each subject and recorded at specified visit intervals throughout the study.

6.3 Physical Examination and Vital Signs

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 1.

Table 1 Evaluations

Physical Examination:	• A brief PE including weight and height and excluding a urogenital examination will be performed during Visit 1 and Visit 16 or ET.
Vital Sign measurements:	• Blood pressure, heart rate and respiratory rate, and body temperature in degrees Celsius will be measured prior to any scheduled blood draws or at ET after the subject has been sitting for at least 2 minutes.
Body height	• Body height will be recorded to the nearest 1.0 cm at Visit 1 and Visit 16 or ET.
Body weight:	• Body weight will be recorded to the nearest 0.1 kg at Visit 1 and Visit 16 or ET.
BM1	• BMI will be calculated using the body weight divided by the body height squared and recorded to the nearest tenth of a decimal point at Visit 1 and Visit 16 or ET.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

Blood will be drawn and analyzed as specified in Table 2. Urine samples will be collected and analyzed as specified in Table 2.

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

All clinically significant abnormal laboratory values will 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 2.

Table 2 List of Laboratory Tests

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

Drugs of Abuse Screen (Urine)

Serum pregnancy test (only for females of child bearing potential)

PK and CCI parameters:

CCI

Serum calcifediol

CCI

CCI

Serum Chemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Blood urea nitrogen
- Calcium (corrected)
- Carbon dioxide
- Chloride
- Creatinine
- Globulin
- Glucose
- Glutamic oxaloacetic transaminase
- Glutamic pyruvic transaminase
- Lactate dehydrogenase
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

Serum Partial Chemistry:
- Calcium (corrected)
- Phosphorus
- Albumin

Serum hepatitis B & C screen

Serum HIV screen

eGFR

Urinary albumin excretion

6.4.2 Sample Collection, Storage, and Shipping

Missed blood and urine 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 and urine samples will be collected and analyzed for clinical laboratory tests. During the entire study, approximately 870 mL of blood will be drawn. Additional blood draws may be needed for any additional, unscheduled visits which are medically necessary.

Blood samples for measurement of certain clinical laboratory tests will be collected and shipped to the central laboratory. The central laboratory will ship the frozen specimens to the designated analytical facilities as detailed in the laboratory manual.

Samples are to be shipped to the central laboratory for each subject as visits are completed. The Investigator will provide a limited access, temperature monitored space for the study drug and a -80°C freezer space for respective serum and plasma aliquots.

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 study coordinator (or designated site personnel) at the site will dispense the appropriate quantity of study drug to each subject, which will be recorded in the source document and on the appropriate eCRF.

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 recorded in the source document and on the appropriate eCRF.

6.6.3 AE Collection Period

All AEs that occur after the ICF has been signed must be reported in detail in the source document and in the appropriate eCRFs 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) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory values 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 are the result of pathology for which there is an overall diagnosis (e.g., 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 (e.g., as an emergency) due to a worsening of the preexisting condition, the worsening of the condition should be captured as an AE. Elective procedures performed where there is no change in the subject's medical condition (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 source documentation and eCRF as procedures.

Any report of pregnancy identified for any female subject or for a female partner of a male subject should be reported immediately (within 24 hours of being informed) to the medical monitor. Pregnancies will be considered 'events of special interest' and will not be captured as serious adverse events (SAEs). The Pregnancy Report Form will be utilized to obtain BL and follow-up information. Pregnancies will be followed to termination or six weeks post-delivery

for determination of resolution to the event. Subjects who become pregnant during treatment must immediately be withdrawn from the study (classified as ET).

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, e.g., 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 source documentation and in the appropriate 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 source documentation and the appropriate 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 3.

Table 3 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 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 and vital signs 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, eCRF 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.

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, IR calcifediol, Cholecalciferol, or Paricalcitol. 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 the following numbers within 24 hours from the time when site personnel first learn about the event.

SAE Fax line: PPD

SAE email: safety@safeharborpv.com

A written report will follow as soon as possible and should consist of the SAE report 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 add this information to both the source documentation and the initial SAE section of the eCRFs, and provide any additional written documentation to the above number 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 sponsor's Clinical Services Department.

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. Pregnancies will be followed until six weeks following delivery to determine the outcome.

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 (Early Termination)

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

- A major protocol deviation occurs;
- A serious or intolerable AE occurs;
- A clinically significant change in a laboratory parameter occurs;
- The sponsor or Investigator terminates the study;
- The subject 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;

No subject replacement is planned.

6.9 Appropriateness of Measurements

AEs, corrected serum calcium and serum phosphorus have been used to assess safety of vitamin D compounds and will be monitored in this study. The safety and tolerability of each study

medication will be determined by analyzing AEs, corrected serum calcium and serum phosphorus.

CCI [redacted] Pre and post-dose averages will be used to minimize the effect of any intrasubject and interassay variability.

7 STUDY ACTIVITIES

7.1 Screening Period

7.1.1 Visit 1 (Days -70 or -42 to -36)

- A signed ICF will be obtained from the subject prior to any study-related procedures
- Review of inclusion/exclusion criteria
- Medical history and demographics
- Review of prior and current medications
- PE (including weight, height and BMI)
- VS assessment
- Serum pregnancy test (for females of child bearing potential)
- Serum hepatitis B and C/HIV screen
- Drugs of abuse screen
- eGFR
- Urinary albumin excretion
- Blood samples will be drawn for the following:
  - Clinical chemistry (full panel) and hematology

  CCI [redacted]
- Dietary questionnaire for calcium intake and counseling, if needed.

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

7.1.2 Visits 2 and 3 (Within Days -7 to -1)

- Review of inclusion/exclusion criteria
- Review of concomitant medications
- AE assessment
- VS assessment
- Serum pregnancy test (for females of child bearing potential) (Visit 2 only)
- Blood samples will be drawn for the following:
  - Clinical chemistry (full panel) and hematology

  CCI [redacted]
- Blood samples will be drawn for:
  - CCI [redacted] calcifediol, and CCI [redacted]

  CCI [redacted]

- CCI [redacted]
- Subjects will be instructed to report to the phase 1 unit for Visit 4 after an overnight fast.

7.2 Treatment Period

7.2.1 Visit 4 (Day 1)

Randomization will occur at the start of this visit.

- Subjects admitted into the phase 1 unit (for approximately 14 to 26 hours) after an overnight fast.
- Subjects will receive standardized meals while housed in the phase 1 unit. These meals will contain approximately 400 mg of elemental calcium and will be administered at approximately 2 (breakfast), 6 (lunch), and 10 (dinner) hours post-dose.
- Review of concomitant medications
- VS assessment
- Blood samples will be drawn from subjects housed in the phase 1 unit at approximately 6:00 a.m. (t=~-2 hours), and 8:00 a.m. (t=~0 hours) and precisely (plus or minus 5 minutes, with exact time noted) at t=2, 4, 6, 12 and 24 hours (for subjects opting overnight stays), post-dose for the following analyses:
  - Chemistry (partial panel)

    CCI [redacted]
  - Serum calcifediol, CCI [redacted]
- Additional blood samples will be drawn from subjects housed in the phase 1 unit at approximately 8:00 a.m. (t=~0 hours) and precisely (plus or minus 5 minutes, with exact time noted) at t=12 and 24 hours (for subjects opting overnight stays) post-dose for the following analysis:

  CCI [redacted]
- AE assessments will be completed at each timed blood draw (n=6)
- Subjects take first dose of study drug 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.

