PROTOCOL CTAP101-CL-2014

Study Title:	A Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Safety and Efficacy of Rayaldee (calcifediol) Extended-release Capsules to Treat Symptomatic Patients Infected with SARS-CoV-2 (REsCue)
Study Number:	CTAP101-CL-2014 (Ver. 8.0, 12 November 2021)
Short Title:	Safety and Efficacy of Rayaldee for Treating Mild to Moderate COVID-19
Study Phase:	2
Product Name:	Rayaldee® (calcifediol) Extended-release Capsules (30 mcg)
Investigator:	[redacted]

Sponsor:
OPKO Pharmaceuticals, LLC
4400 Biscayne Boulevard
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This study will be conducted in compliance with the protocol, US Code of Federal Regulations (CFR) applicable to clinical studies, principles of International Council on Harmonization (ICH) Good Clinical Practice (GCP), the Declaration of Helsinki, and all applicable regulatory requirements.

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SYNOPSIS

Sponsor:

OPKO Pharmaceuticals, LLC

Name of Finished Product:

Rayaldee® (calcifediol) Extended-release Capsules

[Extended-release calcifediol, coded as CTAP101 Capsules]

Name of Active Ingredient:

Calcifediol, calcidiol, 25-hydroxyvitamin D_3

Test Products, Dose, and Mode of Administration:

Rayaldee (900 mcg) or matching placebo in a 900 mcg loading dose split into three equal doses of 300 mcg each administered over three days (on Days 1, 2 and 3) followed by a maintenance dose of 60 mcg/day or matching placebo for 24 days by the oral route (Days 4-27).

Study Title:

A Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Safety and Efficacy of **R**ayaldee (calcifediol) **E**xtended-releas**e** **C**aps**u**l**e**s to Treat Symptomatic Patients Infected with SARS-CoV-2 (**REsCue**)

Study Phase: 2

Rationale:

Insufficient vitamin D (vitD) has been linked to a large number of pathologies including immune disorders and infectious diseases. VitD functions as a key host defense regulator against viral pathogens. High levels of vitD in the blood have been associated with resistance to human immunodeficiency virus type 1 (HIV1) infection. Moreover, low levels of vitD have been associated with higher levels of immune activation and inflammation in HIV and other diseases. While the results of clinical trials studying vitD supplementation have differed, there are several well-designed, large meta-analyses that have supported vitD supplementation as safe and protective against acute respiratory tract infections, with those that were severely vitD deficient receiving the most benefit.

The innate immune response in antigen-presenting cells (monocyte/macrophages and dendritic cells) is initiated and perpetuated by pathogen-associated molecular patterns (PAMPs) of the infecting virus interacting with pattern recognition receptors (eg, Toll-like receptors [TLR]). TLR activation leads to up-regulation of expression of the intracellular vitD receptor (VDR) and CYP27B1 (25-hydroxyvitamin D [25D]-1α-hydroxylase); the latter event up-regulates local generation of the active vitD metabolite, 1,25-dihydroxyvitamin D (1,25D). 1,25D can then engage the VDR in an intracrine mode, which, in turn, controls cathelicidin antimicrobial peptide (*CAMP*) and interleukin 1ß (IL-1ß) gene expression, IL-1ß being a central initiator of the adaptive immune response.

LL37 is a potent, central, endogenously synthesized antimicrobial protein in humans, the product of the *CAMP* gene. Early in infection, LL37 is made principally by innate immune cells, monocyte/macrophages and dendritic cells, initiators of the immune response to both bacterial and viral infections. Owing to serendipity, a retrotransposon bearing a perfect vitD

response element (VDRE: AGGTCAXXXAGGTCA) was inserted into the promoter of the cathelicidin gene in great apes and humans. This ancient event made LL37 production dependent on transactivation of *CAMP* by the 1,25D-activated VDR.

Extensive recent work shows that an insufficient supply of 25D to activated VDR- and CYP27B1-expressing human monocytes/macrophages is associated with a decrease in *CAMP* expression. An insufficient level of 25D in human serum causes inadequate i) intracellular generation of 1,25D, ii) activation of the VDR, iii) transactivation of the *CAMP* gene and iv) production and release of LL37 to combat microbial invasion of the host. The end result is innate and subsequent adaptive immune deficiency.

Raising serum total 25D to sufficiently high levels can resolve the immune-compromised state in the human host. Accomplishing this with vitD supplements is unreliable and is difficult in obesity owing to the increased volume of distribution of the non-polar vitamin. In contrast, treatment with the more polar and extended-release calcifediol (Rayaldee or CTAP101 Capsules) is reliable and, depending on the administered dose, can take as little as 9-12 hours. Treatment with CTAP101 Capsules has been shown to be safe for administration to patients with stage 3 or 4 chronic kidney disease (CKD), as evidenced by United States (US) Food and Drug Administration (FDA) approval of the product in 2016 as Rayaldee® (calcifediol) Extended-release Capsules.

Accumulating data suggest that hyperactive immune response to COVID-19 poses unique risks to the cardiovascular system and plays a role in disease severity. As the disease progresses, a concomitant rise in inflammatory cytokine levels may drive the depletion and exhaustion of T cell populations. On the other hand, vitD is an immune-modulating agent and has been implicated in the pathophysiology of autoimmune diseases, including systemic lupus erythematosus and multiple sclerosis. Vitamin D insufficiency (VDI) is a risk factor for multiple sclerosis and correlates with the disease severity. Thus, [redacted] appropriate treatment with Rayaldee may help to mitigate an overactive, adaptive T- and B-lymphocyte immune system and ameliorate immune cell exhaustion.

We propose a double-blind randomized, placebo-controlled trial of extended-release calcifediol (commercially available as Rayaldee and coded herein as CTAP101 Capsules) in 160 patients presenting with unresolved symptoms of mild to moderate COVID-19 who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) via nasopharynx swab reverse transcription polymerase chain reaction (RT-PCR) or any substitutable FDA-authorized diagnostic test. The hypothesis is that the severity and duration of the disease will be attenuated with increase of serum 25D to levels of ≥50 ng/mL.

Primary Objectives:

The primary objectives of this study are to compare the effects of Rayaldee (CTAP101 Capsules) vs. placebo treatment in patients with mild to moderate COVID-19 on the:

1) Attainment of serum total 25D levels at or above 50 ng/mL by Day 14; and,
2) Severity and duration of disease as evidenced by five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) using the FLU-PRO Plus© questionnaire as the data collection tool.

Estimand:

The study treatment estimand is the difference between 28 days of Rayaldee and placebo treatment in adult patients with confirmed SARS-CoV-2 infection who have unresolved symptoms of mild to moderate COVID-19 in (a) the attainment of serum total 25D levels ≥50 ng/mL as assessed at Day 14, and (b) the number of days to resolution of five symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), as measured by the FLU-PRO Plus© questionnaire with resolution defined as the first aggregate FLU-PRO Plus© symptom score of ≤5 which is maintained for a minimum of three consecutive days.

Secondary Objectives:

The secondary objectives are to compare the effects of Rayaldee (CTAP101 Capsules) vs. placebo treatment on:

1) The number of days to resolution of five symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), as measured by the FLU-PRO Plus© questionnaire, with resolution defined as the first aggregate symptom score of ≤5 which is maintained for a minimum of three consecutive days, with no individual symptom score >1;
2) Resolution, defined as the first score of ≤5 which is maintained for a minimum of three consecutive days (without subsequent relapse), for the aggregate five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) and for each individual symptom, defined as a score of 0 or 1, as measured by the FLU-PRO Plus© questionnaire as of Day 10;
3) Incidence of emergency room/urgent care visits;
4) Incidence of oxygen saturation below 94% (without supplemental oxygen);
5) Incidence and duration of hospitalizations;
6) Incidence of requirement for mechanical ventilation;
7) Mortality rate (as incidence);
8) Severity and duration of COVID-19 illness as evidenced by quality-of-life measures using the FLU-PRO Plus© questionnaire; and,
9) Clinical course of COVID-19 as a function of serum 25D concentrations of <50 ng/mL, 50 to 100 ng/mL and >100 ng/mL at Days 7, 14, 21 and 28, defined as the proportion of subjects in each treatment group with a total score of ≤5 for selected five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) using the FLU-PRO Plus© questionnaire.

[redacted]

[redacted]

Number of Subjects:

Approximately 80 subjects will be randomized to each of the Rayaldee (CTAP101 Capsules) and placebo treatment groups, for a total of 160 subjects.

Safety Evaluations:

The safety and tolerability of Rayaldee (CTAP101 Capsules) will be evaluated by adverse events (AEs), physical examinations (PE), vital signs (VS), electrocardiograms (ECGs), hematology and clinical chemistries. Special attention will be given to changes in the following parameters:

1) Serum total calcium (corrected for serum albumin);
2) Serum phosphorus; and,
3) Estimated glomerular filtration rate (eGFR).

Dose Reduction and Stopping Rules:

Although hypercalcemia is unlikely given the extensive prior experience with Rayaldee (CTAP101 Capsules), any subject who exhibits a confirmed serum total calcium >10.5 and ≤11.0 mg/dL (corrected for serum albumin) based on blood samples obtained on Days 7 and 14 will reduce the daily maintenance dose by one capsule (from 60 mcg to 30 mcg) starting at Day 21. The dose will similarly be reduced based on blood samples obtained on Days 7 and 14 if serum total 25D is confirmed to exceed 100 ng/mL, the maximum targeted level in the FDA-approved Package Insert for Rayaldee (see APPENDIX 2.), starting at Day 21.

Subjects who exhibit confirmed serum total calcium >11.0 mg/dL (corrected for serum albumin) based on blood samples obtained on Days 7, 14 and 21 will suspend dosing until normalization of serum calcium at which time (if applicable) dosing will be resumed at one capsule per day (30 mcg per day). Subjects will be requested to return to the clinic on the earliest possible day of their next scheduled visit (eg, Day 12 for the Day 14 visit) for the confirmatory blood draw.

Subjects who develop severe (CTCAE ≥ 3) abnormalities (low or high) of serum phosphorus, uric acid or plasma iPTH will be withdrawn from study drug treatment.

Enrollment of subjects into the study will be paused if mortality in the treatment arm is ≥ 7% higher compared to the placebo arm until the Data Safety Monitoring Board (DSMB) makes an assessment about causality, and may resume once the DSMB deems it acceptable to continue (if applicable).

Other Evaluations:

Blood samples will be acquired periodically during the study (see APPENDIX 1: Schedule of Events). Blood samples will be assayed for: i) serum total 25D (primary efficacy measure), [redacted] iv) plasma iPTH, v) clinical chemistries and hematology, [redacted] Daily assessments of disease severity and quality-of-life measures will be recorded by each subject using the FLU-PRO Plus© questionnaire.

Sample Size Estimation:

Primary outcome #1 (attainment of serum 25D levels at ≥50 ng/mL): Assuming that no more than 25% of the control group will achieve an increase in serum 25D to ≥50 ng/mL by Day 28 versus greater than 75% in the CTAP101 Capsules group, a sample size of 19 per group will provide 90% power at alpha 0.025 one sided for a Chi-square test of the two groups.

Primary outcome #2 (severity of illness by five symptoms): A sample size of 80 per group (total of 160) is planned. This will provide greater than 80% power at one sided alpha of 0.025 based on a log rank test assuming 50% of subjects in the control group and 70% of the CTAP101 Capsules group will have achieved resolution of symptoms by Day 28. This is based on an expected hazard ratio (of achieving resolution) of 1.74.

Data Safety Monitoring Board (DSMB):

A five-member DSMB will be established which will be comprised of an expert in viral disease pathogenesis, a nephrologist who routinely treats patients with vitD repletion therapies, a statistician and a pulmonary medicine expert. The DSMB will also include an unblinded safety monitor to identify potential safety hazards (eg, hypercalcemia) in order to maintain blinding of treatment assignment and ensure study integrity. The DSMB will meet by teleconference every 3-4 weeks or at the Committee's discretion. Meetings may occur more often should serious adverse events (SAEs) or other safety issues arise. Specific responsibilities and activities of the DSMB will be defined in the DSMB charter.

Statistical Analyses:

The two primary endpoints will be tested hierarchically to maintain an overall one-sided alpha level of 0.025. Therefore, the test of resolution of symptoms based on the aggregate FLU-PRO Plus© symptom score will be performed only if the attainment of serum 25D levels ≥50 ng/mL at Day 14 is significant at <0.025.

The first primary efficacy endpoint, attainment of serum 25D levels at ≥50 ng/mL will be assessed with a Chi-square statistic at Day 14. The serum 25D levels will also be compared between treatment groups at Days 7, 21 and 28 with a Chi-square statistic.

The second primary efficacy endpoint is the number of days to resolution of symptoms, defined as a reduction in the aggregate FLU-PRO-Plus© scores for the selected five COVID-19

symptoms at study drug initiation (Day 1) to or below 5 for a minimum of three consecutive days. The time to resolution is defined as the number of days from Day 1 to the first day of achieving the aggregate ≤5 score for a minimum of three consecutive days, provided that no score greater than 5 is recorded between the two qualifying scores. Resolution will be determined by the first two successive qualifying scores which span a minimum of three consecutive days. For clarity, resolution will be considered as having been achieved if two successive aggregate scores of ≤5 are recorded on the first day of this occurrence and on a subsequent day that is at least two days (but not more than 5 days) later even if no score has been recorded between the two days. Missing symptom score values will be handled as described in Section 9.2. The number of days to resolution will be analyzed with a Cox proportional hazards model with covariates (baseline aggregate FLU-PRO Plus© score for the five COVID-19 symptoms, baseline serum 25D, and body weight).

As a sensitivity analysis of the resolution of symptoms, a tipping point approach will be used starting with the analysis in which scores are available for three consecutive days, with no missing interval, followed by increasing numbers of missing days in the up to five-day interval, that is, 1, 2 and 3 missing days between the two consecutive qualifying scores.

Subgroup analyses for the primary efficacy endpoints will be based on age (≤40 or >40 years), severity of the selected five COVID-19 symptoms at baseline (aggregate FLU-PRO Plus© score of ≤ or > the median score), attained serum 25D at Day 14 (below, within or above the targeted range of 50 to 100 ng/mL), body weight (≤100 or >100 kg), body mass index (BMI; ≤30 or >30), dosing compliance (<80% or ≥80%), gender, race, ethnicity, comorbidities (<1 or ≥1), duration of treatment (≤10 or >10 days) and prior or intercurrent COVID-19 vaccination and/or monoclonal antibody therapy for COVID-19.

In addition, the number of days to resolution of the five aggregated symptoms will be compared based on the serum 25D level at Day 14 (<50 ng/mL vs 50 to 100 ng/mL and 50 to 100 ng/mL vs >100 ng/mL), regardless of the assigned treatment group. The comparison will be done using a Chi-square test. Frequency of relapses will be calculated, if possible, to account for potential worsening of symptoms after resolution (defined immediately above), with relapse being defined as achieving an aggregate FLU-PRO Plus© score >5 for a minimum of three consecutive days.

The following secondary endpoints will be tested statistically with methods described below, and the nominal p-value will be reported for evaluation:

1. The number of days to resolution of five symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), as measured by the FLU-PRO Plus© questionnaire, with resolution defined as the first aggregate symptom score of ≤5 which is maintained for a minimum of three consecutive days (see Section 5.2), with no individual symptom score >1;
2. Resolution, defined as the first score of ≤5 which is maintained for a minimum of three consecutive days (without subsequent relapse), for the aggregate five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) and for each individual symptom, defined as a score of 0 or 1, as measured by the FLU-PRO Plus© questionnaire as of Day 10;
3. Incidence of emergency room/urgent care visits;

4. Incidence of oxygen saturation below 94% (without supplemental oxygen);
5. Incidence of hospitalizations (mean duration of hospitalization will also be presented);
6. Incidence of requirement for mechanical ventilation; and,
7. Mortality rate (as incidence).

