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)

OPKO Pharmaceuticals, LLC

STATISTICAL ANALYSIS PLAN

12 November 2021

(Version 2.0)

Prepared by: [redacted]

SIGNATURE PAGE

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By

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LIST OF ABBREVIATIONS/DEFINITIONS

[redacted]	[redacted]
[redacted]	[redacted]
25D	25-hydroxyvitamin D
[redacted]	[redacted]
[redacted]	[redacted]
AE	adverse event
[redacted]	[redacted]
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
[redacted]	[redacted]
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[redacted]	[redacted]
BMI	body mass index
[redacted]	[redacted]
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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
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[redacted]	[redacted]
ICF	Informed Consent Form
ITT	Intent-to-treat
ICH	International Council for Harmonisation
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IRB/EC	Institutional Review Board/Ethics Committee
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[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PP	per-protocol
PTH	parathyroid hormone
[redacted]	[redacted]
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
[redacted]	[redacted]
SOC	system organ class
[redacted]	[redacted]
TEAE	treatment-emergent adverse events
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1 INTRODUCTION/BACKGROUND

This statistical analysis plan (SAP) describes data analysis specifications for the CTAP101-CL-2014 protocol (version 8.0) entitled, "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)". The SAP follows the International Council on Harmonisation (ICH) Guidelines E3 and E9. All statistical analyses will be performed using SAS®, Version 9.4 or higher. In cases in which the analyses in this SAP differ from those in the study protocol, the analyses in the SAP supersede those in the protocol.

2 STUDY OBJECTIVES

2.1 Primary Objectives

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

- Attainment of serum total 25-hydroxyvitamin D (25D) levels at or above 50 ng/mL by Day 14; and,
- 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.

2.2 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 treatment 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 symptom score of ≤5 which is maintained for a minimum of three consecutive days.

2.3 Secondary Objectives

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

- 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;
- 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;
- Incidence of emergency room/urgent care visits;
- Incidence of oxygen saturation below 94% (or requirement for oxygen supplementation);
- Incidence and duration of hospitalizations;
- Incidence of requirement for mechanical ventilation;
- Mortality rate (as incidence);
- Severity and duration of COVID-19 illness as evidenced by quality-of-life measures using the FLU-PRO Plus© questionnaire; and,

- 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.

3 STUDY DESIGN

3.1 Overview

This is a phase 2 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 any FDA-approved diagnostic test. Subjects will be randomized to receive either oral Rayaldee (CTAP101 Capsules) or matching placebo. Approximately 80 subjects will be randomized in a blinded manner to each of the Rayaldee (CTAP101 Capsules) and placebo treatment groups, for a total of approximately 160 subjects.

3.2 Treatment Administration

Subjects will receive a loading dose (900 mcg Rayaldee or matching placebo) 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.

3.3 Sample Size Calculation

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 one-sided alpha of 0.025 based on a Chi-square test of the two groups.

Primary outcome #2 (severity of illness by selected five COVID-19 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.

4 ANALYSIS POPULATIONS

4.1 Intent-to-treat Population

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

4.2 Safety Population

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

4.3 Full Analysis Population

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.

4.4 Per-Protocol Population

The per-protocol (PP) set, 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.

4.5 Protocol Deviations

Protocol deviations are any intentional or unintentional changes from an Investigational Review Board (IRB) approved protocol that are not approved by the IRB prior to initiation of the change. All known protocol deviations are collected by electronic data capture (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. Detailed definitions of major protocol deviations are delineated in the "CTAP101-CL-2014 Study Protocol Deviation Plan." Upon completion of the study, any subject with a major protocol deviation prior to resolution of the aggregated five symptoms will be excluded from the PP population. All protocol deviations will be presented in by-subject listings, and subjects excluded from the PP population will be documented before database lock.

5 ENDPOINTS

5.1 Primary Safety Endpoints

The safety and tolerability of Rayaldee (CTAP101 Capsules) will be evaluated using the following assessments:

- Adverse Events;
- Physical Examinations;
- Vital Signs;
- Electrocardiograms; and,
- Hematology and Clinical Chemistries.

Special attention will be given to changes in serum total calcium (corrected for serum albumin), serum phosphorus, and estimated glomerular filtration rate (eGFR).

5.2 Primary Efficacy Endpoints

The primary efficacy endpoints are:

1. Attainment of serum total 25D levels ≥50 ng/mL, as assessed at Day 14.
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. 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 each domain 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.