CCI [redacted]

- Subjects will be discharged from the phase 1 unit after the blood draw at 12 hours post-dose unless Subject chooses to stay overnight. Subjects opting to remain in the phase 1 unit for overnight will have 24 hour read completed. Those who do not opt to stay overnight, advance to Visit 5.
- Balance of monthly study drug supply dispensed at discharge to subjects assigned to CTAP101 Capsules and paricalcitol capsules plus low-dose cholecalciferol.

7.2.2 Visits 5 & 6 (Day 2 & 3)

- Visit 5 is only required for subjects not opting overnight stays for Visit 4. Visit 6 is required for all subjects.

  Visits 5 and 6 must be completed at exactly 24 and 48 hours from dose received in Visit 4.
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Chemistry (partial panel)

    CCI [redacted]
  - Serum calcifediol, CCI [redacted]

    CCI [redacted]

7.2.3 Visits 7, 8, 9 (Day 8, 15, 22)

- Review of concomitant medications
- Dosing compliance and dosing diary assessed for subjects assigned to CTAP101 Capsules and paricalcitol capsules plus low-dose cholecalciferol.
- AE assessment
- VS assessment
- Blood samples for the following analyses:
  - Chemistry (partial panel)

    CCI [redacted]
- Subjects instructed to report to the phase 1 unit for Visit 10 after an overnight fast, and to bring along the previously dispensed study drug containers along with any unused study drug.

7.2.4 Visit 10 (Day 29)

- Subjects admitted into the phase 1 unit (for approximately 14 to 26 hours) after an overnight fast unless Subject chooses to stay overnight. Subjects opting to remain in the phase 1 unit

for overnight will have 24 hour read completed. Those who do not opt to stay overnight, advance to Visit 11.

- Dosing compliance and dosing diary assessed for subjects assigned to CTAP101 Capsules and paricalcitol capsules plus low-dose cholecalciferol.
- Subjects will receive standardized meals while housed in the phase 1 unit. These meals will contain 400 mg of elemental calcium and will be administered at approximately 2 (breakfast), 6 (lunch), and 10 (dinner) hours post-dose.
- Review of concomitant medications
- VS assessment
- Pre-dose blood samples will be drawn for the following:
  - Clinical chemistry (full panel) and hematology

  CCI [redacted]
- Blood samples will be drawn from subjects housed in the phase 1 unit at approximately 6:00 a.m. (t=~-2 hours), and 8:00 a.m. (t=~0 hours) and precisely (plus or minus 5 minutes, with exact time noted) at t=2, 4, 6, 12 and 24 hours (for subjects opting overnight stays) post-dose for the following analyses:
  - Clinical chemistry (partial panel)

  CCI [redacted]
  - Serum calcifediol, CCI [redacted]
  - Additional blood samples will be drawn from subjects housed in the phase 1 unit at approximately 8:00 a.m. (t=~0 hours) and precisely (plus or minus 5 minutes, with exact time noted) at t=12 and 24 hours (for subjects opting overnight stays), post-dose for the following analysis:

  CCI [redacted]
- AE assessments will be completed at each timed blood draw (n=6)
- Subjects take next dose of study drug 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.

CCI [redacted]

- Subjects will be discharged from the phase 1 unit after the blood draw at 12 hours post-dose.
- Balance of monthly study drug supply dispensed at discharge to subjects assigned to CTAP101 Capsules and paricalcitol capsules plus low-dose cholecalciferol.

7.2.5 Visits 11 & 12 (Days 30 & 31)

- Visit 11 is only required for subjects not opting overnight stays for Visit 10. Visit 12 is required for all subjects.

  Visits 11 and 12 must be completed at exactly 24 and 48 hours from dose received in Visit 10.
- Review of concomitant medications
- AE assessment
- VS assessment
- Blood samples will be drawn for the following analyses:
  - Chemistry (partial panel)

    CCI [redacted]
  - Serum calcifediol, CCI [redacted]

    CCI [redacted]

7.2.6 Visits 13, 14, 15 (Day 36, 43, 50)

- Review of concomitant medications
- Dosing compliance and dosing diary assessed for subjects assigned to CTAP101 Capsules and paricalcitol capsules plus low-dose cholecalciferol.
- AE assessment
- VS assessment
- Blood samples for the following analyses:
  - Chemistry (partial panel)

    CCI [redacted]
- Subjects instructed to report to the phase 1 unit for Visit 16 with the previously dispensed study drug containers along with any unused study drug.

7.3 End of Study (EOS)

7.3.1 Visit 16 (Day 57) Last study visit (or Early Termination)

- Dosing compliance and dosing diary assessed for subjects assigned to CTAP101 Capsules and paricalcitol capsules plus low-dose cholecalciferol.
- Review of concomitant medications
- AE assessment
- PE (including weight, height and BMI)

- VS assessment
- Serum pregnancy test (for females of child bearing potential)
- Blood samples for the following analyses:
  - Chemistry (full panel) plus hematology
  - CCI calcifediol, CCI

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 Council 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, e.g., central laboratory and PK/[redacted] 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 PK and CCI for each medication will be described. All data collected on eCRFs and from clinical laboratory evaluations will be grouped and listed by population subgroup, subject number, visit, date and time as feasible. 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 subgroup 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 BL 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 database lock. All subjects entered into the clinical database will be included in subject data listings.

9.2 Determination of Sample Size

No formal sample size estimation has been performed for the study.

9.3 Randomization

Each subject will be assigned a unique 7 digit subject identification number which will be retained throughout the study and that will be unique across all sites. The 7 digit subject identification number (SSSNNNN) will consist of a 3-digit site number (SSS) and a 4-digit subject number (NNNN) at the applicable clinical site. Should a subject be withdrawn from the study, that subject's 7 digit identification number will not be reassigned.

Randomization will be accomplished in blocks of 4 subjects in a 1:1:1:1 ratio with subjects being assigned to treatment with CTAP101 Capsules, IR calcifediol, high-dose cholecalciferol or paricalcitol plus low-dose cholecalciferol. Randomization will occur during Visit 4 provided that each subject is deemed eligible for enrollment based, in part, on laboratory assessments obtained at two preceding visits (Visits 1 and 2). Laboratory assessments obtained at Visit 3 will not be considered in the determination of enrollment eligibility. In the event that the treatment groups become unbalanced for mean baseline body weight as enrollment progresses, the randomization scheme (described immediately above) will be suspended and subjects will be assigned to treatment groups by the following alternative procedure:

Step 1: Calculate the mean body weight for subjects who have been previously entered into the treatment period, in aggregate and by treatment group.

Step 2: Compare the subject's body weight (measured at Visit 1) with the current mean body weight of all subjects who have previously been entered into the treatment period. If the subject's weight is equal to or higher than the current mean body weight of all previously treated subjects, then assign the subject to a treatment group (which still has less than 20 subjects) having the lowest mean body weight. If the subject's weight is lower than the current mean body weight of all previously treated subjects, then assign the subject to a treatment group (which still has less than 20 subjects) having the highest mean body weight.

Step 3 (if needed): If a subject cannot be assigned to a treatment group according to Step 2 (above) and there are fewer than 80 subjects assigned to treatment, then assign the subject to a treatment group (which still has less than 20 subjects) with the most similar mean body weight.