Endpoints listed will be summarized. For the analysis of individual symptoms in endpoint #2 above, the threshold of ≤1 is appropriate because it describes minor symptom severity (at worst "a little bit") which seems unlikely to presage a poor outcome. Analysis of the resolution of individual symptoms will be performed using a logistic regression, with baseline symptom score, baseline 25D level, and body weight as covariates. Analysis of the secondary endpoints based on incidence will be performed with a Chi-square test. Mean duration will be analyzed with analysis of covariance (ANCOVA). Mortality will be analyzed as incidence, with logistic regression with baseline symptom score, baseline 25D level and body weight as covariates. Rates only will be reported if there are too few deaths to be formally analyzed.

The severity, duration and clinical course of COVID-19 illness will be compared between treatment groups by analyzing changes in quality-of-life assessments recorded on the FLU-PRO Plus© questionnaire. Five of the six items from the questionnaire to be analyzed are: “Overall, how severe were your infection symptoms today?”, “Overall, how were your infection symptoms today compared to yesterday?”, “How much did your infection symptoms interfere with your usual activities today?”, “Have you returned to your usual activities today?”, “In general, how would you rate your physical health today?”, and “Have you returned to your usual health today?” The scores for: symptom severity range from 0 (no infection symptoms today) to 4 (very severe); symptoms today range from 1 (much better) to 7 (much worse); symptom interference range from 1 (not at all) to 5 (very much). The first of two consecutive scores of ≤1 spanning at least three days and no more than five days will be considered the day of resolution, provided that no intervening scores of >1 are recorded. The scores for return to usual activities or health are either “yes” or “no”, and the first occurrence of “yes” will be deemed to be day of resolution provided that a second “yes” is recorded no more than 5 days later without an intervening “no”. The remaining sixth item to be analyzed is: “physical health range from 1 (poor) to 5 (excellent). The first of two consecutive scores of >4 spanning at least three days and no more than five days will be considered the day of resolution, provided that no intervening scores of <4 are recorded. Each item will be compared between treatment groups using a Cox proportional hazards model with covariates (aggregate FLU-PRO Plus© score for the selected five COVID-19 symptoms at baseline, serum total 25D at baseline, and body weight).

The clinical course of COVID-19 will be examined by subgroups defined by serum total 25D levels <50 ng/mL, 50 to 100 ng/mL and >100 ng/mL at Days 7, 14, 21 and 28.

Inclusion Criteria

Each subject must meet the following criteria to be enrolled and randomized into one of the two treatment groups of this study:

1) Male or female ≥18 years of age;

2) Confirmed within the past 3 days to have SARS-CoV-2 infection as evidenced by a positive nasopharyngeal swab test using RT-PCR or any substitutable FDA-authorized diagnostic test;
3) Confirmed to have only mild or moderate COVID-19 based on the first of the patient reported scores obtained during screening which meets the criterion of a FLU-PRO Plus© score of ≥ 1.5 for each of the chest/respiratory and body/systemic domains, and the absence of clinical signs indicative of more severe disease (eg, oxygen saturation < 94% on room air or respiration rate > 30 bpm);
4) Represents on self-assessment that the current COVID-19 symptoms are not consistent with usual health and that they are the same or worse than on the previous day;
5) Willing to limit the use of vitD therapies or supplements except for normally fortified food products (eg, milk) during the course of the 6-week study;
6) Must demonstrate the ability to comply with all study requirements; and,
7) Must be without any disease state or physical condition that might impair evaluation of safety or which, in the investigator's opinion, would interfere with study participation.

Exclusion Criteria:

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

1) Clinical signs indicative of severe or critical COVID-19 disease (eg, oxygen saturation < 94% on room air or respiration rate > 30 bpm);
2) Pregnant or lactating women who are breastfeeding;
3) Use of systemic glucocorticoid medications in the last six months;
4) Recent history (previous 12 months) of primary hyperparathyroidism, kidney stones, hypercalciuria and/or hypercalcemia;
5) History of a chronic granuloma-forming disease (eg, sarcoidosis);
6) History of tuberculosis or histoplasmosis;
7) History of chronic liver disease;
8) History (previous 12 months) of cardiac event indicative of chronic cardiovascular diseases including congestive heart failure, poorly controlled hypertension and arrhythmias;
9) History in the past five years of multiple myeloma or carcinoma of the breast, lung or prostate;
10) Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of vitD or 25D (eg, small bowel resection, history of Crohn's disease or ulcerative colitis);
11) Ongoing treatment with thiazide diuretics;
12) History of hyperphosphatemia, hyperuricemia and gout;
13) Renal impairment measured as eGFR< 15 mL/min/1.73m² on serum creatinine in the last three months;
14) Serum calcium ≥9.8 mg/dL in the last three months;
15) Evidence of existing or impending dehydration;

16) Known or suspected to have hypersensitivity to any of the constituents of the study drug; and/or,
17) Currently participating in, or have participated in, an interventional/investigational study within 30 days prior to study screening.

TEST PRODUCT, DOSE, AND ROUTE OF ADMINISTRATION

Rayaldee (CTAP101 Capsules) in a 900 mcg loading dose split into three equal doses of 300 mcg each administered over three days (on Days 1, 2 and 3) followed by a maintenance dose of 60 mcg per day for the subsequent 24 days (Days 4-27). Doses will be administered orally at bedtime after fasting for at least 3 hours following dinner. Patients should remain fasted for at least 3 hours after administration of study drug.

CONTROL PRODUCT, DOSE AND ROUTE OF ADMINISTRATION

Placebo in a look-alike 900 mcg loading dose split into three equal doses of 300 mcg each administered over three days (on Days 1, 2, and 3) followed by a look-alike maintenance dose of 60 mcg per day for the subsequent 24 days (Days 4-27). Doses will be administered orally at bedtime after fasting for at least 3 hours following dinner. Patients should remain fasted for at least 3 hours after administration of study drug.

Duration of study

Forty-five days

Concomitant Medications

Allowed, with the exception of:

1) Calcitriol, paricalcitol and doxercalciferol;
2) Thiazide diuretics;
3) Medications that could impair the absorption of fat-soluble nutrients; and,
4) Dietary supplements providing in excess of 0.55 g of elemental calcium per day.

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1,25D	1,25-dihydroxyvitamin D
$1,25D_3$	1,25-dihydroxyvitamin D_3, calcitriol
25D	25-hydroxyvitamin D
$25D_3$	25-hydroxyvitamin D_3, calcifediol, calcidiol
$24,25D_3$	24,25-dihydroxyvitamin D_3
AE	adverse event
ALT	alanine transferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the (concentration) curve
BA	bioavailability
b-hCG	beta-human chorionic gonadotropin
BMI	body mass index
bpm	breaths per minute
CAMP	cathelicidin antimicrobial peptide
CFR	Code of Federal Regulations
CKD	chronic kidney disease
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
eGFR	estimated glomerular filtration rate
ER	extended-release
ET	early termination
FAS	full analysis set (or population)
FDA	Food and Drug Administration
FU	follow-up
GCP	Good Clinical Practice
GFR	glomerular filtration rate
HDPE	high-density polyethylene
HIV(1)	human immunodeficiency virus (type 1)

IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
iCLIP	individual-nucleotide resolution cross-linking and immunoprecipitation
IL-1β	interleukin 1β
IL-6	interleukin 6
iPTH	intact parathyroid hormone
IRB/EC	Institutional Review Board/Ethics Committee
IRT	interactive response technology
ISF	investigator site file
ITT	Intent-to-Treat
LAR	legally authorized representative
MedDRA	Medical Dictionary for Regulatory Activities
PAMPs	pathogen-associated molecular patterns
PBMCs	peripheral blood mononuclear cells
PE	physical examinations
PK	pharmacokinetic(s)
PP	per-protocol
PTH	parathyroid hormone
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SHPT	secondary hyperparathyroidism
SOC	system organ class
SOP	standard operating procedure
TEAE	treatment-emergent adverse events
TLR	Toll-like receptors
t_{max}	time to maximum concentration
US	United States
VDI	vitamin D insufficiency
VDR	vitamin D receptor
VDRE	vitamin D response element
VitD	vitamin D
VS	vital signs

1 INTRODUCTION

1.1 Vitamin D Insufficiency

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

It is widely accepted that serum total 25D is the best indicator of a patient's vitD status. Serum total 25D levels of ≥30 ng/mL are currently considered adequate while levels of <30 ng/mL are considered "insufficient" [Holick et al 2011]. The commonly used reference range for serum total 25D is 30 to 100 ng/mL [Souberbielle et al 2010]. Levels of serum total 25D 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. VitD deficiency (<20 ng/mL) in the US is most common in pigmented (decreased vitD production in skin) and obese (increased volume of distribution of vitD due to adiposity) subjects, the same population that appears to be most susceptible to infection with SARS-CoV-2.

Serum 25D levels above of 40-60 ng/mL have recently been recommended to reduce the risk of infection with severe acute respiratory syndrome 2 (SARS-CoV-2) and higher levels are thought to be useful for patients who become infected [Grant et al, 2020]. Serum levels of ≥50 ng/mL have recently been shown to be required for 25D to modulate vitD-responsive endpoints in patients with chronic kidney disease (CKD), probably via activation by innate immune cells, extra-renal CYP27B1 [Strugnell et al, 2019]. It appears likely that similar high levels are required for 25D to be activated *in vivo* by CYP27B1 expressed in virus-stimulated macrophages.

1.2 Vitamin D and Viral Infections

Insufficient vitD has been linked to a large number of pathologies including immune disorders and infectious diseases. VitD functions as a key host defense regulator against viral pathogens. High levels of vitD has been associated with resistance to human immunodeficiency virus type 1 (HIV1) infection [Jimenez-Souza et al 2018]. Moreover, low levels of vitD have been associated with higher levels of immune activation and inflammation in HIV and other diseases [Jimenez-Souza et al 2018]. While the results of clinical trials studying vitD supplementation to reduce acute respiratory tract infections have differed, there are several well designed large meta-analyses that have supported vitD supplementation as being safe and protective against acute respiratory tract infections with individuals that were severely vitD deficient receiving the most benefit [Martineau et al 2017; Bergman et al 2013].

1.3 Vitamin D and Cathelicidin Gene

Despite extensive efforts to identify novel antimicrobials to address the treatment of patients with SARS-CoV-2 infection, little attention has been paid to endogenous human antimicrobial peptides, such as LL37, that can boost the host's immune response to the virus. Arguably the most effective, endogenous antimicrobial agent known to man, LL37 is the product of the endogenous human cathelicidin antimicrobial peptide (*CAMP*) gene and is secreted from monocyte/macrophages, dendritic cells and neutrophils in response to viral or bacterial infection [Nizet et al 2001]. Expression and secretion of LL37, along with numerous other endogenous antimicrobial activities, requires induction and priming. A key regulatory signal that can prime human macrophages for rapid and robust antimicrobial responses, including deployment of LL37 at the site of infection, is vitD, specifically calcifediol or 25D [Gombart et al 2009]. Like a loaded weapon with the safety left on, macrophages without sufficient serum total 25D as substrate are rendered unable to release LL37, and thus protect the host.

The innate immune response in antigen-presenting cells (monocyte/macrophages and dendritic cells) is initiated and perpetuated by pathogen-associated molecular patterns (PAMPs) derived from the cell wall and other unique signatures of the infecting virus interacting with pattern recognition receptors (eg, Toll-like receptors [TLR]). TLR activation eventually leads to up-regulation of expression of the intracellular vitD receptor (VDR) and CYP27B1 (25D-1α-hydroxylase); the latter event up-regulates generation the active vitD metabolite, 1,25-dihydroxyvitamin D (1,25D). That 1,25D can then engage the VDR in an intracrine mode and controls *CAMP* and interleukin 1ß (IL-1ß) gene expression; IL-1ß is a central initiator of the adaptive immune response.

Using upregulated expression of the potent endogenous antimicrobial *CAMP* mRNA by primary cultures of human monocyte/macrophages as an *ex vivo* read-out, extensive recent work [Rosen et al 2012; Liu et al 2006; Adams et al 2007; Krutzik et al 2008; Liu et al 2009; Edfeldt et al 2010; Fabri et al 2011; Montoya et al 2014; Chun et al 2014; Srikanth et al 2016] shows that insufficient serum levels of 25D (VDI) in the host induces an immune-compromised state. An insufficient level of 25D in human serum causes inadequate i) intracellular generation of 1,25D, ii) activation of the VDR, iii) transactivation of the *CAMP* gene and iv) production and release of LL37 to combat microbial invasion of the host. The end result is innate and subsequent adaptive immune deficiency.

Raising serum total 25D to sufficiently high levels can resolve the immune-compromised state in the human host. Accomplishing this with vitD supplements is unreliable and is difficult in obesity owing to the increased volume of distribution of the non-polar vitamin. In contrast, treatment with the more polar and extended-release calcifediol (Rayaldee or CTAP101 Capsules) is reliable and, depending on the administered dose, can take as little as 9-12 hours. Treatment with CTAP101 Capsules has been shown to be safe for administration to patients with stage 3 or 4 CKD, as evidenced by United States (US) Food and Drug Administration (FDA) approval of the product in 2016 as Rayaldee® (calcifediol) Extended-release Capsules.

Accumulating data suggest that hyperactive immune response to COVID-19 poses unique risks to the cardiovascular system and plays a role in disease severity. As the disease progresses, a concomitant rise in inflammatory cytokine levels may drive the depletion and exhaustion of T cell populations [Diao et al 2020]. On the other hand, vitD is an immune-modulating agent and has been implicated in the pathophysiology of autoimmune diseases, including systemic lupus

erythematosus and multiple sclerosis. VDI is a risk factor for multiple sclerosis and correlates with the disease severity. Thus, [redacted] appropriate treatment with Rayaldee may help to mitigate an overactive, adaptive T- and B-lymphocyte immune system response to the virus and ameliorate immune cell exhaustion [Adams et al 2007; Rosen et al 2012].

1.4 Preclinical Experience

Toxicity associated with calcifediol is consistent with that observed due to vitD overdose and is similar to that seen with 1,25D or calcitriol. Generally, such toxicity is subsequent to hypercalcemia. To study the toxicity of CTAP101 Capsules, an earlier formulation of CTAP101 Capsules was administered to dogs for 3 months and resulted in typical vitD-induced hypercalcemia, hypercalciuria, soft tissue mineralization (eg, kidney, stomach, aorta and heart) and death. Severe adverse reactions to CTAP101 Capsules were observed in dogs treated with 500 or 1,000 mcg per day and were associated with serum 25D or 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 mcg (~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.

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

1.5 Previous Clinical Experience

Rayaldee (CTAP101 Capsules) (30 mcg/capsule) have been approved by the US FDA for the treatment of secondary hyperparathyroidism (SHPT) in adults with stage 3 or 4 CKD and VDI, defined as serum total 25D 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 CTP101 Capsules (CTAP101-CL-1005, CTAP101-CL-1011 and CTAP101-CL-1016), two phase 2 studies, of which one was a single-dose study (CTAP101-CL-2004) and one was a repeat-dose study (CTAP101-CL-2008), and three phase 3 studies (CTAP101-CL-3001, CTAP101-CL-3002 and CTAP101-CL-3003). Studies CTAP101-CL-1011, CTAP101-CL-1016 and CTAP101-CL-2008 were conducted with the current formulation of CTAP101 Capsules (30, 60 or 90 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. All phase 3 trials were conducted with the current formulation of CTAP101 Capsules (30 mcg per capsule).

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 supraphysiologic 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 the maximum concentration (C_{max}) in the blood 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 phase 2 study, daily administration of CTAP101 Capsules increased serum total 25D levels to ≥30 ng/mL in nearly all subjects and decreased mean plasma intact parathyroid hormone (iPTH) from baseline and compared to placebo during 6 weeks of treatment [Sprague et al, 2014]. The mean % decrease in plasma iPTH from baseline in the per-protocol (PP) population was related to the administered dose: -20.9, -32.8, and -39.3 for the 30, 60 and 90 mcg groups, respectively.

The efficacy was confirmed in a larger 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 25D level and with 50% of such subjects achieving a mean reduction in plasma iPTH from baseline of at least 30%. Fewer than 9% of placebo subjects achieved a 30% reduction in plasma iPTH or achieved a normal 25D 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. Subjects in phase 3 trials who were treated with CTAP101 Capsules experience a mean increase in serum calcium of 0.2 mg/dL during a 26-week treatment period compared with a mean increase of 0.1 mg/dL in subjects treated with placebo. Most (74%) of the subjects treated with CTAP101 Capsules received a dose of 60 mcg/day. A total of 4.2% of the active-treated subjects and 2.1% of placebo-treated subjects experienced at least 1 elevation in serum calcium above the upper limit of normal (10.5 mg/dL), none of which were clinically significant.

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 corrected 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 [redacted] than placebo patients (0.2 versus 0.1 mg/dL).

2 STUDY OBJECTIVES

2.1 Study Objectives

2.1.1 Primary Objectives

The primary objectives of this study are to compare the effects of Rayaldee (CTAP101 Capsules) vs. placebo treatment in patients with mild to moderate COVID-19 on the:

1) Attainment of serum total 25D levels at or above 50 ng/mL by Day 14; and,
2) Severity and duration of disease as evidenced by five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) using the FLU-PRO Plus© questionnaire as the data collection tool.

2.1.2 Estimand

The study treatment estimand is the difference between 28 days of Rayaldee and placebo treatment in adult patients with confirmed SARS-CoV-2 infection who have unresolved symptoms of mild to moderate COVID-19 in (a) the attainment of serum total 25D levels ≥50 ng/mL as assessed at Day 14, and (b) the number of days to resolution of five symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), as measured by the FLU-PRO Plus© questionnaire with resolution defined as the first aggregate FLU-PRO Plus© symptom score of ≤5 which is maintained for a minimum of three consecutive days.

2.1.3 Secondary Objectives:

The secondary objectives are to compare the effects of Rayaldee (CTAP101 Capsules) vs. placebo treatment on:

1) The number of days to resolution of five symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), as measured by the FLU-PRO Plus© questionnaire, with resolution defined as the first aggregate symptom score of ≤5 which is maintained for a minimum of three consecutive days, with no individual symptom score >1;
2) Resolution, defined as the first score of ≤5 which is maintained for a minimum of three consecutive days (without subsequent relapse), for the aggregate five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) and for each individual symptom, defined as a score of 0 or 1, as measured by the FLU-PRO Plus© questionnaire as of Day 10;
3) Incidence of emergency room/urgent care visits;
4) Incidence of oxygen saturation below 94% (without oxygen supplementation);
5) Incidence and duration of hospitalizations;
6) Incidence of requirement for mechanical ventilation;
7) Mortality rate (as incidence);
8) Severity and duration of COVID-19 illness as evidenced by quality-of-life measures using the FLU-PRO Plus© questionnaire; and,

9) Clinical course of COVID-19 as a function of serum 25D concentrations of <50 ng/mL, 50 to 100 ng/mL and >100 ng/mL at Days 7, 14, 21 and 28, defined as the proportion of subjects in each treatment group with a total score of ≤5 for five symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) using the FLU-PRO Plus© questionnaire.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design

This is a phase 2, single or multi-center, randomized, double-blind placebo-controlled study to evaluate the safety and efficacy of Rayaldee (CTAP101 Capsules) to treat adult subjects with unresolved symptoms of mild to moderate COVID-19 who test positive for SARS-CoV-2 via nasopharynx swab and subsequent reverse transcription polymerase chain reaction (RT-PCR) or any substitutable FDA-authorized diagnostic test. Subjects will be randomized to receive either oral Rayaldee (CTAP101 Capsules) or matching placebo administered according to the following regimen: a loading dose (900 mcg split into three equal doses of 300 mcg each administered on Days 1, 2 and 3) followed by 24 daily maintenance doses (60 mcg on Days 4 to 27) administered at bedtime after fasting for at least 3 hours following dinner.

3.2 Rationale for Study Design and Control Group

The proposed study design is based on the hypothesis that the severity and duration of COVID-19 symptoms will be attenuated with an increase of serum 25D to levels of ≥50 ng/mL. A placebo-controlled trial is appropriate because there is currently no therapy that has been demonstrated to be effective in treating COVID-19 symptoms.

The FLU-PRO Plus© questionnaire [Powers et al, 2016 and 2018] will be used by the enrolled subjects to self-assess their COVID-19 symptoms on a daily basis at bedtime. This questionnaire was specifically designed and validated to evaluate in clinical trials the presence, severity and duration of symptoms associated with viral infections. It contains 32 items, grouped into 6 domains, that provide a comprehensive evaluation of such symptoms. It supports the primary efficacy endpoint of the time to resolution of five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), defined as a reduction in the aggregate FLU-PRO Plus© symptom score for these five symptoms recorded at study drug initiation (Day 1) to or below 5 for a minimum of three consecutive days. These five symptoms are part of the chest/respiratory and body/systemic domains of the FLU-PRO Plus© questionnaire for which average scores of ≥1.5 were required for inclusion in the study. Trouble breathing, chest congestion and dry or hacking cough are symptoms indicative of potentially inadequate oxygenation and an impending requirement for supplemental oxygen and hospitalization. Body aches and pains and chills and shivering are symptoms indicative of systemic inflammatory responses associated with active viral infection. Resolution of each of these five symptoms will be analyzed separately, as well, as secondary efficacy endpoints.

COVID-19 patients are expected to (but may not) present with serum total 25D levels averaging approximately 20-25 ng/mL, unless vitD becomes acknowledged as a possible prophylaxis against SARS-CoV-2 infection, based on information gathered from OPKO's prior PK studies conducted in healthy US volunteers and based on information from many US studies published in the medical literature. CKD is known risk factor for COVID-19 and patients with CKD will present with even lower 25D levels as advancing kidney disease is known to be associated with declining 25D levels [Levin et al 2007]. Phase 3 studies conducted by OPKO in large numbers of patients with stage 3-4 CKD have shown that baseline serum total 25D levels average below 20 ng/mL [Sprague et al 2016]. Further, these studies have shown that Rayaldee is safe in the CKD population at the proposed doses.

Few studies, to date, focused on treating COVID-19 have included CKD patients and many ongoing studies with anti-viral therapies have specifically excluded such patients. COVID-19 disproportionately affects patients with underlying disorders, and a significant percentage of COVID-19 patients have underlying CKD. Therefore, CKD patients with COVID-19 are available for recruitment and will be allowed to participate in the present study. Many subjects in each arm of this study may, therefore, have stage 3 or 4 CKD, defined as an estimated glomerular filtration rate (eGFR) of 15 to <60 mL/min/1.73m^2.

Data from Studies CTAP101-CL-1011, CTAP101-CL-1020 and 170074 show that an oral loading dose of 900 mcg of Rayaldee (CTAP101 Capsules) in the fasting state (approximately 25% BA) will raise serum 25D levels within ~9-12 hours by about 20-35 ng/mL, depending on the subject's body weight (the higher the body weight, the lower the expected increase in 25D). Many COVID-19 subjects are expected to have higher than normal body mass index (BMI) values in view of the latest reported US data. Each maintenance dose of Rayaldee (CTAP101 Capsules) (60 mcg/day) will increase serum 25D by another 0.6 ng/mL, as shown in Studies CTAP101-CL-3001, CTAP101-CL-3002 and CTAP101-CL-3003 [Sprague et al, 2016]. It follows that subjects having a baseline 25D level of ~25 ng/mL will reach ~45-60 ng/mL after the loading dose and ~59-74 ng/mL after 24 days of maintenance dosing. Subjects with slightly lower baseline levels of 25D will reach proportionately lower levels on treatment. There will be some subjects who have a higher baseline 25D level. For this reason, 25D levels will be checked at Days 7, 14 and 21and dosing will be adjusted if levels exceed 100 ng/mL. FDA has approved Rayaldee (CTAP101 Capsules) to raise levels up to a target of 100 ng/mL in kidney patients (see APPENDIX 2.: Package Insert).

3.3 Evaluations

Blood samples will be acquired periodically during the study (see APPENDIX 1: Schedule of Events). Blood samples will be assayed for: i) serum total 25D (primary efficacy measure), [redacted] iv) plasma iPTH, v) clinical chemistries and hematology, and [redacted] markers of the adaptive immune response to SARS-CoV-2 infection. [redacted] Daily assessments of disease severity and quality-of-life measures will be recorded by each subject using the FLU-PRO Plus© questionnaire.

3.4 Study Endpoints

3.4.1 Primary Efficacy Endpoints

The primary efficacy endpoints are:

1) Attainment of serum total 25D levels at or above 50 ng/mL, as assessed at Day 14; and,
2) The number of days to resolution of the selected five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), defined as a reduction in the aggregate symptom score recorded on Day 0 (prior

to study drug initiation) by the FLU-PRO Plus© questionnaire to or below 5 for a minimum of three consecutive days. A statistically significant difference (P<0.025 one sided) between the treatment groups in the time to resolution of symptoms in favor of treatment with CTAP101 Capsules will be deemed a successful outcome.

On each day during the study, subjects will record once daily (during a 24-hour period starting in the evening before the subject goes to sleep) the severity of COVID-19 symptoms using the FLU-PRO Plus© questionnaire.

3.4.2 Secondary Efficacy Endpoints

The secondary endpoints are :

1. The number of days to resolution of five symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), as measured by the FLU-PRO Plus© questionnaire, with resolution defined as the first aggregate symptom score of ≤5 which is maintained for a minimum of three consecutive days, with no individual symptom score >1;
2. Resolution, defined as the first score of ≤5 which is maintained for a minimum of three consecutive days (without subsequent relapse), for the aggregate five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) and for each individual symptom, defined as a score of 0 or 1, as measured by the FLU-PRO Plus© questionnaire as of Day 10;
3. Incidence of emergency room/urgent care visits;
4. Incidence of oxygen saturation below 94% (without supplemental oxygen);
5. Incidence and duration of hospitalizations;
6. Incidence of the requirement for mechanical ventilation;
7. Mortality rate (as incidence);
8. Severity and duration of COVID-19 illness as evidenced by quality-of-life measures including ability to perform usual activities and opinion of overall health status, using the FLU-PRO Plus© questionnaire; and,
9. Clinical course of COVID-19 as a function of serum 25D concentrations of <50 ng/mL, 50 to 100 ng/mL and >100 ng/mL at Days 7, 14, 21 and 28, defined as the proportion of subjects in each treatment group with a total score of ≤5 for the selected five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) using the FLU-PRO Plus© questionnaire.

Endpoint items 3-7 are all based on incidence over the entire 42 day study period.

Once daily (during a 24 hour period starting in the evening before bedtime), subjects will record their ability to perform usual activities and their opinion of overall health status in a diary using FLU-PRO© Plus questionnaire.

3.4.3 Exploratory Endpoints

The exploratory endpoints include:

[redacted]

[redacted] Baseline is defined as values obtained at Visit 1.

3.4.4 Primary Safety Endpoints

The safety and tolerability of Rayaldee (CTAP101 Capsules) will be evaluated by AEs, physical examinations (PE), vital signs (VS), electrocardiograms (ECGs), hematology and clinical chemistries. Special attention will be given to changes in the following parameters:

1) Serum total calcium (corrected for serum albumin);
2) Serum phosphorus; and,
3) eGFR.

3.5 Study Duration

The study is expected to be completed within approximately 8-12 weeks from the time of initial subject enrollment (first subject consented) to study completion for the last subject (last subject out/last visit complete). Each enrolled subject will participate in the study after randomization for up to 42 days (Day 1 through Day 42).

4 STUDY POPULATION SELECTION

4.1 Study Population

The targeted population for this study is symptomatic male or nonpregnant female subjects 18 years of age or older who have been recently diagnosed with unresolved symptoms of mild to moderate COVID-19. All prospective and enrolled subjects will be encouraged to make arrangements for transportation to the study site that are safe and do not adversely expose other people to infection.

4.2 Inclusion Criteria

Each subject must meet the following criteria to be enrolled and randomized into one of the two treatment groups of this study:

1) Male or female ≥ 18 years of age;
2) Confirmed within the past 3 days to have SARS-CoV-2 infection as evidenced by a positive nasopharyngeal swab test using RT-PCR or any substitutable FDA-authorized diagnostic test;
3) Confirmed to have only mild or moderate COVID-19 based on the first of the patient reported scores obtained during screening which meets the criterion of a FLU-PRO Plus© score ≥ 1.5 for each of the chest/respiratory and body/systemic domains, and the absence of clinical signs indicative of more severe disease (eg, oxygen saturation < 94% on room air or respiration rate >30 bpm);
4) Represents on self-assessment that the current COVID-19 symptoms are not consistent with usual health and that they are the same or worse than on the previous day;
5) Willing to limit the use of vitD therapies or supplements except for normally fortified food products (eg, milk) during the course of the 6-week study;
6) Must demonstrate the ability to comply with all study requirements; and,
7) Must be without any disease state or physical condition that might impair evaluation of safety or which, in the investigator's opinion, would interfere with study participation.

4.3 Exclusion Criteria

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

1) Clinical signs indicative of severe or critical COVID-19 severity (eg, oxygen saturation < 94% on room air or respiration rate > 30 bpm);
2) Pregnant or lactating women who are breastfeeding;
3) Use of systemic glucocorticoid medications in the last six months;
4) Recent history (previous 12 months) of primary hyperparathyroidism, kidney stones, hypercalciuria and/or hypercalcemia;
5) History of a chronic granuloma-forming disease (eg, sarcoidosis);
6) History of tuberculosis or histoplasmosis;
7) History of chronic liver disease;

8) History of (previous 12 months) of cardiac event indicative of chronic cardiovascular diseases including congestive heart failure, poorly controlled hypertension and arrhythmias;
9) History in the past five years of multiple myeloma or carcinoma of the breast, lung or prostate;
10) Any surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of vitD or 25D (eg, small bowel resection, history of Crohn's disease or ulcerative colitis);
11) Ongoing treatment with thiazide diuretics;
12) History of hyperphosphatemia, hyperuricemia and gout;
13) Renal impairment measured as eGFR< 15 mL/min/1.73m² on serum creatinine in the last three months;
14) Serum calcium ≥9.8 mg/dL in the last three months;
15) Evidence of existing or impending dehydration;
16) Known or suspected to have hypersensitivity to any of the constituents of the study drug; and/or,
17) Currently participating in, or have participated in, an interventional/investigational study within 30 days prior to study screening.

5 STUDY TREATMENTS

5.1 Description of Rayaldee (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)
Storage conditions:	20-25°C (68-77°F); excursions allowed to 15°C to 30°C (59°F to 86°F); protect from light and heat.

5.2 Description of Placebo Capsules

Dosage form:	Soft gel capsule
Dose strength:	0 mcg calcifediol ER capsule
Product description:	Blue oval capsules printed single-sided, centered with the logo O in white. Each bottle contains 30 capsules.
Active component:	None
Non-active components:	Paraffin wax, mineral oil, mono- and diglycerides, dehydrated alcohol, lauroyl polyoxylglycerides, butylated hydroxytoluene, hypromellose, modified starch, carageenan, sodium phosphate dibasic, sorbitol and sorbitan solution, FD&C Blue #1, titanium dioxide, medium chain triglycerides (coconut oil) and ink (white, which may contain titanium dioxide, isopropyl alcohol, propylene glycol, hydroxypropylmethyl cellulose 2910)
Storage conditions:	20-25°C (68-77°F); excursions allowed to 15°C to 30°C (59°F to 86°F); protect from light and heat

5.3 Treatments Administered

5.3.1 Dosing Instructions

Study drug should **NOT** be administered to individuals known to be allergic to any component of the drug.

Subjects will be instructed to take a loading dose of 10 capsules (300 mcg) of study drug per day on Days 1, 2 and 3 at bedtime after fasting for at least 3 hours following dinner, with any non-alcoholic liquid, by the oral route. On Days 4-27, subjects will take a maintenance dose of 2 capsules per day at bedtime unless otherwise directed. Patients should remain fasted for at least 3 hours after administration of study drug.

Study drug will be provided in containers labeled as investigational study drug as per the Packaging and Labeling below in Section 5.9. The interactive response technology (IRT) will dispense an appropriate bottle configuration to each patient per the dosing requirements. Each bottle will contain either active drug or a matching placebo.