9.4 Analysis Populations

CCI [redacted]

The safety population will include all subjects who are randomly assigned to treatment and receive at least 1 dose of study drug. CCI [redacted] 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 paricalcitol concentrations to facilitate the calculation of at least 1 postdose PK parameter using validated methods.

All planned analyses will be specified in an accompanying statistical analysis plan (SAP).

9.5 Demographics and Baseline Characteristics

Demographic and BL characteristics will be summarized for the ITT, Safety, PP and PK populations. BL 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.

9.6 Subject Disposition and Withdrawal

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

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.

9.7 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. 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 subgroup using frequency counts and percentages for each anatomical/therapeutic/chemical Class Level 2 and 4 and generic drug name. All medications recorded on the eCRF, including start and stop (or ongoing as of) dates, AE number (if applicable), indication, dose, unit, route, and frequency will be listed. For the purpose of inclusion in prior or concomitant medication tables, incomplete medication start and stop dates will be imputed and then categorized into prior or concomitant medication categories.

9.8 Pharmacokinetic Analysis

Parameters to be calculated in the PK population from observed and BL-adjusted serum calcifediol CCI include, but may not be limited to the parameters listed in Table 4.

Table 4 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.
$t_{1/2}$	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.

As an exploratory analysis, PK parameters for serum calcifediol will be compared between study arms. These analyses could include simple statistical summaries or using an ANOVA model, if feasible.

CCI

[redacted]

9.10 Safety Analysis

All Safety subjects will be included in the safety analysis. Statistical summary analysis of safety data will be descriptive only.

9.10.1 Primary Endpoints Analyses

9.10.1.1 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 subgroup 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 subgroup. 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 subgroup. 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.

9.10.1.2 Vital Signs

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

9.10.1.3 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.

9.10.2 Secondary Endpoint Analyses

Secondary safety endpoints will include incidence of hypercalcemia and drug-related hyperphosphatemia. The number (n, %) of subjects with hypercalcemia (two consecutive visits with serum calcium above 10.3 mg/dL) or hyperphosphatemia (two consecutive visits with serum phosphorus above 5.5 mg/dL) will be calculated.

9.11 Efficacy Analyses

9.11.1 Primary Endpoint Analyses

As this study is descriptive in nature there is no planned primary endpoint analyses. Descriptive analysis and plots will be created for the ITT and PP populations of serum calcifediol, CCI [redacted]

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 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 (e.g., an IRB).

10.3 Ethical Conduct of the Study

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

10.4 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).

10.5 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.

10.6 Study Monitoring

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

The study will be monitored by the sponsor or designee at all stages of study conduct from inception to completion in accordance with current ICH/GCP. The Investigator will allocate adequate time for such monitoring activities. This monitoring will be in the form of site visits and other communication and will include review of original source documents, 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.

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 (e.g., pharmacy, diagnostic laboratory), and has adequate space to conduct the monitoring visit.

10.7 Case Report Forms and Study Records

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays.

Data collected during this study must be recorded on the appropriate source documents. All source documents should be completed 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 is randomized. All data generated from external sources, (e.g., 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.

10.8 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, dosing non-compliance, 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.

10.9 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.

10.10 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.

10.11 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.

10.12 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

	Screen	Wash out	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	-70 or -42 to -36	-63 or -35 to -8	-7 to -2	-1	1	2	3	8	15	22	29	30	31	36	43	50	57
					(GCRC)						(GCRC)						
Hours					-2, 0, 2, 4, 6, 12	24 hrs	48 hrs				-2, 0, 2, 4, 6, 12	24 hrs	48 hrs				
Study drug dispensed					1[a,b]						1[a,b]						
Dosing compliance and dosing diary assessed								1	1	1	1			1	1	1	1
Sign ICF	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 child bearing potential)	1		1														1
Serum Hepatitis B & C/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)					6	1	1	1	1	1	6	1	1	1	1	1	

	Screen	Wash out	Baseline		Treatment												EOS /ET
(Continued)																	
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	-70 or -42 to -36	-63 or -35 to -8	-7 to -2	-1	1	2	3	8	15	22	29	30	31	36	43	50	57
					(GCRC)						(GCRC)						
Hours					-2, 0, 2, 4, 6, 12	24 hrs	48 hrs				-2, 0, 2, 4, 6, 12	24 hrs	48 hrs				
Urine drugs of abuse screen	1																
CCI [redacted]																	

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 Day 1 and 29 from monthly study drug supply.

[c] [redacted]

APPENDIX 2 CALCIFEDIOL IR CAPSULES (HIDROFEROL)

SUMMARY OF PRODUCT CHARACTERISTICS
(Translation)

1. NAME OF THE MEDICINAL PRODUCT

Hidroferol 0.266 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 0.266 mg (266 micrograms) of calcifediol (15,960 IU of vitamin D).

Excipients with known effect:

Each capsule contains 4.98 mg of ethanol, 31.302 mg of sorbitol (70% v/v) (E-420), 0.958 mg of sunset yellow (E-110) and other excipients.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule

Soft gelatine orange-coloured capsule.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

In adults:

Treatment of vitamin D deficiency in cases in which the initial administration of high doses is required or where administration spaced out over time may be preferred, as in the following situations:

- As an adjuvant for treating osteoporosis;
- In patients with malabsorption syndrome
- Renal osteodystrophy
- Bone problems caused by treatment with corticosteroids.

4.2 Posology and method of administration

Posology

The dietary intake of vitamin D and exposure to sunlight varies between patients and must be taken into account when calculating the appropriate dose of vitamin D analogues, such as calcifediol.

The dose, frequency and duration of treatment will be determined according to the plasma levels of 25-OH-cholecalciferol, the type and situation of the patient and other comorbidities such as obesity, malabsorption syndrome and corticosteroid treatment. The dose which generates serum calcium levels of between 9–10 mg/dL should be administered.

The plasma determination of 25-OH-cholecalciferol is considered the most acceptable way of diagnosing vitamin D deficiency. It can be accepted that there is vitamin D deficiency with serum levels of 25-OH-cholecalciferol < 20 ng/mL and vitamin D insufficiency with serum levels of 25-OH-cholecalciferol between 20 and 24 ng/mL.

In normal subjects, the mean serum concentrations range between 25 and 40 ng/mL of 25-OH-cholecalciferol.

The recommended dose is one capsule (0.266 mg of calcifediol) once a month.

- Vitamin D insufficiency: The administration of one capsule (0.266 mg of calcifediol) a month for 2 months is recommended.
- Vitamin D deficiency: The initial administration of one capsule (0.266 mg of calcifediol) a month for 4 months is recommended.
- As an adjuvant in the treatment of osteoporosis in patients with vitamin D deficiency, the administration of one capsule (0.266 mg of calcifediol) a month for 3–4 months is recommended.

There are populations at high risk of vitamin D deficiency in whom it may be necessary to administer higher doses or more prolonged regimens, after analytically testing the extent of the deficiency and completing regular checks of serum levels of 25-OH-cholecalciferol.

- Renal osteodystrophy: Taking one capsule (0.266 mg of calcifediol) per week or every two weeks is recommended.
- Bone problems caused by corticosteroids: Taking one capsule (0.266 mg of calcifediol) a month is recommended.
- In patients with higher vitamin D deficiencies or malabsorption syndrome, repeating the initial dose weekly (0.266 mg of calcifediol) is recommended, followed by one capsule once a month for 4 months, checking the plasma concentration of 25-OH-cholecalciferol. Depending on these levels, an increase in the dose or frequency of administration may be required. Once the value within the interval has been established, the treatment will be suspended or the regimen will be more spaced out.