Drug accountability will be performed at each visit until the end of the 28-day treatment period. All procedures being performed during the course of this clinical study are listed sequentially by visit in Section 7: Study Activities, and may be found as a table in APPENDIX 1: Schedule of Events.

5.3.2 Dose Reduction and Stopping Rules

Although hypercalcemia is unlikely given the extensive prior experience with Rayaldee (CTAP101 Capsules), any subject who exhibits a confirmed serum total calcium >10.5 and ≤11.0 mg/dL (corrected for serum albumin) based on blood samples obtained on Days 7 and 14 will reduce the daily maintenance dose by one capsule (from 60 mcg to 30 mcg) starting at Day 21. The dose will similarly be reduced based on blood samples obtained on Days 7 and 14 if serum total 25D is confirmed to exceed 100 ng/mL, the maximum targeted level in the FDA-approved Package Insert for Rayaldee (see APPENDIX 2.), starting at Day 21.

Subjects who exhibit confirmed serum total calcium >11.0 mg/dL (corrected for serum albumin) based on blood samples obtained on Days 7, 14 and 21 will suspend dosing until normalization of serum calcium at which time (if applicable) dosing will be resumed at one capsule per day (30 mcg per day). Subjects will be requested to return to the clinic on the earliest possible day of their next scheduled visit (eg, Day 12 for the Day 14 visit) for the confirmatory blood draw.

Subjects who develop severe (CTCAE ≥ 3) abnormalities (low or high) of serum phosphorus, uric acid or plasma iPTH will be withdrawn from study drug treatment but will continue in the study.

Enrollment of subjects into the study will be paused if mortality in the treatment arm is ≥ 7% higher compared to the placebo arm until the Data Safety Monitoring Board (DSMB) makes an assessment about causality, and may resume once the DSMB deems it acceptable to continue (if applicable).

5.3.3 Overdose and Toxicity

Excessive administration of calcifediol can cause hypercalcemia, hyperphosphatemia, hypercalciuria, hypervitaminosis or over-suppression of iPTH. Common symptoms of vitD overdosage may include constipation, decreased appetite, dehydration, fatigue, irritability, muscle weakness, or vomiting. Treatment of acute accidental overdosage with calcifediol should consist of general supportive measures (eg, phosphate binders for hyperphosphatemia). If the overdosage is discovered within a short time, emesis can be induced or gastric lavage performed to prevent further absorption. Serial serum calcium measurements should be obtained and any

electrocardiographic abnormalities due to hypercalcemia assessed. All supplemental calcium must be discontinued. Treatment with standard medical care is required if persistent and markedly elevated serum calcium levels occur. Any occurrence of accidental overdose or toxicity that requires medical intervention should be reported as an adverse event.

5.3.4 Method of Assigning Subjects to Treatment Groups

After signing the informed consent form (ICF), prior to any study-related activities, each subject will be assigned a 5 digit identification number and will retain this number throughout the study. The 5 digit identification number (SS-EEE) will consist of a 2-digit study site number (SS) and a 3-digit consecutive enrollment number (EEE). Should a subject be withdrawn from the study, that subject's 5 digit identification number will not be reassigned.

Approximately 250 subjects will be screened to enroll approximately 160 subjects who meet screening criteria. The IRT will provide study treatment group assignments for these subjects using a computer-generated randomization code. Subjects will be randomized in a blinded manner into 1 of 2 treatment groups (approximately 80 subjects per group) in a 1:1 ratio of Rayaldee (CTAP101 Capsules) or placebo, respectively.

5.4 Prior and Concomitant Therapy

Subjects should be willing to limit the use of vitD therapy and vitD supplements except for normally fortified food products (eg, milk) during the course of the 6-week study other than the study drug. Standard of care medications for CKD (VitD, calcitriol, paricalcitol and doxercalciferol) should be suspended during the treatment period. Excluded therapies at enrollment include thiazide diuretics, 1α-hydroxylated vitD analogs (calcitriol, paricalcitol and doxercalciferol) and vitD supplements (cholecalciferol and ergocalciferol). Current treatment with cytochrome P450 inhibitors, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole, which may inhibit enzymes involved in vitD metabolism and may alter serum levels of calcifediol, must be evaluated by the investigator and may be a reason for exclusion from the study. Medications that could impair the absorption of fat-soluble nutrients and dietary calcium supplements providing more than 0.5 g of elemental calcium are not allowed.

5.5 Diet Restrictions

Subjects should follow their dietary plan if one has been prescribed.

5.6 Subject Activity Restrictions

Subjects should maintain their usual pattern of sun exposures and activities as allowed under any health, government or local isolation/quarantine or personal-protection requirements for infection containment.

5.7 Pregnancy and Contraception

All female subjects who have the possibility to become pregnant (not surgically sterile or postmenopausal) and male subjects with female partners who have the possibility to become pregnant must agree to use effective contraception (such as implants, injectables, combined oral

contraceptives, intrauterine device, sexual abstinence, vasectomy or vasectomized partner) for the duration of the study.

5.8 Treatment Compliance

Study treatment compliance during the treatment period will be assessed via a patient diary and at all specified visits in person. 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 dosing records and the number of capsules remaining in bottles of study drug assigned to each subject) at Days 7, 14, 21 and 28 (end of treatment). Overall dosing compliance is defined as taking between 80% and 120% of the scheduled doses for the period of time that the subject participates in the study.

5.9 Packaging and Labeling

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

All study drug labels will include the protocol number, sponsor identification and address, bottle contents, route of administration, bottle number, area for subject identification, investigational use caution statements, storage conditions and instructions for use.

5.10 Storage and Accountability

Rayaldee (CTAP101 Capsules) and matching placebo capsules will be shipped to each site using standardized shipment and temperature monitoring procedures. While at the study site, study drug will be stored at controlled room temperature (20-25°C or 68-77°F) with excursions allowed to 15°C to 30°C (59°F to 86°F), and protected from light and heat per label instructions in the supplied packaging, with access granted to authorized personnel only. A temperature log recording the daily storage temperatures will be maintained at the sites. 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. A study drug accountability and dispensing log will record the study drug disposition. Each site's overall inventory of study drug supplies will be verified periodically throughout the course of the study. All opened and unopened bottles of study drug capsules including subject returns are to be retained at each site until the sponsor or designee has performed a complete accountability, following which study drug will be returned to the sponsor or designee.

5.11 Investigational Product Retention at Study Sites

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.

5.12 Blinding

All subjects, study personnel and the sponsor (and its designees, with the exception of unblinded member(s) of the DSMB and/or data management team) will be blinded as to whether a given subject is in the Rayaldee (CTAP101 Capsules) or placebo treatment group until after database lock or until the decision to break the blind is determined (eg, as a result of an emergent event). When the investigator determines that knowledge of treatment group assignment is required for medical management of an individual subject, the blind for the subject will be broken using the IRT system in accordance with sponsor instructions.

Further, all subjects, study personnel and the sponsor (and its designees, with the exception of unblinded member(s) of the DSMB and/or data management team) will be blinded to serum total 25D and [redacted] laboratory data obtained during treatment until after database lock.

Final unblinded site-specific data will be provided to the study sites within 3 months of finalizing the clinical study report.

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 in a format (digital or hardcopy) that is safe and prevents infection. If any material change occurs that affects the conduct of the study or the subject's willingness to participate in the study, the subject or LAR will be required to sign an updated consent form.

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

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

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

6.2 Medical History and Concomitant Medications

A medical history, including demographics and concomitant medications, will be recorded at the screening visit (Visit 1). Any symptom related to COVID-19 that started prior to initial dose, does not need to be reported as medical history. Concomitant medications will be recorded at each additional study visit.

6.3 Brief Physical Examinations and Vital Signs

Brief PE and assessments of VS (to include height, weight and BMI) and COVID-19 disease severity will be performed at screening scheduled as soon as possible after a subject is verified to be infected with SARS-CoV-2. Evaluations are presented in Table 1. Routine monitoring of VS and ongoing assessments of COVID-19 disease severity will be performed at subsequent visits.

Table 1 Evaluations

Physical Examinations:	Brief PE.
Vital Sign Measurements:	Height, weight and BMI determination at screening visit (Day -3 to 0) and weight and BMI determination using screening height at the end of the treatment period (Visit 5/Day 28+2). Blood pressure, heart and respiratory rate, temperature and oxygen saturation (pulse oximetry) will be measured and recorded after the subject has been sitting for at least 2 minutes prior to any scheduled blood draws at every visit.
Electrocardiogram (ECG)	ECG will be performed at screening visit (Day -3 to 0), Visit 3 (Day 14±2) and Visit 5 (Day 28+2),
COVID-19 Severity and Quality-of-life Assessments:	On each day during the study, subjects will record once daily at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

6.4 Clinical Laboratory Tests

6.4.1 Laboratory Parameters

Blood will be drawn at Screening and on Days 7, 14, 21 and 28 and analyzed as specified in Table 2. Samples also will be collected for analyses of biomarkers associated with SARS-CoV-2 infection, host immune status and vitD metabolism.

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

All clinically significant abnormal laboratory values should be recorded as AEs and the investigator will follow-up (FU) according to Section 6.7.6 Clinical Significance.

Subjects will be in a seated or supine position during blood collection.

Table 2 List of Laboratory Tests

Hematology:
- Hematocrit
- Hemoglobin
- Platelet count
- Red blood cell count
- White blood cell count
- Peripheral blood neutrophils
- Peripheral mononuclear monocytes

Serum b-hCG Pregnancy Test (only for females of childbearing potential, defined as either not surgically sterile or not diagnosed as postmenopausal)[1]

Biomarkers, PD and PK parameters:
- [redacted]
- Plasma iPTH
- Serum total 25-hydroxyvitamin D (25D) (blinded)*
- [redacted]

**Data will not be available until after database lock.*

Serum Chemistry:
- Albumin
- Alkaline phosphatase
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Blood urea nitrogen
- Total calcium (corrected)
- Carbon dioxide
- Chloride
- Creatinine
- Estimated glomerular filtration rate (eGFR)[2]
- Glucose
- Lactate dehydrogenase
- Magnesium
- Phosphorus
- Potassium
- Sodium
- Total bilirubin
- Direct bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Uric acid

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

6.4.2 Sample Collection, Storage, and Shipping

Missed blood samples should not be drawn or collected (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. Any detailed instructions will be provided

[1] Performed at screening, and again at subsequent visits only after a positive urine pregnancy test.
[2] Calculated value.

separately from this protocol to the laboratory. Blood samples will be collected and analyzed for clinical laboratory and [redacted] biomarker tests.

The laboratory may ship specimens to other designated outside specialty facilities as appropriate. Approximately 385 mL of blood will be drawn from each subject during the course of the study. This volume will include overage/backup volume as described in the study laboratory manual. Additional blood draws may be needed for unscheduled or repeat visits. Every effort has been made to minimize the total amount of blood to be drawn. Samples are to be shipped to the central laboratory for each subject as visits are completed.

6.4.3 Clinical Supplies

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

6.5 Dispensing Study Drug

The IRT will provide study drug assignments. The study coordinator or pharmacist (or designated site personnel) will obtain the study drug assignments for each subject and dispense the appropriate number of containers/capsules, which will be recorded in the drug accountability records. Study drug will be shipped to the subject's home after confirmation of randomization, or if appropriate and feasible under current site access procedures, study drug can be dispensed directly to subjects or hand-delivered by qualified site personnel for same day dispensing, as needed.

All subjects, study personnel and the sponsor (and its designees, with the exception of unblinded member(s) of the DSMB and/or data management team) will be blinded to treatment and serum total 25D and [redacted] data until the last subject completes the study and the data have been locked.

6.6 Data Safety Monitoring Board (DSMB)

A five-member DSMB will be established which will be comprised of an expert in viral disease pathogenesis, a nephrologist who routinely treats patients with vitD repletion therapies, a statistician and a pulmonary medicine expert. The DSMB will also include an unblinded safety monitor to identify potential safety hazards (eg, hypercalcemia) in order to maintain blinding of treatment assignment and ensure study integrity. The DSMB will meet by teleconference every 3-4 weeks or at the Committee's discretion. Meetings may occur more often should serious adverse events (SAEs) or other safety issues arise.Specific responsibilities and activities of the DSMB will be defined in the DSMB charter.

6.7 Adverse Events Assessments

6.7.1 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 deemed clinically significant) or disease temporally associated with the use of a medicinal product whether or not considered related to the medicinal product.

6.7.2 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 electronic case report form (eCRF) including the date of onset, description, severity, duration, relationship of the AE to the investigational study drug, action(s) taken and outcome. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be reported on the appropriate eCRF.

6.7.3 AE Collection Period

Adverse events which are determined as non-serious events that occur after the ICF has been signed and after the initiation of study drug will be documented in the source document and followed to a satisfactory resolution, until the investigator deems the event to be chronic or the subject to be stable, or until the subject's participation in the study ends. Adverse events that occur after the ICF has been signed but prior to the initiation of study drug will be captured as medical history. Serious adverse events that occur after the ICF has been signed must be reported to the sponsor (as per protocol Section 6.7.7.3) and will be documented in the source document and followed to a satisfactory resolution, until the investigator deems the event to be chronic or the subject to be stable, or until the subject's participation in the study ends.

New or changes in COVID-19 symptoms are expected over the course of the COVID-19 infection and should not be reported as AEs unless intervention was required or in the opinion of the investigator they are considered clinically significant. All COVID-19 SAEs should be reported regardless.

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, action taken with study drug (if applicable), 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 (eg, pneumonia),

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 or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, then sign(s) or symptom(s) should be recorded as an AE(s). Changes in laboratory values are judged to be clinically significant 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, the diagnosis only should be reported as an AE.

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

Any report of pregnancy identified for any female subject or for a female partner of a male subject should be reported immediately (within 24 hours of being informed) by submitting the Pregnancy Reporting Form to OPKO safety within 24 hours of awareness to safetyreporting@opko.com.

Pregnancies will be considered 'events of special interest' and will not be captured as serious adverse events (SAEs). Investigators should follow specific procedures for reporting them to OPKO Pharmacovigilance. Pregnancies will be followed to termination or six weeks post-delivery for determination of resolution to the event. Subjects who become pregnant during treatment must immediately be withdrawn from study drug treatment.

The Medical Dictionary for Regulatory Activities (MedDRA), Version 23.0 or later, will be used to code all AEs.

6.7.4 Severity

The intensity of the AE will be rated by the investigator per Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

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

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

6.7.5 Relationship

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

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

6.7.6 Clinical Significance

Changes in unblinded laboratory values, vital signs or other diagnostic procedure outcomes/results 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 abnormalities will automatically be considered clinically significant unless the investigator indicates not clinically significant directly on the laboratory paperwork or source documentation.

6.7.7 Serious Adverse Events

6.7.7.1 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.

6.7.7.2 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 Rayaldee (CTAP101 Capsules). Categories are:

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

6.7.7.3 Reporting Serious Adverse Events

Any AE considered serious by the investigator that meets the previously mentioned criteria must be reported to OPKO Pharmacovigilance at the following number within 24 hours from the time when site personnel first learn about the event.

SAFETY REPORTING Contact: OPKO Pharmacovigilance

Fax: [redacted]

E-mail: [redacted]

The IRB/IEC should be made aware according to currently prescribed institutional guidelines. A written report should be provided consisting of the SAE Form and other necessary source documents. If the subject is hospitalized because of or during the course of an SAE, then the investigator should attempt to obtain a copy of the hospital discharge summary and any pertinent laboratory or diagnostic reports, and provide them to the sponsor or designee as soon as possible.

For any information not available at the time of the first report that becomes available later, the investigator should update the SAE Form and eCRFs and provide any additional documentation to OPKO Pharmacovigilance and IRB/IEC 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 DSMB and IRB/EC.

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

A subject experiencing one or more SAEs will receive treatment and FU evaluations by the investigator, or they will be referred to another appropriate physician for treatment and FU.

All SAEs will be followed to at least Day 42 or until resolution. Should the event become indistinguishable from the chronic disease condition, the subject will be followed for 14 days after the last investigational study drug administration and subsequently all events will be closed.

6.7.8 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 14 days following discontinuation of study drug administration.

6.8 Concomitant Medication Assessments

The study coordinator or designee will record concomitant medication history (previous three months) in the source document and eCRF.

6.9 Removal of Subjects from the Study or Study Drug / Stopping Criteria

The investigator may discontinue a subject from study drug treatment for any of the following reasons:

- A major protocol deviation occurs;
- A serious or intolerable AE occurs;
- The subject has a confirmed pregnancy;
- A clinically significant change in a laboratory parameter occurs (eg, increase in serum calcium above upper limit allowed); and,
- A clinically significant change in ECG at Visit 3 occurs as compared to baseline (eg, prolongation of QT interval).

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

- The subject requests to be discontinued from the study (withdraws consent); or,
- The subject is lost to follow-up.

Subjects who develop severe (CTCAE ≥ 3) abnormalities (low or high) of serum phosphorus, uric acid or plasma iPTH will be withdrawn from study drug treatment.

Enrollment of subjects into the study will be paused if mortality in the treatment arm is $\geq 7\%$ higher compared to the placebo arm until the DSMB makes an assessment about causality, and may resume once the DSMB deems it acceptable to continue (if applicable).

No subject replacement is planned. All subjects withdrawn from treatment will continue in the study until study completion and perform all assessments unless consent is withdrawn. The investigator will be requested to make all reasonable efforts to obtain clinical status at FU.

6.10 Appropriateness of Measurements

The safety and tolerability of Rayaldee (CTAP101 Capsules) will be determined by analyzing AEs, serum 25D, calcium (corrected for serum albumin) and phosphorus, and eGFR.

7 STUDY ACTIVITIES

7.1 Screening and Randomization (Visit 1/Day -3 to 1)

7.1.1 Screening (Day -3 to 0)

Visit to occur within 3 days after positive RT-PCR test or any substitutable FDA-authorized diagnostic test for SARS-CoV-2 infection.

- Review study ICF (A signed ICF will be obtained from each subject prior to any study-related procedures).
- Review of inclusion/exclusion criteria.
- Medical history and demographics.
- Review of prior medications (previous three months).
- Brief PE.
- VS assessment (weight, height and BMI).
- ECG.
- Blood samples will be obtained for the following:
  - Hematology, serum chemistry (full panel and eGFR determination) (see Table 2);
  - Serum b-hCG pregnancy test (for females of childbearing potential);
  - [redacted]
  - Plasma iPTH and serum 25D; and,
  - [redacted]
- Training provided on study drug dosing, storage and use.
- Diary instructions provided for assessment activities. Subject will be trained to assess and record in the diary AT VISIT the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.
- Subject will assess and record in the diary at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

7.1.2 Randomization and Initial Treatment (Day 1)

- Day 1 is considered to be the day on which the first loading dose is administered. Initial dosing may not necessarily coincide with the day on which randomization occurs if study drug is not received by the subject on the day of randomization.
- If qualified, subjects will be randomized to treatment with active or placebo study drug following receipt and review of laboratory test results. Study drug will be shipped to subject's home or if appropriate and feasible under current site access procedures, study drug can be dispensed directly to subjects or hand-delivered by qualified site personnel for same day dispensing, as needed.
- Subject will self-administer 10 study drug capsules at bedtime after fasting for at least 3 hours following dinner and record the dose in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.

7.2 Days 2-6

- No study site visits.
- On each of Days 2 and 3, subject will self-administer 10 study drug capsules at bedtime after fasting for at least 3 hours following dinner and record the doses in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.
- From Day 4 onwards, subject will self-administer 2 study drug capsules each day, unless otherwise directed, at bedtime after fasting for at least 3 hours following dinner and record the doses in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.
- Subjects will assess and record in the diary each day at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

7.3 Visit 2 (Day 7 ± 2)

Activities to be performed during site visit:

- Review of concomitant medications.
- AE assessment.
- VS assessment.
- Blood samples will be obtained for the following:
  - Hematology, serum chemistry (full panel and eGFR Determination) (see Table 2);
  - [redacted]
  - Plasma iPTH and serum 25D; and,
  - [redacted]
- Urine pregnancy test for females of childbearing potential (a positive test result will be confirmed with a serum b-hCG test).
- Study drug reconciliation/compliance review with subject (study drug returned to subject after visit review).
- Diary review with subject.
- Subject will self-administer 2 study drug capsules, unless otherwise directed, at bedtime and record the dose in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.
- Subject will assess and record in the diary at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

7.4 Days 8-13

- No study site visits.
- Subject will self-administer 2 study drug capsules each day, unless otherwise directed, at bedtime after fasting for at least 3 hours following dinner and record the doses in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.
- Subject will assess and record in the diary each day at bedtime the severity of COVID-19 symptoms using the FLU-PRO Plus© questionnaire.

7.5 Visit 3 (Day 14 ± 2)

Activities to be performed during site visit:

- Review of concomitant medications.
- AE assessment.
- VS assessment.
- ECG (prolonged QT-interval will be referred to a Cardiologist for review).
- Blood samples will be obtained for the following analyses:
  - Hematology, serum chemistry (full panel and eGFR determination) (see Table 2);
  - [redacted]
  - Plasma iPTH and serum 25D; and,
  - [redacted]
- Urine pregnancy test for females of childbearing potential (a positive test result will be confirmed with a serum b-hCG test).
- Study drug reconciliation/compliance review with subject (study drug returned to subject after visit review).
- Diary review with subject.
- Subject will self-administer 2 study drug capsules at bedtime, unless otherwise directed, after fasting for at least 3 hours following dinner and record the dose in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.
- Subject will assess and record in the diary at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

7.6 Days 15-20

- No study site visits.
- Subject will self-administer 2 study drug capsules, unless otherwise directed, each day at bedtime after fasting for at least 3 hours following dinner and record the doses in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.
- Subject will assess and record in the diary each day at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

7.7 Visit 4 (Day 21 ± 2)

Activities to be performed during site visit:

- Review of concomitant medications.
- AE assessment.
- VS assessment.
- Blood samples will be obtained for the following analyses:
  - Hematology, serum chemistry (full panel and eGFR determination) (see Table 2);
  - [redacted]
  - Plasma iPTH and serum 25D; and,

- [redacted]
- Urine pregnancy test for females of childbearing potential (a positive test result will be confirmed with a serum b-hCG test).
- Study drug reconciliation/compliance review with subject (study drug returned to subject after visit review).
- Diary review with subject.
- Subject will self-administer 2 study drug capsules, unless otherwise directed, at bedtime after fasting for at least 3 hours following dinner and record the dose in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.
- Subject will self-assess and record in the diary at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

7.8 Days 22-27

- No study site visits.
- Subject will self-administer 2 study drug capsules each day, unless otherwise directed, at bedtime after fasting for at least 3 hours following dinner and record the doses in the diary. Subject should remain fasted for at least 3 hours after administration of study drug.
- Subject will assess and record in the diary each day at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

7.9 Visit 5 (Day 28 + 2) (End of Treatment/Early Termination)

Activities to be performed during site visit:

- Review of concomitant medications.
- AE assessment.
- VS assessment (weight and BMI).
- Brief PE.
- ECG (prolonged QT-interval will be referred to a Cardiologist for review).
- Blood samples will be obtained for the following analyses:
  - Hematology, serum chemistry (full panel and eGFR determination) (see Table 2);
  - [redacted]
  - Plasma iPTH and serum 25D; and,
  - [redacted]
- Urine pregnancy test for females of childbearing potential (a positive test result will be confirmed with a serum b-hCG test).
- Study drug reconciliation/compliance review with subject (treatment complete – no further study drug dispensed).
- Diary review with subject.

Subject will assess and record in the diary at bedtime the severity of COVID-19 symptoms using the FLU-PRO Plus© questionnaire.

7.10 Days 29-41

- No study site visits.
- Subject will assess and record in the diary each day at bedtime the severity of COVID-19 symptoms and quality-of-life using the FLU-PRO Plus© questionnaire.

7.11 Visit 6 (Day 42 ± 4 (Follow-up – Telephone Visit))

- Upon awakening in the morning, subject will assess and record in the diary the severity of COVID-19 and quality-of-life using the FLU-PRO Plus© questionnaire.

Subject will self-report via telephone to site staff:

- Review of concomitant medications.
- AE assessment.
- Diary review with subject.

8 QUALITY CONTROL AND ASSURANCE

The study will be conducted in accordance with the protocol, ICH/GCP (International Council for 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 (on site and/or remote) will evaluate study conduct, data integrity, protocol, and GCP compliance. The 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. Any issues arising from these reviews will be communicated directly to the investigator in the monitoring report with recommendations for any Corrective and Preventive Action plans. The DSMB will be apprised of any serious continuing non-compliance.

To ensure the quality of the clinical data across all subjects, a Clinical Data Management review will be performed by the Data Manager 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. 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

All analyses will be performed using SAS® or other appropriate statistical software. All data collected on eCRFs, diary (from ePRO) and from clinical laboratory evaluations will be grouped and listed by population sub-group, subject, visit, date and time as feasible. Summary tables will be presented by population as appropriate. Descriptive summaries of categorical outcomes will include the proportion of subjects. Descriptive summaries of quantitative measures will include the number of subjects, mean, standard deviation (SD), median, minimum, and maximum or as appropriate. In descriptive summary tables, if needed, the geometric mean will be calculated as the n^{th} root of the resulting product of the values, and the coefficient of variation (in percent, %CV) will be calculated as 100* (SD/[arithmetic mean]).

Arithmetic means, SDs, medians, and geometric means will be reported with two significant figures more than the reported values. Minimum and maximum values will be reported with the same accuracy as the reported source data. The %CV will be rounded to 1 decimal place.

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

In the event there are multiple results at a given visit and/or time point, the following logic will be applied for purposes of summarization by visit or time point: for pre-dose measurements and selection of a baseline value, the more recent non-missing result will be used, preferably the result recorded on Day 0 (the day prior to first administration of study drug), if available; for post-dose measurements, the earliest of the results will be selected. If multiple laboratory results are available for the same date and time and the discrepancy could not be resolved, then the arithmetic mean of the results could be used unless specified in the data management plan or data handling conventions finalized before breaking the study randomization blind. All subjects entered into the clinical database will be included in subject data listings.

Specific analysis details will be provided in the Statistical Analysis Plan.

9.2 Missing Data

For the primary endpoint based on achievement of serum 25D level ≥50 ng/mL at Day 14, missing results due to intercurrent illness, hospitalization or death will be imputed as lack of achieving serum 25D levels. For the time-to-event primary efficacy endpoint based on aggregated symptom scores, the analysis is based on the proportion of subjects resolved over the total population. Missing scores occurring prior to resolution are considered as lack of resolution and kept in the denominator. This should provide a conservative estimate of the proportion resolved. Missing results after the first day of achieving a score of ≤5 and followed by up to 5 days with score ≤5, as defined in Section 9.10.1 for determining resolution, will not be imputed as lack of resolution.

For the time-to-event secondary efficacy endpoint based on aggregated symptom scores, the analysis is based on the proportion of subjects resolved over the total population. Missing scores occurring prior to resolution are considered as lack of resolution, and kept in the denominator, but missing results after the first day of achieving a score of ≤5, and followed by up to 5 days

with score ≤5, provided that no individual score is ≥1, as defined in Section 5.2 for determining resolution, will not be imputed as lack of resolution.

Similarly, for symptom scores, missing results prior to resolution of symptoms due to intercurrent illness, hospitalization, or death will be imputed as lack of resolution, and missing results after the first day of achieving a score of ≤1 and followed by up to 5 days with score ≤1, as defined in Section 9.10.1 for determining resolution, will not be imputed as lack of resolution. This strategy is appropriate given the consistent trend in symptoms toward improvement over time, as observed in blinded data from this ongoing study.

For subjects who have achieved resolution of symptoms, missing daily symptom scores beyond the time of resolution will not be imputed. Subjects will be instructed to report any symptoms that recur after resolution.

If responder status is not determinable for a subject with missing serum 25D results used in the efficacy analyses, responder status will be imputed using multiple imputation. The missing serum 25D results will be imputed 50 times to generate 50 complete data sets by using the SAS procedure MI using the logistic regression method with adjustment for covariates including treatment group, gender, age, race, dosing compliance and baseline and other serum 25D concentration determinations. The seed used will be 201901. Each of the 50 complete datasets will be analyzed using a Chi-square test and the SAS MIANALYZE procedure will be used to generate valid statistical inferences by combining results from the 50 analyses using Rubin's formula. No other efficacy data will be imputed.

The secondary endpoints based on incidence will not be imputed. These endpoints, for example hospitalization or mechanical ventilation, will either occur, or will be assumed not to have occurred. Since these items require clinical care, the occurrence will unlikely go unreported. If there are more than 10% of subjects who are truly missing and lost to follow up, a tipping point approach will be used, first assuming that none of the events occurred in the missing subjects, and then if all missing subjects had the event. If there is a difference based on these extremes, the number of missing subjects assumed to have the event will be increased by 2 in the treated group, while holding the incidence in the placebo group as observed, until the tipping point is found. Missing values from the quality of life components of FLU-PRO Plus© questionnaire will not be imputed. The analysis of these items will be based on observed cases only with resolution requiring at least a three-day duration.

AEs with missing onset date will be treated as TEAEs and missing onset date will be imputed as Day 1, unless the event end date indicates that the event resolved prior to the administration of the investigational study drug. In this case, it will be documented in medical history. AEs with partial onset date will similarly 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.

If an AE has missing severity or relationship to study drug, the missing severity will be set to severe and the missing relationship will be set to Related in all summary tables.

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.

9.3 Planned Data Safety Monitoring:

A five-member DSMB will be established which will be comprised of an expert in viral disease pathogenesis, a nephrologist who routinely treats patients with vitD repletion therapies, a statistician and a pulmonary medicine expert. The DSMB will also include an unblinded safety monitor to identify potential safety hazards (eg, hypercalcemia) in order to maintain blinding of treatment assignment and ensure study integrity. The DSMB will meet by teleconference every 3-4 weeks or at the Committee's discretion. Meetings may occur more often should serious adverse events (SAEs) or other safety issues arise.issues. Specific responsibilities and activities of the DSMB will be defined in the DSMB charter.

9.4 Determination of Sample Size

Primary outcome #1 (attainment of serum 25D levels at ≥50 ng/mL): Assuming that no more than 25% of the control group will achieve an increase in serum 25D to ≥50 ng/mL by Day 28 versus greater than 75% in the CTAP101 Capsules group, a sample size of 19 per group will provide 90% power at alpha 0.025 one sided for a Chi-square test of the two groups.

Primary outcome #2 (severity of illness by five symptoms): A sample size of 80 per group (total of 160) is planned. This will provide greater than 80% power at one sided alpha of 0.025 based on a log rank test assuming 50% of subjects in the control group and 70% of the CTAP101 Capsules group will have achieved resolution of symptoms by Day 28. This is based on an expected hazard ratio (of achieving resolution) of 1.74.

9.5 Analysis Populations

The intent-to-treat (ITT) population will include all randomized subjects.

The full analysis set (FAS) or population is a subset of the ITT set from which subjects are excluded who did not receive any study drug or have a baseline aggregate five symptom score of ≤5. For the secondary analyses of individual symptom scores and quality-of-life responses, further subjects who do not have a baseline score of >1 for that symptom or response will be excluded.

A PP population, defined as subjects who do not have a major protocol deviation prior to resolution of the aggregated five symptoms, will also be used as supportive evidence of efficacy. Subjects who are non-compliant with the requirements of the protocol after achieving resolution of the five COVID-19 symptoms will be included in the PP set due to the expectation that such subjects will likely discontinue prematurely from the study.

The safety population includes all subjects who received any amount of study treatment and will be the population for safety evaluations.

For each analysis population, baseline subject characteristics, including age, sex, race, ethnicity, height, weight, BMI and eGFR will be summarized by study arm (CTAP101 Capsules and placebo). Primary, secondary [redacted] outcomes will be summarized by study arm and FU time points, using CONSORT guidelines to present descriptive statistics, including mean, median, standard deviation, quartiles, interquartile range, minimum, and maximum values for subjects within the site, overall and by treatment group. Continuous variables will be summarized using means, standard deviations, and quartiles, while categorical variables will be summarized using frequencies and percentages.