In general, the doses must be reduced when symptoms improve because the requirements for vitamin D analogues normally decrease after recovery of the bone.

It is useful to know the serum concentrations of 25-OH-cholecalciferol 3 months after starting the supplementation to confirm that they are within the desirable or preferred interval (30–60 ng/mL). Once the value within the interval has been established, the treatment will be suspended or the regimen will be more spaced out.

Paediatric population

The medicinal product Hidroferol 0.1 mg/mL oral drops in solution has been authorised for use in children, with lower dose concentration.

Method of administration

Oral route.

The capsule may be taken with water, milk or juice.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients included in section 6.1.
- Hypercalcaemia (calcaemia > 10.5 mg/dL), hypercalciuria (abnormally high excretion of calcium in the urine).
- Calcium lithiasis.
- Hypervitaminosis D.

4.4 Special warnings and precautions for use

- The serum levels of 25-OH-cholecalciferol reflect the patient's vitamin D status, but in order to obtain an adequate clinical response to the oral administration of calcifediol, there must also be adequate calcium intake in the diet. Therefore, to control the therapeutic effects, in addition to the 25-OH-cholecalciferol, the calcium, phosphorous, alkaline phosphatase, and urinary calcium and phosphorous in the serum must be monitored over 24 hours; a drop in the

serum levels of alkaline phosphatase normally precedes the appearance of hypercalcaemia. Once these parameters are normal in the patient and the patient is on a maintenance treatment regimen, the above-mentioned measurements must be taken, in particular the serum levels of 25-OH-calciferol and calcium.

- Hepatic or gallbladder insufficiency: In the event of hepatic insufficiency, an inability to absorb calcifediol may occur through bile salts not being produced.
- Renal insufficiency: Administration with caution is advised. The use of this medicinal product in patients with chronic kidney disease must be accompanied by regular checks of plasma calcium and phosphorous, and to prevent hypercalcaemia. As the kidneys will give rise to calcitriol, in the event of severe renal insufficiency (renal creatinine clearance less than 30 mL/minute) a very significant decrease in the pharmacological effects may occur.
- Cardiac insufficiency: Particular caution is required. The individual's calcium level must be monitored at all times, particularly in patients undergoing treatment with digitalis medication, as it may cause hypercalcaemia and the appearance of arrhythmia; it is advised to perform these measurements twice a week at the start of treatment.
- Hypoparathyroidism: 1-alpha-hydroxylase shall be activated by the CCI , therefore in the event of parathyroid insufficiency, the calcifediol activity may decrease.
- Renal calculi: The calcium level must be controlled as vitamin D, by increasing calcium absorption, may aggravate the symptoms. Vitamin D levels must only be administered in these patients if the benefits outweigh the risks.
- In patients with long-term immobilisation, dose reduction may be necessary on occasion to avoid hypercalcaemia.
- There are diseases that affect the intestine's capacity to absorb vitamin D, as in the case of malabsorption syndrome or Crohn's disease.
- Patients with sarcoidosis, tuberculosis or other granulomatous diseases: It must be used with caution, given that in these diseases there is greater sensitivity to the effect of vitamin D and increase the risk of suffering from adverse reactions at lower doses of the medicinal product than the recommended ones. The serum and urinary calcium concentrations should be checked in these patients.
- The patient and their family and/or carers must be informed of the importance of complying with the indicated posology and the recommendations regarding diet and taking calcium supplements concomitantly in order to prevent overdose.
- Interference with laboratory tests: Patients must be advised that this medicinal product contains a component that may cause changes in laboratory test results:

Measurement of cholesterol: Calcifediol may interfere with the Zlatkis-Zak method, giving rise to false increases in serum cholesterol levels.

Elderly patients:

Elderly patients generally have a greater need for vitamin D due to a decrease in the capacity of the skin to produce cholecalciferol from its precursor 7-dehydrocholesterol, due to a reduction in exposure to sunlight, and due to changes in renal function or digestive dysfunctions that may reduce vitamin D absorption.

Excipients warnings

This medicinal product contains 1% of ethanol (alcohol), which corresponds to a quantity of 4.98 mg/capsule.

This medicinal product contains sorbitol. Patients with hereditary intolerance to fructose must not take this medicinal product.

This medicinal product may cause allergic reactions because it contains sunset yellow S (E-110). It may cause asthma, especially in patients who are allergic to acetylsalicylic acid.

4.5 Interaction with other medicinal products and other forms of interaction

- **Phenytoin, phenobarbital, primidone** and other enzyme inducers: Enzyme inducers can reduce the plasma concentrations of calcifediol and inhibit their effects through induction of their hepatic metabolism.
- **Cardiac glycosides:** Calcifediol may cause hypercalcaemia, which can in turn strengthen the inotropic effects of digoxin and its toxicity, causing cardiac arrhythmia.
- Medicinal products that reduce the absorption of calcifediol, such as **cholestyramine, colestipol or orlistat,** may cause a decrease of the effects. Spacing out the doses of these medicinal products and vitamin D supplements by at least 2 hours is recommended.
- **Paraffin and mineral oil:** Due to the liposolubility of calcifediol, it can be dissolved in paraffin and decrease its intestinal absorption. The use of another type of laxative or at least spacing out the doses is recommended.
- **Thiazide diuretics:** Concomitant administration of a thiazide diuretic (hydrochlorothiazide) with vitamin D supplements, in patients with hypoparathyroidism can give rise to hypercalcaemia, which can be temporary or require suspension of treatment with the vitamin D analogue.
- Some antibiotics, such as **penicillin, neomycin and chloramphenicol,** can increase calcium absorption.
- **Phosphate binders such as magnesium salts:** As vitamin D has an effect on the transport of phosphate in the intestine, kidneys and bones, it may cause hypermagnesaemia; the dose of phosphate binders must be adjusted in accordance with serum phosphate concentrations.
- **Verapamil:** There are studies in which possible inhibition of anti-angina action has been recorded, through antagonism of its actions.
- **Vitamin D:** The concomitant administration of any vitamin D analogue must be avoided as this may cause additive positive effects and hypercalcaemia.
- **Calcium supplements:** The uncontrolled intake of additional preparations containing calcium must be avoided.
- **Corticosteroids:** counteract the effects of vitamin D analogues, such as calcifediol.

Interaction with food and drink

Foods that can be supplemented with vitamin D must be taken into account as this may cause additive effects.

4.6 Fertility, pregnancy and lactation

Pregnancy

No controlled studies with calcifediol have been carried out in pregnant women.

Animal studies have demonstrated toxicity for reproduction (see section 5.3).

Hidroferol 0.266 mg soft capsules must not be used during pregnancy.

Breast-feeding

Calcifediol is excreted in breast milk.

The risk for newborn babies/children cannot be ruled out. Maternal intake of high doses of calcifediol may cause high levels of calcitriol in breast milk and cause hypercalcaemia in the breastfed baby.

Hidroferol 0.266 mg soft capsules must not be used while breastfeeding.

4.7 Effects on ability to drive and use machines

Hidroferol has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The undesirable effects of calcifediol are, generally, rare (≥1/1,000 to <1/100) although sometimes they are moderately significant.

The most significant undesirable effects relate to the excessive intake of vitamin D, which means they are usually associated with overdose or prolonged treatments, in particular when it is combined with high doses of calcium. Doses of vitamin D analogues required to produce hypervitaminosis vary considerably between individuals. The most typical undesirable effects are due to possible hypercalcaemia, and they can appear at an early or a late stage.

Endocrine disorders:

Pancreatitis, among the delayed symptoms of hypercalcaemia.

Metabolism and nutrition disorders:

Increase in blood urea nitrogen (BUN), albuminuria, hypercholesterolaemia, hypercalcaemia

Nervous system disorders:

If moderate hypercalcaemia has occurred, the following may appear: weakness, fatigue, drowsiness, headache, irritability.

Eye disorders:

On rare occasions (≥1/10,000 to <1/1,000), photophobia and conjunctivitis with corneal calcifications may occur at very high doses.

Cardiac disorders:

In the event of hypercalcaemia, cardiac arrhythmia may occur.

Gastrointestinal disorders:

Nausea, vomiting, dryness of the mouth, constipation, taste disorders, with a metallic taste, abdominal cramps; in the event of progressive hypercalcaemia, anorexia may occur.

Hepatobiliary disorders:

With high levels of calcaemia, an increase in transaminase (ALT and AST) may occur.

Musculoskeletal and connective tissue disorders:

In the event of hypercalcaemia, initially bone and muscle pain, and calcifications in the soft tissues may occur.

Renal and urinary disorders:

Manifestations of hypercalcaemia are: nephrocalcinosis and deterioration of renal function (with polyuria, polydipsia, nocturia and proteinuria)

General disorders and administration site conditions:

Delayed symptoms of hypercalcaemia are: rhinorrhea, pruritus, hyperthermia, and decrease in libido.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Spanish System of Pharmacovigilance of Medicinal Products for Human Use: www.notificaRAM.es.

4.9 Overdose

Symptoms:

The administration of vitamin D at high doses or over long periods of time may cause hypercalcaemia, hypercalciuria, hyperphosphataemia and renal insufficiency. Initial symptoms of intoxication may include the following: weakness, fatigue, drowsiness, headache, anorexia, dryness of the mouth, metallic taste, nausea, vomiting, abdominal spasms, polyuria, polydipsia, nocturia, constipation or diarrhoea, dizziness, tinnitus, ataxia, exanthema, hypotony (in particular in babies), muscle or bone pain and irritability.

Among the most delayed symptoms of hypercalcaemia are: rhinorrhea, pruritus, decrease in libido, nephrocalcinosis, renal insufficiency, osteoporosis in adults, arrested growth in children, weight loss, anaemia, conjunctivitis with calcification, photophobia, pancreatitis, increase in the blood urea nitrogen (BUN), albuminuria, hypercholesterolaemia, increase in transaminase (ALT and AST), hyperthermia, generalised vascular calcification, convulsions and calcification of the soft tissue. Rarely, patients may develop hypertension or psychotic symptoms; serum alkaline phosphatase can decrease; water-electrolyte imbalance together with moderate acidosis may give rise to cardiac arrhythmia.

In more serious situations in which calcaemia exceeds 12 mg/dL, fainting, metabolic acidosis and coma may occur. Although the symptoms of overdose are usually reversible, renal or heart failure may occur.

It is accepted that serum levels of 25-OH-cholecalciferol greater than 150 ng/mL may be associated with an increase in the incidence of undesirable effects.

The increase in calcium, phosphate, albumin and blood urea nitrogen, and cholesterol and transaminase in the blood is typical of this overdose.

Treatment:

The treatment for intoxication by calcifediol consists of:

1. Withdrawing treatment (with calcifediol) and any calcium supplement that is being administered.
2. Following a low-calcium diet. To increase the excretion of calcium, administering large volumes of fluids, both orally and parenterally, is recommended, and if necessary, to administer glucocorticoids and forced loop diuretics such as furosemide.
3. If the intake has occurred within the last 2 hours, gastric lavage and forced emesis can be performed. If the vitamin D has already passed through the stomach, a paraffin or mineral oil laxative can also be administered. If the vitamin D has already been absorbed, haemodialysis or peritoneal dialysis with a calcium-free dialysis solution can be used.

As a consequence of long-term administration of calcifediol, Hypercalcaemia may persist for approximately 4 weeks after the suspension of treatment. The signs and symptoms of hypercalcaemia are normally reversible, but metastatic calcification may cause severe renal insufficiency, cardiac insufficiency or death.

5. PHARMACOLOGICAL PROPERTIES

5.1 CCI properties

Pharmacological group: Vitamin D and analogues. Calcifediol. ATC code: A11CC06

Mechanism of action

Vitamin D has two main forms: D2 (ergocalciferol) and D_3 (cholecalciferol). Vitamin D_3 is synthesised in the skin through exposure to sunlight (ultraviolet radiation) and it is obtained in the diet. Vitamin D_3 must undergo a two-step metabolic process to be active; the first step occurs in the microsomal fraction of the liver where it is hydroxylated in position 25 (25-hydroxycholecalciferol or calcifediol); the second process takes place in the kidneys where 1.25-dihydroxycholecalciferol or calcitriol is formed through intervention of the enzyme 25-hydroxycholecalciferol 1-hydroxylase; the conversion to 1.25-hydroxycholecalciferol is regulated by its own concentration, by the CCI and by the calcium and phosphate serum concentration; there are other metabolites with unknown function. From the kidneys, 1.25-hydroxycholecalciferol is transported to the destination tissues (intestine, bone, possibly kidney and parathyroid glands) by binding to specific plasma proteins.

CCI effects

Vitamin D primarily increases the absorption of calcium and phosphorus in the intestine and promotes normal bone formation and mineralisation, and acts on three levels:

Intestine: it stimulates the absorption of calcium and phosphorus in the small intestine.

Bone: calcitriol stimulates bone formation by increasing calcium and phosphate levels and it stimulates the actions of the osteoblasts.

Kidneys: calcitriol stimulates the tubular reabsorption of calcium.

In the parathyroid glands: vitamin D inhibits the secretion of the CCI.

5.2 Pharmacokinetic properties

Absorption

Calcifediol or 25-hydroxycholecalciferol, such as vitamin D analogues, is absorbed in the intestine if the absorption of fats is normal, through the chylomicrons, principally in the middle sections of the small intestine; approximately 75–80% is absorbed this way.

Distribution

Calcifediol is the main circulating form of vitamin D. The serum concentrations of 25(OH)-cholecalciferol reflect the organism's vitamin D reserves which are usually between 25 and 40 ng/mL (62.5 to 100 nmol/L) in healthy individuals. Following the oral administration of calcifediol, the time in which the maximum serum concentration is reached is approximately 4 hours. Its half-life is around 18 to 21 days and its storage in the adipose tissue is less significant than that of vitamin D, due to its lower liposolubility; calcifediol is stored in the adipose and muscle tissue for extended periods of time. The pharmaceutical form of soft capsules offers a 22% higher bioavailability than the pharmaceutical form of an oral solution in vials. This difference is not considered clinically significant given that the dose must be determined on an individual basis depending on the serum levels of 25-OH-cholecalciferol and calcium, and these levels must be controlled during the treatment.

Metabolism or Biotransformation

Elimination

Calcifediol is principally excreted in the bile.