9.6 Demographics and Baseline Characteristics

Baseline subject characteristics, including age, sex, race, ethnicity, height, weight, BMI and eGFR, will be tabulated for the both the treatment and placebo control population. Age (years) will be calculated as (date of ICF - date of birth + 1)/365, or as reported age (to the nearest month) at study entry if date of birth is not collected.

9.7 Subject Disposition and Withdrawal

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

9.8 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 sub-group. 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.

9.9 Safety Analyses

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

9.9.1 Adverse Events

All AEs will be collected on the eCRF and coded via SOC and preferred term using MedDRA version 23.0 or higher. Additionally, the intensity of all AEs will be coded using CTCAE v. 5.0. AEs with missing onset date will be treated as TEAEs and missing onset date will be imputed as the date of Visit 1, unless the event end date indicates that the event resolved prior to Visit 1, in

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

Diagnostic procedures will be collected separately in the eCRF and coded via SOC and preferred term using MedDRA version 23.0 or higher in a manner similar to AEs.

9.9.2 Vital Signs

Observed VS values will be summarized descriptively at Visit 1 and changes from baseline will be descriptively summarized by treatment and control group. Summaries will include n (%), mean, SD, median, minimum, and maximum. Vital sign values will be listed.

9.9.3 Secondary Safety Analyses

Secondary safety endpoints for will include incidence of hypercalcemia and drug-related hyperphosphatemia. The number (n, %) of subjects with hypercalcemia (serum calcium >10.5 mg/dL) or hyperphosphatemia (> 4.5 mg/dL) will be compared between study arms using a Chi-square test statistic (alpha=0.05).

9.10 Efficacy Analyses

9.10.1 Primary Endpoints

The two primary efficacy endpoints will be tested hierarchically to maintain an overall one-sided alpha level of 0.025. Therefore, the test of resolution of symptoms based on the aggregate FLU-PRO Plus© symptom score will be performed only if the attainment of serum 25D levels ≥50 ng/mL at Day 14 is significant at <0.025.

The first primary efficacy endpoint, attainment of serum 25D levels at ≥50 ng/mL, will be assessed with a Chi-square statistic at Day 14. The serum 25D levels will also be compared between treatment groups at Days 7, 21 and 28 with a Chi-square statistic.

The second primary efficacy endpoint is the time to resolution of symptoms, defined as a reduction in the aggregate FLU-PRO Plus© scores recorded on Day 0 (prior to study drug initiation) for the selected five COVID-19 symptoms to or below 5 for a minimum of three consecutive days. The time to resolution is defined as the number of days from Day 1 to the first day of achieving the aggregate ≤5 score for a minimum of three consecutive days, provided that no score greater than 5 is recorded between the two qualifying scores. The number of days to resolution will be determined by the first two successive qualifying scores which span a minimum of three consecutive days, provided that no score greater than 5 is recorded between the two qualifying scores. For clarity, resolution will be considered as having been achieved if two successive aggregate scores of ≤5 are recorded on the first day of this period and on a subsequent day that is at least two days (but not more than 5 days) later even if no score has been recorded between the two days. Missing symptom score values will be handled as described in Section 9.2. The number of days to resolution will be analyzed with a Cox proportional hazards model with covariates (baseline aggregate FLU-PRO Plus© score for the selected five symptoms, baseline serum 25D, and body weight).

As a sensitivity analysis of the resolution of symptoms, a tipping point approach will be used starting with the analysis in which scores are available for three consecutive days, with no missing interval, followed by increasing numbers of missing days in the up to five-day interval, that is, 1, 2, and 3 missing days between the two consecutive qualifying scores. The duration of resolved days, assessed as achieving resolution for four, five, six or seven consecutive days without evidence of relapse, will be summarized by treatment group.

Subgroup analyses for the primary efficacy endpoints will be based on age (≤40 or >40 years), severity of the selected five COVID-19 symptoms at baseline (aggregate FLU-PRO Plus© score of ≤ or > the median score), attained serum 25D at Day 14 (below, within or above the targeted range of 50 to 100 ng/mL), body weight (≤100 or >100 kg), BMI (≤30 or >30), dosing compliance (<80% or ≥80%), gender, race, ethnicity, number of comorbidities (<1 or ≥1), duration of treatment (≤10 or >10 days) and prior or intercurrent COVID-19 vaccination and/or monoclonal antibody therapy for COVID-19.

In addition, the number of days to resolution of the five aggregated symptoms will be compared based on the serum 25D level at Day 14 (<50 ng/mL vs 50 to 100 ng/mL and 50 to 100 ng/mL vs >100 ng/mL), regardless of the assigned treatment group. The comparisons will be done using a Chi-square test. Frequency of relapses will be calculated, if possible, to account for potential worsening of symptoms after resolution (defined above), with relapse being defined as achieving an aggregate score >5 for a minimum of three consecutive days.

9.10.2 Secondary Endpoints

The following secondary endpoints will also be tested statistically with methods described below, and the resulting nominal p-value will be reported for evaluation:

1) The number of days to resolution of five symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering), as measured by the FLU-PRO Plus© questionnaire, with resolution defined as the first aggregate symptom score of ≤5 which is maintained for a minimum of three consecutive days, with no individual symptom score >1;

2) Resolution, defined as the first score of ≤5 which is maintained for a minimum of three consecutive days (without subsequent relapse), for the aggregate five COVID-19 symptoms (trouble breathing, chest congestion, dry or hacking cough, body aches and pains, and chills and shivering) and for each individual symptom, defined as a score of 0 or 1, as measured by the FLU-PRO Plus© questionnaire as of Day 10;
3) Incidence of emergency room/urgent care visits;
4) Incidence of oxygen saturation below 94% (or requirement for supplemental oxygen);
5) Incidence of hospitalizations (mean duration of hospitalization will also be presented);
6) Incidence of requirement for mechanical ventilation; and,
7) Mortality rate (as incidence).

Endpoints listed will be summarized. For the analysis of individual symptoms in endpoint #2 above, the threshold of ≤1 is appropriate because it describes minor symptom severity (at worst "a little bit") which seems unlikely to presage a poor outcome. Analysis of the resolution of individual symptoms will be performed using a logistic regression, with baseline symptom score, baseline 25D level, and body weight as covariates. Analysis of the secondary endpoints based on incidence will be performed with a Chi-square test. Mean duration will be analyzed with analysis of covariance (ANCOVA). Mortality will be analyzed as incidence, with logistic regression with baseline symptom score, baseline 25D level and body weight as covariates. Rates only will be reported if there are too few deaths to be formally analyzed.

The severity, duration and clinical course of COVID-19 illness will be compared between treatment groups by analyzing changes in quality-of-life assessments recorded on the FLU-PRO Plus© questionnaire. Five of the six items from the questionnaire to be analyzed are: : "Overall, how severe were your infection symptoms today?", "Overall, how were your infection symptoms today compared to yesterday?", "How much did your infection symptoms interfere with your usual activities today?", "Have you returned to your usual activities today?", "In general, how would you rate your physical health today?", and "Have you returned to your usual health today?" The scores for: symptom severity range from 0 (no infection symptoms today) to 4 (very severe); symptoms today range from 1 (much better) to 7 (much worse); symptom interference range from 1 (not at all) to 5 (very much). The first of two consecutive scores of ≤1 spanning at least three days and no more than five days will be considered the day of resolution, provided that no intervening scores of >1 are recorded. The scores for return to usual activities or health are either "yes" or "no", and the first occurrence of "yes" will be deemed to be day of resolution provided that a second "yes" is recorded no more than 5 days later without an intervening "no". The remaining sixth item to be analyzed is: "physical health range from 1 (poor) to 5 (excellent). The first of two consecutive scores of >4 spanning at least three days and no more than five days will be considered the day of resolution, provided that no intervening scores of <4 are recorded. Each item will be compared between treatment groups using a Cox proportional hazards model with covariates (aggregate FLU-PRO Plus© score for the selected five COVID-19 symptoms at baseline, serum total 25D at baseline, and body weight).

The clinical course of COVID-19 will be examined by subgroups defined by serum total 25D levels <50 ng/mL, 50 to 100 ng/mL and >100 ng/mL at Days 7, 14, 21 and 28.

[redacted]

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Study Administrative Structure

The sponsor and principal investigator will provide oversight and responsibility of all designated personnel, laboratories, and other participating organizations.

10.2 Institutional Review Board/Ethics Committee Approval

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

10.3 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

Prior to screening for the study each patient and parent(s)/legal guardian /or LAR will be informed in detail about the study drugs to be administered and the nature of the clinical investigation with its risks and discomforts to be expected. The basic elements of informed consent as specified by the FDA (21 CFR 50.25) and ICH-GCP will be followed.

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 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 (digital or hardcopy) 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 or patient information is amended during the study, the investigator must follow all applicable regulatory requirements pertaining to approval of the amended ICF by the Institutional Review Board/Ethics Committee (IRB/EC) and use of the amended form (including ongoing subjects).

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. Each 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.

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 investigator will allocate adequate time for such monitoring activities. This monitoring will be in the form of on-site and/or remote 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 be reflected in the Clinical Monitoring Plan.

The investigator will ensure that the monitor or other compliance or quality assurance reviewers are given access to all the above noted study-related documents and study related facilities (eg, pharmacy, diagnostic laboratory), and has adequate space to conduct the monitoring visit. If the monitoring visit is being conducted remotely, adequate precautions are to be taken to ensure the confidentiality of all study related documents.

10.7 Essential Documents Required Prior to Study Initiation

Prior to the start of the study, Investigator's and study site compliance with all pre-investigational requirements will be evaluated and confirmed based on the site essential documents. The list may include:

- Appropriate local health authority documentation properly signed and dated by the required Investigators (i.e., the submission package);
- Signed copy (original) of the approved protocol and Investigator's Brochure;
- Completed and signed statement of Investigator;
- Signed Clinical Trial Agreement;
- Curriculum vitae for the Investigator and sub-Investigators;
- IRB/IEC name and address; and membership list;
- Letter of approval from the IRB/IEC for both protocol (identified by protocol title and number), informed consent form (identified by protocol title and number) and other study related patient materials;
- Provisions for direct access to source/data documents if necessary for study-related monitoring, audits, IRB/IEC review and regulatory inspection.

Upon satisfactory receipt of all required regulatory documents, Sponsor will arrange that IP be delivered to each study site. Supply of all other study materials will be the responsibility of OPKO Pharmaceuticals, LLC and/or designee. Subject entry should not begin until after the required regulatory documents are confirmed as received and the Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of study protocol, instructions for eCRF completion, AE reporting and overall responsibilities including those for drug accountability and study file maintenance.

The investigator and/or designee or study monitor will prepare an investigator site file (ISF). This file should be used for all study related documents. The investigator will be responsible for keeping the ISF updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

10.8 Investigator Site File (ISF)

All documents required for the conduct of the study as specified in the ICH-GCP guidelines will be maintained by the Investigator in an orderly manner in the ISF and made available for monitoring and/or auditing by the Sponsor or designee, strategic partners and/or Regulatory Authorities.

10.9 Case Report Forms and Study Records

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 each investigative site on the EDC system and eCRFs. All eCRFs will be completed in a timely manner as data are available in the source for each subject. As EDC will

be utilized, instructions, training records, and a log will be maintained to identify the designated site personnel who can enter data and/or sign off on an eCRF.

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

All eCRFs should be completed within 2 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.

10.10 Protocol Deviations

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

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

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

Protocol deviations and associated handling of these will be described in a separate study plan.

Protocol deviations will be reported to the IRB as per IRB post-approval reporting requirements.

10.11 Data Generation and Analysis

The investigators are responsible for the accuracy, completeness, and timeliness of the data reported on the eCRF. Study data management, monitoring, statistical analysis, and reporting will be performed by the Data Manager 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.

10.12 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.

10.13 Financial Disclosure

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

10.14 Publication and Disclosure Policy

Data derived from the study are the exclusive property of OPKO Pharmaceuticals LLC. Any publication or presentation related to the study must be approved by OPKO Pharmaceuticals LLC in writing before submission of the manuscript.

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.

10.15 Final Report

A final study report will be developed at study closure. This report will comprise clinical and statistical integrated reports, according to the ICH E3 guidelines.

11 REFERENCE LIST

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APPENDIX 1. SCHEDULE OF EVENTS

	Screening and Randomization (Day-3 to 1)		Treatment Period (Days 1-28)								Follow-up (Days 29-42)	
	Visit 1			Visit 2		Visit 3		Visit 4		Visit 5 / ET		Visit 6[a]
	Days -3 to 0	Day 1[b]	Days 2-6[c]	Day 7 (± 2)	Days 8-13[c]	Day 14 (± 2)	Days 15-20[c]	Day 21 (± 2)	Days 22-27[c]	Day 28 (+ 2)	Days 29-41[c]	Day 42 (± 4)
Study Procedure	Screening	Randomization and initiation of treatment										
Informed Consent	X											
Inclusion/exclusion criteria	X											
Medical history and demographics	X											
Prior and concomitant medications	X			X		X		X		X		X
Adverse events				X		X		X		X		X
Physical examinations[d]	X									X		
Vital signs[e]	X			X		X		X		X		
ECG[f]	X					X				X		
Randomization[g]		X										

[a] Visit performed by telephone.
[b] Day 1 is considered to be the day on which the first loading dose is administered. Initial dosing may not necessarily coincide with the day on which randomization occurs if study drug is not received by the subject on the day of randomization.
[c] All assessments performed by subject at home.
[d] Brief physical exam.
[e] Blood pressure, heart and respiratory rate, temperature and oxygen saturation (pulse oximetry) will be measured and recorded after the subject has been sitting for at least 2 minutes prior to any scheduled blood draws at every visit. Height, weight and BMI at screening; weight and BMI at Visit 5.
[f] Subject will be referred to a Cardiologist in the event of QT-prolongation.
[g] Study drug will be shipped to the patient's home after confirmation of randomization or dispensed directly to subjects or hand-delivered by qualified site personnel for same day dispensing, as needed. Date of receipt is Day 1 (first dose).

	Screening and Randomization (Day-3 to 1)		Treatment Period (Days 1-28)								Follow-up (Days 29-42)	
	Visit 1			Visit 2		Visit 3		Visit 4		Visit 5 / ET		Visit 6[a]
	Days -3 to 0	Day 1[b]	Days 2-6[c]	Day 7 (± 2)	Days 8-13[c]	Day 14 (± 2)	Days 15-20[c]	Day 21 (± 2)	Days 22-27[c]	Day 28 (+ 2)	Days 29-41[c]	Day 42 (± 4)
Study Procedure	Screening	Randomization and initiation of treatment										
Training on study drug administration and diary reporting	X											
Diary instructions dispensed	X											
Study drug dispensed and shipped or hand delivered to subject		X										
Study drug administration - loading dose (self-administered)		X[h]	X[i]									
Study drug administration - maintenance dose (self-administered)			X[j]	X[j]	X[j]	X[j]	X[j]	X[j]	X[j]			
Subject self-assessment for severity of COVID-19 symptoms and QOL using the FLU-PRO Plus© questionnaire (diary)[k]	X	X	X	X	X	X	X	X	X	X	X	X

[h] Study drug (10 capsules) will be administered at bedtime after fasting for 3 hours. Subject must continue to fast for 3 hours after administration of study drug.
[i] Days 2 and 3 only. Study drug (10 capsules on each day) will be administered at bedtime after fasting for 3 hours. Subject must continue to fast for 3 hours after administration of study drug.
[j] Maintenance dose starting on Day 4 through Day 27 (2 capsules, unless otherwise directed, administered at bedtime after fasting for 3 hours. Subject must continue to fast for 3 hours after administration of study drug).
[k] Completed at Screening visit on site and thereafter once each day at bedtime (except Day 42 – once when subject wakes up).