5.3 Preclinical safety data

High doses of vitamin D (from 4 to 15 times the recommended doses in humans) have been shown to be teratogenic in animals, but there are only a few studies that have been carried out in humans. Vitamin D may cause hypercalcaemia in the mother which also gives rise to supravalvular aortic stenosis syndrome, retinopathy and mental delay in children or newborn infants.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Absolute anhydrous ethanol

Medium-chain triglycerides

Gelatine

Vegetable glycerine

Sorbitol (70%) (E-420)

Titanium dioxide (E-171)

Sunset yellow (E-110)

Purified water

6.2 Incompatibilities

Not applicable

6.3 Shelf life

30 months

6.4 Special precautions for storage

No special precautions for storage are required.

6.5 Nature and contents of container

Container containing 5 or 10 capsules in Al-Al blister or in PVC/PVDC-Al blister.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

FAES FARMA S.A.

Máximo Aguirre, 14

ES-48940 Leioa (Bizkaia)

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

August 2015

10. DATE OF REVISION OF THE TEXT

August 2015

APPENDIX 3 HIGH DOSE CHOLECALCIFEROL CAPSULES (InVita D3 50,000 IU)

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

InVita D3 50,000 IU soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 50,000 IU colecalciferol (equivalent to 1.25 mg vitamin D3)

Excipients with known effect:

Each capsule contains 0.082 mg Allura Red AC (E129).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule

Red, oval-shaped, soft capsule. It contains a slightly yellow oily liquid. Each capsule has "50" printed in white ink. Capsule dimensions are 12.5mm x 8.5mm.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

The treatment of vitamin D3 deficiency.

4.2 Posology and method of administration

Posology

1 capsule contains 50,000 IU vitamin D3.

- Paediatric posology
  - Due to lack of clinical data, InVita D3 is not recommended.
- Pregnancy and breastfeeding
  - Due to lack of clinical data, InVita D3 is not recommended.
- Adults
  - Higher doses may be required in certain situations, see below.
  - Treatment of vitamin D3 deficiency (<25 nmol/l) 50,000 IU/week (1 capsule) for 6-8 weeks, followed by maintenance therapy (1400-2000 IU/day may be required, such as 1 capsule per month; follow up 25(OH)D measurements should be made approximately three to four months after initiating maintenance therapy to confirm that the target level has been achieved.)
- Certain populations are at high risk of Vitamin D3 deficiency, and may require higher doses and monitoring of serum 25(OH)D:
  - Institutionalised or hospitalised individuals
  - Dark skinned individuals
  - Individuals with limited effective sun exposure due to protective clothing or consistent use of sun screens
  - Obese individuals
  - Patients being evaluated for osteoporosis

- Use of certain concomitant medications (eg, anticonvulsant medications, glucocorticoids)
- Patients with malabsorption, including inflammatory bowel disease and coeliac disease
- Those recently treated for Vitamin D3 deficiency, and requiring maintenance therapy.

Special populations

Renal impairment

InVita D3 should not be used in combination with calcium in patients with severe renal impairment.

Hepatic impairment

No posology adjustment is required in patients with hepatic impairment.

Method of administration

Oral – The capsules should be swallowed whole with water.

Patients should be advised to take InVita D3 preferably with a meal (see section 5.2 Pharmacokinetic properties - "Absorption").

4.3 Contraindications

- Hypersensitivity to the active substance(s) or to any of the excipients.
- Hypercalcaemia and/or hypercalciuria.
- Nephrolithiasis and/or nephrocalcinosis
- Serious renal impairment
- Hypervitaminosis D
- Pseudohypoparathyroidismas the vitamin D requirement may be reduced due to phases of normal vitamin D sensitivity, involving the risk of prolonged overdose. Better-regulatable vitamin D derivatives are available for this.
- Pregnancy
- Children and adolescents (under 18 years of age)

4.4 Special warnings and precautions for use

Vitamin D3 should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account.

Caution is required in patients receiving treatment for cardiovascular disease (see section 4.5 Interaction with other medicinal products and other forms of interaction - cardiac glycosides including digitalis).

InVita D3 should be prescribed with caution in patients with sarcoidosis, due to a possible increase in the metabolism of Vitamin D3 in its active form. In these patients the serum and urinary calcium levels should be monitored.

Allowances should be made for the total dose of Vitamin D3 in cases associated with treatments already containing Vitamin D3, foods enriched with Vitamin D3, cases using milk enriched with Vitamin D3, and the patient's level of sun exposure.

There is no clear evidence for causation between Vitamin D3 supplementation and renal stones, but the risk is plausible, especially in the context of concomitant calcium supplementation. The

need for additional calcium supplementation should be considered for individual patients. Calcium supplements should be given under close medical supervision.

Oral administration of high-dose Vitamin D3 (500,000 IU by single annual bolus) was reported to result in an increased risk of fractures in elderly subjects, with the greatest increase occurring during the first 3 months after dosing.

4.5 Interaction with other medicinal products and other forms of interaction

Concomitant use of anticonvulsants (such as phenytoin) or barbiturates (and possibly other drugs that induce hepatic enzymes) may reduce the effect of Vitamin D3 by metabolic inactivation.

In cases of treatment with thiazide diuretics, which decrease urinary elimination of calcium, monitoring of serum calcium concentration is recommended.

Concomitant use of glucocorticoids can decrease the effect of Vitamin D3.

In cases of treatment with drugs containing digitalis and other cardiac glycosides, the administration of Vitamin D3 may increase the risk of digitalis toxicity (arrhythmia).

Strict medical supervision is needed, together with serum calcium concentration and electrocardiographic monitoring if necessary.

Simultaneous treatment with ion exchange resin such as cholestyramine, colestipol hydrochloride, orlistat or laxative such as paraffin oil may reduce the gastrointestinal absorption of Vitamin D3.

The cytotoxic agent actinomycin and imidazole antifungal agents interfere with Vitamin D3 activity by inhibiting the conversion of 25-hydroxyVitamin D3 to 1,25- dihydroxyVitamin D3 by the kidney enzyme, 25-hydroxyVitamin D3-1-hydroxylase.

4.6 Fertility, pregnancy and lactation

In pregnancy and lactation the high strength formulation is not recommended and a low strength formulation should be used.

Pregnancy

There are no or limited amount of data from the use of colecalciferol in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3 Preclinical safety data). The recommended daily intake for pregnant women is 400 IU, however, in women who are considered to be Vitamin D3 deficient a higher dose may be required (up to 2000 IU/day- 10 drops with the oral drops presentation).

During pregnancy women should follow the advice of their medical practitioner as their requirements may vary depending on the severity of their disease and their response to treatment Vitamin D3 and its metabolites are excreted in breast milk.

Breast-feeding

Vitamin D3 can be prescribed while the patient is breast-feeding if necessary. This supplementation does not replace the administration of Vitamin D3 in the neonate

Fertility

There is no data regarding treatment with vitaminD3 and its effects on fertility.

4.7 Effects on ability to drive and use machines

There are no data on the effects of InVita D3 on the ability to drive. However, an effect on this ability is unlikely.

4.8 Undesirable effects

Adverse reactions are listed below, by system organ class and frequency. Frequencies are defined as: uncommon (>1/1,000, <1/100) or rare (>1/10,000, <1/1,000).

Metabolism and nutrition disorders

Uncommon: Hypercalcaemia and hypercalciuria

Skin and subcutaneous disorders:

Rare: pruritus, rash, and urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard.