	Screening and Randomization (Day-3 to 1)		Treatment Period (Days 1-28)								Follow-up (Days 29-42)	
	Visit 1			Visit 2		Visit 3		Visit 4		Visit 5 / ET		Visit 6[a]
	Days -3 to 0	Day 1[b]	Days 2-6[c]	Day 7 (± 2)	Days 8-13[c]	Day 14 (± 2)	Days 15-20[c]	Day 21 (± 2)	Days 22-27[c]	Day 28 (+ 2)	Days 29-41[c]	Day 42 (± 4)
Study Procedure	Screening	Randomization and initiation of treatment										
Study drug administration recorded in diary		X	X	X	X	X	X	X	X			
Study drug return and compliance review				X		X		X		X		
Diary review				X		X		X		X		X
Laboratory Assessments												
Hematology[l] and serum chemistry[m]	X			X		X		X		X		
Serum ß-hCG[n]	X			X		X		X		X		
Urine pregnancy test				X		X		X		X		
Biomarkers, PD and PK parameters[o]	X			X		X		X		X		

[l] Hematocrit, Hemoglobin, Platelet count, Red blood cell count, White blood cell count, Peripheral blood neutrophils, peripheral mononuclear monocytes.

[m] Albumin, Alkaline phosphatase, Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Blood urea nitrogen, Total calcium (corrected), Carbon dioxide, Chloride, Creatinine, Estimated glomerular filtration rate (eGFR) (calculated), Glucose, Lactate dehydrogenase, Magnesium, Phosphorus, Potassium, Sodium, Total bilirubin, Direct bilirubin, Total cholesterol, Total protein, Triglycerides, Uric acid.

[n] Performed at screening and at subsequent visits only following a positive urine pregnancy test result.

[o] [redacted] plasma iPTH and serum total 25D; [redacted].

APPENDIX 2. PACKAGE INSERT FOR RAYALDEE® (REV. APRIL 2021)

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

RAYALDEE® (calcifediol) extended-release capsules, for oral use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
RAYALDEE is a vitamin D_3 analog indicated for the treatment of secondary hyperparathyroidism in adults with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. (1)
Limitations of Use:
RAYALDEE is not indicated in patients with stage 5 chronic kidney disease or end-stage renal disease on dialysis. (1)

----------DOSAGE AND ADMINISTRATION----------
- The initial dose of **RAYALDEE** is 30 mcg administered orally once daily at bedtime. Serum calcium should be below 9.8 mg/dL before initiating treatment. (2)
- Monitor serum calcium, phosphorus, 25-hydroxyvitamin D and intact parathyroid hormone (PTH) 3 months after starting therapy or changing dose. (2.2, 5.3)
- Increase the dose to 60 mcg once daily after 3 months if intact PTH is above the treatment goal. Ensure serum calcium is below 9.8 mg/dL, phosphorus is below 5.5 mg/dL and 25-hydroxyvitamin D is below 100 ng/mL before increasing the dose. (2.2)
- Suspend dosing if intact PTH is persistently abnormally low, serum calcium is consistently above the normal range or serum 25-hydroxyvitamin D is consistently above 100 ng/mL. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Extended-release 30 mcg capsules (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- *Hypercalcemia:* Excessive administration of vitamin D compounds, including **RAYALDEE**, can cause hypercalcemia and hypercalciuria. Severe hypercalcemia due to substantial overdosage of vitamin D and its' metabolites may require emergency attention. Patients should be informed about the symptoms of elevated calcium. (5.1)
- *Digitalis toxicity:* Potentiated by hypercalcemia of any cause. Monitor serum calcium and signs and symptoms of digitalis toxicity more frequently when initiating or adjusting the dose of **RAYALDEE**. (5.2)
- *Adynamic Bone Disease:* Monitor for abnormally low levels of intact PTH levels when using **RAYALDEE**, and adjust dose if needed. (2.2, 5.3)

----------ADVERSE REACTIONS----------
The most common adverse reactions (≥3% and more frequent than placebo) were anemia, nasopharyngitis, increased blood creatinine, dyspnea, cough, congestive heart failure and constipation. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact OPKO Pharmaceuticals, LLC at 1-844-729-2539 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Co-administration of cytochrome P450 inhibitors, such as ketoconazole, may alter serum levels of calcifediol. (7.1)
- Co-administration of thiazides may cause hypercalcemia. (7.2)
- Cholestyramine may impair the absorption of calcifediol. (7.3)
- The half-life of calcifediol is reduced by drugs stimulating microsomal hydroxylation, such as phenobarbital or other anticonvulsants. (7.4)

----------USE IN SPECIFIC POPULATIONS----------
- Lactation: Monitor infants exposed to RAYALDEE through breast milk for seizures, vomiting, constipation and weight loss (8.2)

See 17 for PATIENT COUNSELING INFORMATION
Revised: 4/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

RAYALDEE is a vitamin D_3 analog indicated for the treatment of secondary hyperparathyroidism in adult patients with stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels less than 30 ng/mL.

Limitations of Use

RAYALDEE is not indicated for the treatment of secondary hyperparathyroidism in patients with stage 5 chronic kidney disease or in patients with end-stage renal disease on dialysis.

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosage and Administration Information

- Ensure serum calcium is below 9.8 mg/dL before initiating treatment [*see Warnings and Precautions (5.1)*].
- Instruct patients to swallow RAYALDEE capsules whole.
- Instruct patients to skip a missed dose and to resume taking the medicine at the next regularly scheduled time. Do not administer an extra dose.

2.2 Starting Dose and Dose Titration

- The initial dose of RAYALDEE is 30 mcg administered orally once daily at bedtime.
- The maintenance dose of RAYALDEE should target serum total 25-hydroxyvitamin D levels between 30 and 100 ng/mL, intact parathyroid hormone (PTH) levels within the desired therapeutic range, serum calcium (corrected for low albumin) within the normal range and serum phosphorus below 5.5 mg/dL.
- Monitor serum calcium, serum phosphorus, serum total 25-hydroxyvitamin D and intact PTH levels at a minimum of 3 months after initiation of therapy or dose adjustment, and subsequently at least every 6 to 12 months.
- Increase the dose to 60 mcg orally once daily at bedtime after approximately 3 months, if intact PTH remains above the desired therapeutic range. Prior to raising the dose, ensure serum calcium is below 9.8 mg/dL, serum phosphorus is below 5.5 mg/dL and serum total 25-hydroxyvitamin D is below 100 ng/mL.
- Suspend dosing if intact PTH is persistently and abnormally low to reduce the risk of adynamic bone disease [*see Warnings and Precautions (5.3)*], if serum calcium is consistently above the normal range to reduce the risk of hypercalcemia [*see Warnings and Precautions (5.1)*], or if serum total 25-hydroxyvitamin D is consistently above 100 ng/mL. Restart at a reduced dose after these laboratory values have normalized.

3 DOSAGE FORMS AND STRENGTHS

RAYALDEE 30 mcg extended-release capsules are blue oval soft capsules labeled with "O" in white ink.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Hypercalcemia

Hypercalcemia may occur during RAYALDEE treatment *[see Adverse Reactions (6.1)]*. Acute hypercalcemia may increase the risk of cardiac arrhythmias and seizures and may potentiate the effect of digitalis on the heart *[see Warnings and Precautions (5.2)]*. Chronic hypercalcemia can lead to generalized vascular calcification and other soft-tissue calcification. Severe hypercalcemia may require emergency attention.

Hypercalcemia may be exacerbated by concomitant administration of high doses of calcium containing preparations, thiazide diuretics, or other vitamin D compounds. In addition, high intake of calcium and phosphate concomitantly with vitamin D compounds may lead to hypercalciuria and hyperphosphatemia. In these circumstances, frequent serum calcium monitoring and RAYALDEE dose adjustments may be required. Patients with a history of hypercalcemia prior to initiating therapy with RAYALDEE should be monitored more frequently for possible hypercalcemia during therapy.

Patients should be informed about the symptoms of elevated serum calcium, which include feeling tired, difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination, and weight loss.

5.2 Digitalis Toxicity

Hypercalcemia of any cause, including RAYALDEE [*see Warnings and Precautions (5.1)*], increases the risk of digitalis toxicity. In patients using RAYALDEE concomitantly with digitalis compounds, monitor both serum calcium and patients for signs and symptoms of digitalis toxicity and increase the frequency of monitoring when initiating or adjusting the dose of RAYALDEE *[see Dosage and Administration (2)]*.

5.3 Adynamic Bone Disease

Adynamic bone disease with subsequent increased risk of fractures may develop if intact PTH levels are suppressed by RAYALDEE to abnormally low levels. Monitor intact PTH levels and adjust RAYALDEE dose, if needed *[see Dosage and Administration (2.2)]*.

6 ADVERSE REACTIONS

The following important adverse reactions are discussed in greater detail in other sections of the label:

- Hypercalcemia [*see Warnings and Precautions (5.1)*]

- Adynamic Bone Disease *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed cannot be directly compared to rates in other trials and may not reflect the rates observed in clinical practice.

The data in Table 1 are derived from two pivotal studies described below [*see Clinical Studies (14)*]. These data reflect exposure of 285 subjects to RAYALDEE 30 or 60 mcg daily for up to 6 months (mean 24 weeks, range 1 to 31 weeks). The mean age of the study population was 66 years old (range 25-85 years). Half of the subjects were male, 65% were White, and 32% were African-American or Black. At baseline, subjects had secondary hyperparathyroidism, stage 3 (52%) or 4 (48%) chronic kidney disease without macroalbuminuria and serum total 25-hydroxyvitamin D levels less than 30 ng/mL. The most common causes of chronic kidney disease were diabetes and hypertension and the mean estimated GFR at baseline was 31 mL/min/1.73m^2. At baseline, mean plasma intact PTH was 148 pg/mL, mean serum calcium was 9.2 mg/dL, mean serum phosphorus was 3.7 mg/dL and mean serum 25-hydroxyvitamin D was 20 ng/mL.

Table 1 shows common adverse reactions associated with the use of RAYALDEE in the pooled placebo-controlled trials. These adverse reactions were not present at baseline, occurred more commonly on RAYALDEE than on placebo, and occurred in at least 1.4% of patients treated with RAYALDEE.

Table 1. Common Adverse Reactions in Placebo-controlled Trials Reported in ≥1.4% of RAYALDEE-Treated Subjects

Adverse Reaction	Placebo N=144	RAYALDEE N=285
	%	%
Anemia	3.5	4.9
Nasopharyngitis	2.8	4.9
Blood creatinine increased	1.4	4.9
Dyspnea	2.8	4.2
Cough	2.1	3.5
Cardiac failure congestive	0.7	3.5
Constipation	2.8	3.2
Bronchitis	0.7	2.8
Hyperkalemia	0.7	2.5
Osteoarthritis	0.7	2.1
Hyperuricemia	0.7	1.8
Contusion	0.0	1.8
Pneumonia	0.7	1.4
Chronic obstructive pulmonary disease	0.0	1.4

Increase in Serum Calcium

Patients randomized to RAYALDEE experienced a greater mean (SE) increase in serum calcium (P<0.001) than patients randomized to placebo [i.e., 0.2 (0.02) mg/dL on RAYALDEE versus 0.1 (0.03) mg/dL on placebo from baseline to trial end]. Six subjects (2%) in the RAYALDEE treatment group and no subjects (0%) in the placebo group required dose reductions for protocol-defined hypercalcemia (two consecutive serum calcium values greater than 10.3 mg/dL). A total of 4.2% of RAYALDEE treated subjects and 2.1% of placebo treated subjects experienced at least one elevation in serum calcium above the upper limit of normal (10.5 mg/dL).

Increase in Serum Phosphorus

Patients randomized to RAYALDEE experienced a greater mean (SE) increase in serum phosphorus than patients randomized to placebo [i.e., 0.2 (0.03) mg/dL on RAYALDEE versus 0.1 (0.04) mg/dL on placebo from baseline to trial end]. One subject (0.4%) in the RAYALDEE treatment group met protocol-defined hyperphosphatemia (two consecutive serum phosphorus values greater than 5.5 mg/dL deemed to be study drug related) compared to no subjects in the placebo group. A total of 45% of RAYALDEE treated subjects and 44% of placebo treated subjects experienced at least one elevation in serum phosphorus above the upper limit of normal (4.5 mg/dL).

7 DRUG INTERACTIONS

7.1 CYP3A Inhibitors

Cytochrome P450 inhibitors, such as ketoconazole, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin or voriconazole, may inhibit enzymes involved in vitamin D metabolism (CYP24A1 and CYP27B1), and may alter serum levels of calcifediol. Dose adjustment of RAYALDEE may be required, and serum 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with a strong CYP3A4 inhibitor.

7.2 Thiazides

Thiazides are known to induce hypercalcemia by reducing excretion of calcium in the urine.

Concomitant administration of thiazides with RAYALDEE may cause hypercalcemia. Patients may require more frequent serum calcium monitoring in this setting *[see Warnings and Precautions (5.1)]*.

7.3 Cholestyramine

Cholestyramine has been reported to reduce intestinal absorption of fat-soluble vitamins and may impair the absorption of calcifediol, the active ingredient in RAYALDEE. Dose adjustment of RAYALDEE may be required, and serum total 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with cholestyramine.

7.4 Other Agents

Phenobarbital or other anticonvulsants or other compounds that stimulate microsomal hydroxylation reduce the half-life of calcifediol, the active ingredient in RAYALDEE. Dose adjustment of RAYALDEE may be required, and serum total 25-hydroxyvitamin D, intact PTH and serum calcium concentrations should be closely monitored if a patient initiates or discontinues therapy with phenobarbital or other anticonvulsants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no human data with calcifediol use in pregnant women to identify a drug-associated risk for major birth defects, miscarriage or adverse maternal or fetal outcomes. There are risks to the mother and fetus associated with chronic kidney disease in pregnancy *(see Clinical Considerations)*. In animal reproduction studies, calcifediol increased skeletal and soft tissue malformation when rabbits were given once daily oral doses representing ≥6 times the human dose of 60 mcg/day, based on body surface area (mg/m^2), during the period of organogenesis. No adverse developmental effects were observed in rats given up to 15 times the human dose, based on body surface area (mg/m^2), during organogenesis.

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

Clinical Considerations

Disease-associated maternal and/or embryo/fetal risk

Chronic kidney disease in pregnancy increases the maternal risk for hypertension, miscarriage, preterm labor, and preeclampsia. Chronic kidney disease increases the fetal risk for intrauterine growth restriction (IUGR), prematurity, polyhydramnios, still birth, and low birth weight.

Data

Animal Data

Calcifediol was given orally to pregnant rats and rabbits during the period of organogenesis (in rats, from gestation day [GD] 6 to 15; in rabbits, from GD 6 to 18). Rats were given 0, 12, 40, 60 mcg/kg/day; and rabbits were given 0, 5, 25, 50 mcg/kg/day, representing up to 15 and 13 times, respectively, a human dose of 60 mcg/kg, based on body surface area (mg/m^2).

In rats, no adverse developmental effects were observed at calcifediol doses up to 60 mcg/kg/day. In rabbits, increased incidences of domed skull, enlarged atrium of the heart, and dilatation of pulmonary artery, were observed at doses of 25 and 50 mcg/kg/day (representing 6 and 13 times the human dose of 60 mcg/day, respectively, based on body surface area (mg/m^2). Rats were given calcifediol during the pre/postnatal period (GD 15 to weaning). No adverse

effects on gestation, parturition, lactation or survival of offspring were observed at calcifediol doses up to 60 mcg/kg/day.

8.2 Lactation

Risk Summary

There is no information available on the presence of calcifediol in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production. Infants potentially exposed to calcifediol through breast milk should be monitored for signs and symptoms of hypercalcemia *(see Clinical Considerations)*. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RAYALDEE and any potential adverse effects on the breastfed child from RAYALDEE or from the underlying maternal condition.

Clinical Considerations

Monitor infants exposed to calcifediol through breast milk for signs and symptoms of hypercalcemia, including seizures, vomiting, constipation and weight loss. Consider monitoring of serum calcium in the infant.

8.4 Pediatric Use

The safety and efficacy of RAYALDEE have not been established in pediatric patients.