4.9 Overdose

Symptoms of overdose

Ergocalciferol (vitamin D2) and colecalciferol (vitamin D3) have a relatively low therapeutic index. The threshold for vitamin D intoxication is between 40,000 and 100,000 IU daily for 1 to 2 months in adults with normal parathyroid function. Infants and small children may react sensitively to far lower concentrations. Therefore, it is warned against intake of vitamin D without medical supervision.

Overdose leads to increased serum and urinary phosphorus levels, as well as hypercalcaemic syndrome and consequently calcium deposits in the tissues and above all in the kidneys (nephrolithiasis, nephrocalcinosis) and the vessels.

Discontinue InVita D3 when calcaemia exceeds 10.6 mg/dl (2.65 mmol/l) or if the calciuria exceeds 300 mg/24 hours in adults or 4-6 mg/kg/day in children.

Chronic overdosage may lead to vascular and organ calcification, as a result of hypercalcaemia.

The symptoms of intoxication are little characteristic and manifest as nausea, vomiting, initially also diarrhoea, later constipation, loss of appetite, weariness, headache, muscle pain, joint pain, muscle weakness, persistent sleepiness, azotaemia, polydipsia and polyuria and, in the final stage, dehydration. Typical biochemical findings include hypercalcaemia, hypercalciuria, as well as increased serum 25 hydroxy colecalciferol concentrations.

Treatment of overdose

Symptoms of chronic vitamin D overdosage may require forced diuresis as well as administration of glucocorticoids or calcitonin.

Overdosage requires measures for treating the - often persisting and under certain circumstances life- threatening - hypercalcaemia.

The first measure is to discontinue the vitamin D preparation; it takes several weeks to normalise hypercalcaemia caused by vitamin D intoxication.

Depending on the degree of hypercalcaemia, measures include a diet that is low in calcium or free of calcium, abundant liquid intake, increase of urinary excretion by means of the drug furosemide, as well as the administration of glucocorticoids and calcitonin.

If kidney function is adequate, calcium levels can be reliably lowered by infusions of isotonic sodium chloride solution (3–6 liters in 24 hours) with addition of furosemide and, in some circumstances, also 15 mg/kg body weight/hour sodium edetate accompanied by continuous calcium and ECG monitoring. In oligoanuria, in contrast, haemodialysis (calcium-free dialysate) is necessary.

No special antidote exists.

It is recommended to point out the symptoms of potential overdose to patients under chronic therapy with higher doses of vitamin D (nausea, vomiting, initially also diarrhoea, later constipation, anorexia, weariness, headache, muscle pain, joint pain, muscle weakness, persistent sleepiness, azotaemia, polydipsia and polyuria).

5 PHARMACOLOGICAL PROPERTIES

5.1

5.2 Pharmacokinetic properties

The pharmacokinetics of Vitamin D3 is well known.

Absorption

Vitamin D3 is well absorbed from the gastro-intestinal tract in the presence of bile, so the administration with the major meal of the day might therefore facilitate the absorption of Vitamin D3.

Distribution and biotransformation

It is hydroxylated in the liver to form 25-hydroxy-cholecalciferol and then undergoes further hydroxylation in the kidney to form the active metabolite 1, 25-dihydroxy- cholecalciferol (calcitriol).

Elimination

The metabolites circulate in the blood bound to a specific α – globin, Vitamin D3 and its metabolites are excreted mainly in the bile and faeces.

Characteristics in Specific Groups of Subjects or Patients

A 57% lower metabolic clearance rate is reported in subjects with renal impairment as compared with that of healthy volunteers.

Decreased absorption and increased elimination of Vitamin D3 occurs in subjects with malabsorption.

Obese subjects are less able to maintain Vitamin D3 levels with sun exposure, and are likely to require larger oral doses of Vitamin D3 to replace deficits.

5.3 Preclinical safety data

Pre-clinical studies conducted in various animal species have demonstrated that toxic effects occur in animals at doses much higher than those required for therapeutic use in humans.

In toxicity studies at repeated doses, the effects most commonly reported were increased calciuria and decreased phosphaturia and proteinuria. Hypercalcaemia has been reported in high doses. In a state of prolonged hypercalcaemia, histological alterations (calcification) were more frequently borne by the kidneys, heart, aorta, testes, thymus and intestinal mucosa.

Colecalciferol has been shown to be teratogenic at high doses in animals.

At doses equivalent to those used therapeutically, colecalciferol has no teratogenic activity.

Colecalciferol has no potential mutagenic or carcinogenic activity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

all-rac-α-tocopherol (E307)
Medium Chain Triglycerides
Glycerol
Gelatine
Allura Red AC (E129)
Opacode® White imprinting ink
Shellac (E904)
Titanium dioxide (E171)
Simethicone

6.2 Incompatibilities

Not applicable

6.3 Shelf life

24 months

6.4 Special precautions for storage

Do not store above 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container

3 capsules packed in PVDC/Aluminium foil blisters, inserted into a cardboard carton.

6.6 Special precautions for disposal

Any unused product should be disposed of in accordance with the local requirements.

7 MARKETING AUTHORISATION HOLDER

Consilient Health Limited,
5th Floor, Beaux Lane House,
Mercer Street Lower,
Dublin 2,
Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PL 24837/0074

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

21/07/2016

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21/07/2016

APPENDIX 4 LOW DOSE CHOLECALCIFEROL CAPSULES (InVita D3 800 IU)

SUMMARY OF PRODUCT CHARACTERISTICS

1. Name of the medicinal product

InVita D3 800 IU soft capsules

2. Qualitative and quantitative composition

Each capsule contains colecalciferol (vitamin D3) 800 IU (equivalent to 0.02 mg vitamin D3).

Excipients with known effect:

Each capsule contains 0.01 mg Allura Red AC (E129).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Soft capsule

Pink, oval-shaped, soft capsule. It contains a slightly yellow oily liquid. Each capsule has "0.8" printed in white ink. Capsule dimensions are 10.5mm x 7mm.

4. Clinical particulars

4.1 Therapeutic indications

Prophylaxis and treatment of vitamin D deficiency in adults and adolescents with an identified risk.

In addition to specific osteoporosis treatment of patients who are at risk of vitamin D deficiency, preferably in combination with calcium.

4.2 Posology and method of administration

Posology

Recommended dose: One capsule per day.

Higher doses can be necessary in treatment of vitamin D deficiency, where the dose should be adjusted dependent upon desirable serum levels of 25-hydroxycolecalciferol (25(OH)D), the severity of the disease and the patient´s response to treatment.

The daily dose should not exceed 4,000 IU (5 capsules per day).

Dosage in hepatic impairment

No dose adjustment is required.

Dosage in renal impairment

InVita D3 should not be used in patients with severe renal impairment (see section 4.3).

Paediatric population

InVita D3 is not recommended in children under 12 years of age

Method of administration

The capsules should be swallowed whole with water.

4.3 Contraindications

- Diseases and/or conditions resulting in hypercalcaemia or hypercalciuria.
- Nephrolithiasis.
- Nephrocalcinosis
- Hypervitaminosis D.

• Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

InVita D3 should be prescribed with caution to patients suffering from sarcoidosis due to risk of increased metabolism of vitamin D into its active form. These patients should be monitored with regard to the calcium content in serum and urine.

During long-term treatment, serum calcium levels should be followed and renal function should be monitored through measurements of serum creatinine. Monitoring is especially important in elderly patients on concomitant treatment with cardiac glycosides or diuretics (see section 4.5) and in patients with a high tendency to calculus formation. In case of hypercalciuria (exceeding 300 mg (7.5 mmol)/24 hours) or signs of impaired renal function the dose should be reduced or the treatment discontinued.

InVita D3 should be used with caution in patients with impairment of renal function and the effect on calcium and phosphate levels should be monitored. The risk of soft tissue calcification should be taken into account. In patients with severe renal insufficiency, vitamin D in the form of cholecalciferol is not metabolised normally and other forms of vitamin D should be used.

The content of vitamin D (800 IU) in InVita D3 should be considered when prescribing other medicinal products containing vitamin D. Additional doses of vitamin D should be taken under close medical supervision. In such cases it is necessary to monitor serum calcium levels and urinary calcium excretion frequently.

4.5 Interaction with other medicinal products and other forms of interaction

Thiazide diuretics reduce the urinary excretion of calcium. Due to the increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics.

Concomitant use of phenytoin or barbiturates may reduce the effect of vitamin D since the metabolism increases.

Excessive dosing of vitamin D can induce hypercalcaemia, which may increase the risk of digitalis toxicity and serious arrhythimias due to the additive inotropic effects. The electrocardiogram (ECG) and serum calcium levels of patients should be closely monitored.

Glucocorticoid steroids may increase vitamin D metabolism and elimination. During concomitant use, it may be necessary to increase the dose of InVita D3 tablets.

Simultaneous treatment with ion exchange resins such as cholestyramine or laxatives such as paraffin oil may reduce the gastrointestinal absorption of vitamin D. Orlistat may potentially impair the absorption of colecalciferol as it is fat-soluble.

The cytotoxic agent actinomycin and imidazole antifungal agents interfere with vitamin D activity by inhibiting the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D by the kidney enzyme, 25-hydroxyvitamin D-1-hydroxylase.

4.6 Fertility, pregnancy and lactation

Pregnancy

Vitamin D deficiency is harmful for mother and child. There are no signals that recommended doses of vitamin D3 are harmful for the embryo/fetus. High doses of vitamin D have been shown to have teratogenic effects in animal experiments. Overdose of vitamin D must be avoided during pregnancy, as prolonged hypercalcaemia can lead to physical and mental retardation, supravalvular aortic stenosis and retinopathy of the child.

InVita D3 can be used up to 2,000 IU/day only in case of a Vitamin D deficiency.

InVita D3 is not recommended during pregnancy in patients without a vitamin D deficiency as the daily intake should not exceed 600 IU vitamin D.

Breast-feeding

Vitamin D3 and metabolites pass into the breast-milk. No adverse events have been observed in infants. InVita D3 can be used at recommended doses during lactation in case of a vitamin D deficiency.

Fertility

Normal endogenous levels of vitamin D are not expected to have any adverse effects on fertility.

4.7 Effects on ability to drive and use machines

There are no data about the effect of this product on driving capacity. An effect is, however, unlikely.

4.8 Undesirable effects

Adverse reactions frequencies are defined as: uncommon ≥ 1/1,000, < 1/100), rare ≥1/10,000, <1/1,000) or not known (cannot be estimated from the available data

Immune system disorders

Not known (cannot be estimated from the available data): Hypersensitivity reactions such as angio-oedema or laryngeal oedema.

Metabolism and nutrition disorders

Uncommon: Hypercalcaemia and hypercalciuria.

Skin and subcutaneous disorders

Rare: Pruritus, rash and urticaria.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

Overdose can lead to hyper-vitaminosis D. An excess of vitamin D causes abnormally high levels of calcium in the blood, which can eventually severely damage the soft tissues, and kidneys. Tolerable Upper Intake Level for vitamin D3 (colecalciferol) is set at 4000 IU (100 µg) per day. Vitamin D3 should not be confused with its active metabolites. colecalciferol

Symptoms of hypercalcaemia may include anorexia, thirst, nausea, vomiting, constipation, abdominal pain, muscle weakness, fatigue, mental disturbances, polydipsia, polyuria, bone pain, nephrocalcinosis, renal calculi and in severe cases, cardiac arrhythmias. Extreme hypercalcaemia may result in coma and death.

Persistently high calcium levels may lead to irreversible renal damage and soft tissue calcification.

Treatment of hypercalcaemia: The treatment with vitamin D must be discontinued. Treatment with thiazide diuretics, lithium, vitamin A, and cardiac glycosides must also be discontinued. Rehydration, and, according to severity, isolated or combined treatment with loop diuretics, bisphosphonates, calcitonin and corticosteroids should be considered. Serum electrolytes, renal function and diuresis must be monitored. In severe cases, ECG and CVP should be followed.

5. Pharmacological properties

5.1 CCI [redacted]

5.2 Pharmacokinetic properties

Vitamin D

Sun exposure: UVB light converts 7-dehydrocholesterol, found in the skin, to colecalciferol.

Absorption: Vitamin D is easily absorbed in the small intestine. Food intake potentially increases the absorption of vitamin D.

Distribution and biotransformation: Colecalciferol and its metabolites circulate in the blood bound to a specific globulin. Colecalciferol is converted in the liver by hydroxylation to 25-hydroxycholecalciferol. It is then further converted in the kidneys to 1,25-dihydroxycholecalciferol. 1,25-dihydroxycholecalciferol is the active metabolite responsible for increasing calcium absorption. Vitamin D, which is not metabolised, is stored in adipose and muscle tissues.

After a single oral dose of colecalciferol, the maximum serum concentrations of the primary storage form are reached after approximately 7 days. $25(OH)D_3$ is then slowly eliminated with an apparent half-life in serum of about 50 days. Colecalciferol and its metabolites are excreted mainly in the bile and faeces.

Elimination: Vitamin D is excreted mainly in bile and faeces with a small percentage found in urine.

5.3 Preclinical safety data

At doses far higher than the human therapeutic range teratogenicity has been observed in animal studies. No other relevant data is available that has not been mentioned elsewhere in the SmPC (see section 4.6 and 4.9).

6. Pharmaceutical particulars

6.1 List of excipients

Capsule fill

all-rac-α-tocopherol (E307)

Medium Chain Triglycerides

Capsule shell

Glycerol

Gelatine

Medium Chain Triglycerides

Allura Red AC (E129)

Printing ink

Shellac (E904)

Titanium dioxide (E171)
Simethicone

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Do not store above 30°C.
Keep the blister(s) in the outer carton to protect from light.

6.5 Nature and contents of container

28 or 90 capsules packed in PVDC/Aluminium foil blisters, inserted into a cardboard carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Consilient Health Limited,
5th Floor, Beaux Lane House,
Mercer Street Lower,
Dublin 2,
Ireland

8. Marketing authorisation number(s)

PL 24837/0070

9. Date of first authorisation/renewal of the authorisation

18/03/2016

10. Date of revision of the text

23rd December 2016

APPENDIX 5 INVESTIGATOR'S SIGNATURE

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
Study Number:	CTAP101-CL-4001
Final Date:	16 August 2019

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/IEC/REB, 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 drug, as described in this protocol, and any other information provided by the sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document provided by 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 drug 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-4001 Protocol v11.0

Approval	PPD Medical 19-Aug-2019 16:50:36 GMT+0000

Approval	PPD 19-Aug-2019 17:45:42 GMT+0000

Signature Page for RIM-CLIN-000570 v11.0