8.5 Geriatric Use

Of the total number of subjects in phase 3 placebo-controlled clinical studies of RAYALDEE, 63% were ≥65 years of age and 22% were ≥75 years of age. No overall differences in the safety or efficacy of RAYALDEE were observed between subjects older than 65 years and younger subjects.

8.6 Renal Impairment

No difference in efficacy was observed between patients with stage 3 chronic kidney disease or those with stage 4 disease in subgroup analysis. Safety outcomes were similar in these subgroups. The safety and efficacy of RAYALDEE in the treatment of secondary hyperparathyroidism in patients with stage 2 or stage 5 chronic kidney disease and patients with end-stage renal disease on dialysis have not been established [see *Indications and Usage (1)*].

10 OVERDOSAGE

Excessive administration of RAYALDEE can cause hypercalciuria, hypercalcemia, hyperphosphatemia, or oversuppression 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 RAYALDEE 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.

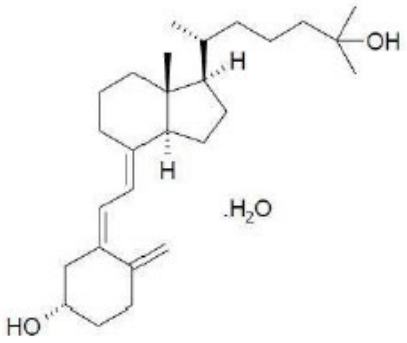
Discontinue supplemental calcium. Treat with standard medical care if persistent and markedly elevated serum calcium levels occur.

Calcifediol is not significantly removed by dialysis.

11 DESCRIPTION

Calcifediol, USP, the active ingredient in RAYALDEE, is synthetically manufactured as calcifediol monohydrate. Calcifediol is also known as calcidiol, 25-hydroxycholecalciferol or 25-hydroxyvitamin D_3.

Calcifediol monohydrate is a white crystalline powder, has a calculated molecular weight of 418.65 and is soluble in alcohol and fatty oils but practically insoluble in water. Chemically, calcifediol monohydrate is (3β,5Z,7E)-9,10-secocholesta-5,7,10(19)-triene-3,25-diol mono-hydrate and its structural formula is:



RAYALDEE is formulated as extended-release capsules containing 30 mcg of calcifediol. Each capsule contains the following excipients: mineral oil, monoglycerides and diglycerides, paraffin, hypromellose, lauroyl polyoxylglycerides, dehydrated alcohol and butylated hydroxytoluene. The capsule shells contain modified starch, carrageenan, sodium phosphate, dibasic, sorbitol sorbitan solution, FD&C Blue #1, titanium dioxide and purified water. Medium chain triglyceride (fractionated coconut) oil is used as a lubricant during manufacture, and trace amounts may be present in the final formulation.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Calcifediol (25-hydroxyvitamin D_3) is a prohormone of the active form of vitamin D_3, calcitriol (1,25-dihydroxyvitamin D_3). Calcifediol is converted to calcitriol by cytochrome P450 27B1 (CYP27B1), also called 1-alpha hydroxylase, primarily in the kidney. Calcitriol binds to the vitamin D receptor in target tissues and activates vitamin D responsive pathways that result in increased intestinal absorption of calcium and phosphorus and reduced parathyroid hormone synthesis.

12.2 Pharmacodynamics

In repeat-dose clinical studies with RAYALDEE, increased levels of serum total 25-hydroxyvitamin D were associated with corresponding increases in serum total

1,25-dihydroxyvitamin D concentrations and reductions in circulating plasma intact PTH observed within the first two weeks of RAYALDEE treatment *[see Clinical Studies (14)]*.

12.3 Pharmacokinetics

Absorption

No food effect study was conducted with 30 mcg and 60 mcg doses of RAYALDEE. However, a food effect study with a supratherapeutic dose of 450 mcg in healthy subjects showed an approximately 5-fold increase in maximum serum calcifediol concentration (C_{max}) and a 3.5-fold increase in AUC_{0-t} when RAYALDEE was administered with a high fat, high calorie meal compared to fasting.

Exposure to calcifediol increased proportionally over the dose range of 30 to 90 mcg following repeated daily administration of RAYALDEE at bedtime to subjects with secondary hyperparathyroidism, chronic kidney disease and vitamin D insufficiency. Steady-state levels of serum total 25-hydroxyvitamin D are reached after approximately 3 months *[see Clinical Studies (14)]*.

Distribution

Calcifediol is extensively bound to plasma proteins (>98%). The mean apparent volume of distribution is 8.8 L in healthy subjects following a single oral dose of RAYALDEE, and 30.1 L in subjects with stage 3 or 4 chronic kidney disease following repeated dosing.

Elimination

The mean elimination half-life of calcifediol is approximately 11 days in healthy individuals following a single dose of RAYALDEE, and approximately 25 days in patients with stage 3 or stage 4 chronic kidney disease following repeated once daily dosing.

Metabolism

Production of calcitriol from calcifediol is catalyzed by the 1-alpha-hydroxylase enzyme, CYP27B1, located in the kidney and other tissues. CYP24A1, located in all vitamin D-responsive tissues, catabolizes both calcifediol and calcitriol to inactive metabolites.

Excretion

Excretion of calcifediol occurs primarily through the biliary fecal route.

Specific Populations

Age, Gender and Race

Based on a population pharmacokinetic analysis, age, gender and race had no meaningful impact on steady-state concentrations of calcifediol following RAYALDEE administration.

Hepatic Impairment

The pharmacokinetics of RAYALDEE have not been investigated in patients with hepatic impairment.

Renal Impairment

Based on the population pharmacokinetics analysis, there was no meaningful difference in calcifediol steady-state concentrations following repeated RAYALDEE administration in patients with stage 3 or stage 4 chronic kidney disease.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No neoplastic changes attributable to calcifediol were observed at subcutaneous doses of 3, 10 and 33 mcg/kg/day in a 26-week rasH2 transgenic mouse study.

In vitro or in vivo mutagenicity studies have not been performed with RAYALDEE.

Calcifediol has not been shown to have significant effects on fertility in rats.

14 CLINICAL STUDIES

The efficacy and safety of RAYALDEE were evaluated in two identical multicenter, randomized, placebo-controlled, double-blind trials in patients with secondary hyperparathyroidism, stage 3 or 4 chronic kidney disease and serum total 25-hydroxyvitamin D levels between 10 and 30 ng/mL. Subjects were stratified by chronic kidney disease stage and randomized in a 2:1 ratio to receive RAYALDEE or a matching placebo at bedtime over 26 weeks. The dose of RAYALDEE was 30 mcg once daily for the first 12 weeks and either 30 or 60 mcg once daily for the last 14 weeks. The dose was increased to 60 mcg at the start of week 13 if the plasma intact PTH level was greater than 70 pg/mL, the serum 25-hydroxyvitamin D level was less than 65 ng/mL and the serum calcium level was less than 9.8 mg/dL.

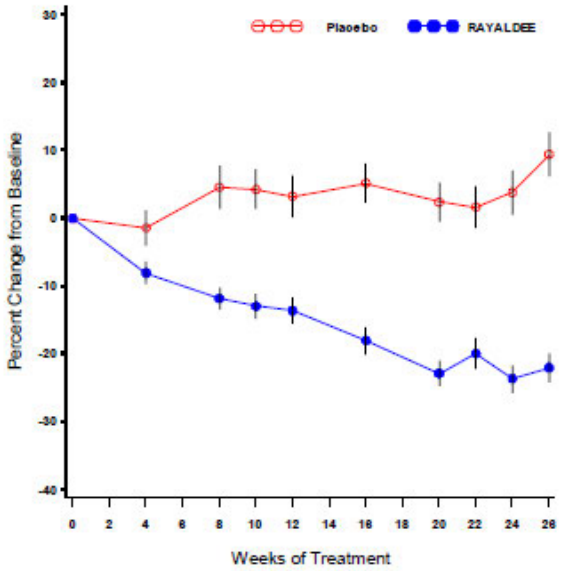
A total of 213 subjects were randomized in one trial (72 received placebo and 141 received RAYALDEE), and 216 subjects were randomized in the second trial (72 received placebo and 144 received RAYALDEE). The subjects' mean age was 66 years (range 25-85), 50% were male, 65% White, 32% African-American or Black and 3% Other. At baseline, subjects had secondary hyperparathyroidism, and stage 3 (52%) or stage 4 (48%) chronic kidney disease without macroalbuminuria. The most common causes of chronic kidney disease were diabetes and hypertension and the mean estimated GFR was 31 mL/min/1.73m^2. Mean baseline intact PTH was 130 pg/mL for subjects with stage 3 disease (n=222) and 166 pg/mL for subjects with stage 4 disease (n=207). Mean serum calcium was 9.2 mg/dL, mean serum phosphorus was 3.7 mg/dL and mean serum 25-hydroxyvitamin D was 20 ng/mL. Of the 429 subjects randomized, 354 (83%) completed the studies.

The primary analysis compared the proportion of individuals who experienced an at least 30% reduction in plasma intact PTH from baseline to end of trial (average of weeks 20, 22, 24 and 26). A larger proportion of patients randomized to RAYALDEE experienced an at least 30% reduction in plasma intact PTH from baseline compared to placebo in both trials [33% versus 8% in the first trial (P<0.001) and 34% versus 7% in the second trial (P<0.001)].

A description of mean (SE) percent change in plasma intact PTH from baseline across study visits in the two trials combined is shown in Figure 1. Serum total 25-hydroxyvitamin D levels increased to at least 30 ng/mL in 80% and 83% of subjects treated with RAYALDEE vs. 3% and 7% of subjects treated with placebo (P<0.001) in the two studies, respectively. Average steady-

state 25-hydroxyvitamin D levels were 50 and 56 ng/mL for subjects receiving 30 mcg daily, and 69 and 67 ng/mL for subjects receiving 60 mcg daily, in the first and second studies, respectively.

Figure 1. Mean (±SE) Percent Change from Baseline in Plasma Intact PTH in the Per Protocol Populations (Pooled Data from Two Phase 3 Studies)



The Per Protocol (PP) population consisted of all subjects with at least 2 intact PTH values in the calculated baseline and efficacy assessment period (EAP) values and who did not have a major protocol deviation during the treatment period of the study. The PP population comprised 83% of randomized subjects.

16 HOW SUPPLIED/STORAGE AND HANDLING

RAYALDEE is supplied as 30 mcg calcifediol in blue, oval extended-release capsules, imprinted O:

Bottles of 30 [*NDC 70301-1001-1*]

Bottles of 60 [*NDC 70301-1001-2*]

Store at 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F) [*see USP Controlled Room Temperature*].

17 PATIENT COUNSELING INFORMATION

- Tell patients to take RAYALDEE at bedtime and to swallow the capsules whole.
- Inform patients if they miss a dose, to take RAYALDEE at the next scheduled time. Do not take an extra dose to make up for the missed dose.
- Inform patients that they will need routine monitoring of laboratory parameters such as calcium, iPTH and total 25-hydroxyvitamin D while taking RAYALDEE.

- Advise patients to contact a health care provider if they develop symptoms of elevated calcium (e.g., feeling tired, having difficulty thinking clearly, loss of appetite, nausea, vomiting, constipation, increased thirst, increased urination or weight loss).
- Advise patients to inform their physician of all use of medications, including prescription and nonprescription drugs, supplements and herbal preparations, and of any changes in medical condition. Patients should also be advised to inform their physicians, when receiving a newly prescribed medication, that they are taking RAYALDEE.
- Inform lactating women about the need to monitor infants exposed to RAYALDEE through breast milk for signs of hypercalcemia to include seizures, vomiting, constipation and weight loss *[see Use in Specific Populations (8.2)]*.

RAYALDEE® is a registered trademark of EirGen Pharma Ltd.

Patent: https://www.opko.com/what-we-do/our-research/patents

Manufactured for:
OPKO Pharmaceuticals, LLC
4400 Biscayne Blvd.
Miami FL 33137 USA

APPENDIX 3. PATIENT REPORTED OUTCOMES

Participant ID: _____ Participant Initials:_____Date:____/____/____

FLU-PRO Plus®

People experience viral respiratory tract infections in different ways. We would like to know about the symptoms you have been experiencing during the past 24 hours. For each symptom, please mark one box ☐ under the response that best matches your experience. Mark [redacted] if you did not have that symptom in the past 24 hours.

What time is it?_____AM / PM (please circle)

Please rate the extent to which you had each symptom during the past 24 hours.

[redacted]

Runny or dripping nose
Congested or stuffy nose
Sinus pressure
Scratchy or itchy throat
Sore or painful throat
Difficulty swallowing
Teary or watery eyes
Sore or painful eyes
Eyes sensitive to light
Trouble breathing
Chest congestion
Chest tightness
Dry or hacking cough
Wet or loose cough
Felt nauseous (feeling like you wanted to throw-up)
Stomach ache
Felt dizzy
Head congestion
Headache

August 20, 2015 FLU-PRO Version 2.0

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Research Tool in Development: [redacted]

Participant ID: _____ Participant Initials:_____Date:____/____/____

Please rate the extent to which you had each symptom during the past 24 hours.

	[redacted]
Lack of appetite	
Sleeping more than usual	
Body aches or pains	
Weak or tired	
Chills or shivering	
Felt cold	
Felt hot	
Sweating	

In the past 24 hours, how often have you had any of the following symptoms?

	[redacted]
Sneezing	
Coughing	
Coughed up mucus or phlegm	

	[redacted]
How many times did you vomit?	
How many times did you have diarrhea?	

In the past 24 hours, did you have any of the following symptoms?

	[redacted]
Loss of smell	
Loss of taste	

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Research Tool in Development: [redacted]

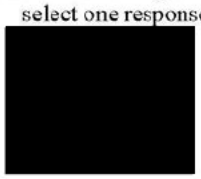
FLU-PRO^{c} GLOBAL ADDITIONAL DAILY DIARY ITEMS

Items to be asked in daily diary for the length of the study along with the FLU-PRO symptom items.

1. Overall, how severe were your infection symptoms today? (Please select one response only)

2. Overall, how were your infection symptoms today compared to yesterday? (Please select one response only)

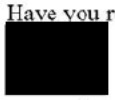
3. How much did your infection symptoms interfere with your usual activities today? (Please select one response only)



4. Have you returned to your usual activities today?

5. In general, how would you rate your physical health today? (Please select one response only)

6. Have you returned to your usual health today?



APPENDIX 4. INVESTIGATOR SIGNATURE

Study Title:	A Randomized, Double-Blind Placebo-Controlled Study to Evaluate the Safety and Efficacy of **R**ayaldee (calcifediol) **E**xtended-releas**e** **C**aps**u**l**e**s to Treat Symptomatic Patients Infected with SARS-CoV-2 (**REsCue**)
Study Number:	CTAP101-CL-2014
Final Date:	12 November 2021

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 Pharmaceuticals, LLC or its designee(s).

Not to implement any deviations from or changes to the protocol without agreement from the sponsor and prior review and the written approval from IRB/EC, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements).

That I am thoroughly familiar with the appropriate use of the investigational drugs, as described in this protocol, and any other information provided by the sponsor including, but not limited to, the following: the current Investigator's Brochure (IB) or equivalent document provided by OPKO Pharmaceuticals, LLC or its designee(s).

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

That I have been informed that certain regulatory authorities require the sponsor to obtain and supply details about the investigator's ownership interest in the sponsor or the study drug, and more generally about his/her financial ties with the sponsor. OPKO Pharmaceuticals, LLC will use and disclose the information solely for the purpose of complying with regulatory requirements.

Hence, I:

- Agree to supply OPKO Pharmaceuticals, LLC 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 Pharmaceuticals, LLC may disclose this information about such ownership interests and financial ties to regulatory authorities.

Signed:_____ Date:_____

Printed Name:_____

Signature Page for CTAP101-CL-2014 Protocol v8.0

Approval	[redacted] 14-Nov-2021 13:41:16 GMT+0000
Approval	[redacted] 33:01 GMT+0000
Approval	[redacted] 14-Nov-2021 21:33:27 GMT+0000
Approval	[redacted] 21 04:37:19 GMT+0000

Signature Page for RIM-CLIN-001501 v8.0