   An aggregate score for the primary efficacy endpoint related to the selected five COVID-19 symptoms is deemed appropriate in view of the observed heterogeneity in COVID-19 symptom profiles. Not all subjects experience the same symptoms or degree of symptom severity. For example, some subjects experience trouble breathing but are free of dry or hacking cough. Others have no difficulty breathing but report chest congestion or coughing. This situation supports an argument against focusing on one or two symptoms, as a significant number of subjects may not have experienced those symptoms. It also supports an argument to use an aggregate score, since consideration of a larger number of symptoms makes the endpoint applicable to a larger number of subjects. Based on analysis of blinded data obtained from the study, more than 92% of subjects who received at least one dose of study drug had an aggregate symptom score higher than 5 at baseline (Day 0). The main reason why a few subjects do not have an aggregate baseline score higher than 5 is that they get well rather quickly, even before starting study drug. Such subjects will be excluded from the FAS.

The time to resolution is defined as the number of days from Day 1 (study drug initiation) to the first day of achieving the ≤5 score for a minimum of three consecutive days. 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 longer than 5 days) later even if no score has been recorded between the two days.

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.

5.3 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% (or requirement for 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 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 an electronic diary using FLU-PRO© Plus questionnaire.

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

6 STATISTICAL METHODOLOGY AND ANALYSES

6.1 General Considerations

All analyses will be performed using SAS® Version 9.4 or higher. All data collected on eCRFs, diaries (from ePRO), and from clinical laboratory evaluations will be grouped and listed by treatment 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 number and 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, and geometric means will be reported with two significant figures more than the reported values. Median, 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 treatment 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 most 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 cannot be resolved, then the arithmetic mean of the results will 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.

6.2 Handling of Missing Values

For the primary efficacy 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 the targeted serum 25D levels. For the time-to-event primary efficacy endpoint based on aggregate 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 5.2 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 individual 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 5.2 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 generally 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 are instructed to report any symptoms that recur after resolution.

If responder status is not determinable for subjects 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 likely not 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, as defined in Section 5.2.

The number of days with missing FLU-PRO Plus© questionnaires per subject will be summarized as the total number of missing as well as the number missing before and after resolution.

Adverse events (AEs) with missing onset date will be treated as treatment-emergent adverse events (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 definitely 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.

6.3 Interim Analyses, Final Analyses, and Unblinding

No formal interim analysis is planned for this 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).

The final analysis will occur after the database has been locked and the data are unblinded.

Unblinded site-specific raw data will be shared with each participating clinical site within 3 months after the clinical study report is finalized.

6.4 Pooling of Sites

Data will be pooled and analyzed across sites. Each site will follow the same protocol, will receive the same training, and will have consistent monitoring and data collection.

6.5 Treatment Compliance and Extent of Exposure

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 by the oral route. On Days 4-27, subjects will take a maintenance dose of 2 capsules (60 mcg) per day at bedtime unless otherwise directed. Extent of exposure will be assessed as the total dosage of Rayaldee (CTAP101 Capsules) received.

Study treatment compliance during the treatment period will be assessed via a patient diary and in person at all specified visits. Treatment compliance (%) will be calculated as the number of capsules that should have been taken versus the actual number taken, as evidenced by dosing records. 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. Treatment compliance and extent of exposure will be listed by subject and summarized by treatment group.

6.6 Subject Disposition

Subject disposition will be tabulated and descriptively summarized for all randomized subjects by treatment group and overall. The primary reason for premature study discontinuation will be detailed together with the number and proportions of subjects discontinuing for each reason.

6.7 Demographic and Baseline Characteristics

For each analysis population, baseline subject characteristics including age, sex, race, ethnicity, height, weight, body mass index (BMI) and eGFR will be summarized by study arm (CTAP101 Capsules and placebo). 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.

6.8 Prior and Concomitant Medications

Prior medications are defined as any continuing or new medication used within 12 weeks and discontinued before initiation of treatment on Day 1. Concomitant medications are defined as any continuing or new medication taken after treatment initiation on Day 1 or anytime thereafter until the end of the study. World Health Organization Drug Dictionary (WHODrug) 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 treatment 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.

6.9 Safety Analyses

All subjects in the Safety population will be included in the safety analysis. Statistical summary analysis of safety data will be descriptive and performed by treatment group. 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.

6.9.1 Adverse Events

All AEs will be collected on the eCRF and coded via system organ class (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. 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 treatment 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 treatment 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 treatment 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.

6.9.2 Physical Examinations

A brief physical examination will be performed at the screening (Visit 1) and at Visit 5/ET. Any results that are clinically significant will be reported on the MH/AE page of the CRF as appropriate. The number and percentage of subjects with transitions from normal at Screening to

clinically significant at Visit 5/ET will be presented by treatment group. A listing of physical examination data for all subjects will also be provided.

6.9.3 Vital Signs

Height, weight and BMI determinations will be recorded at Screening (Visit 1) and body weight and BMI (using screening height) at the end of the treatment period (Visit 5/ET). Observed vital sign values will be summarized descriptively by treatment group at Screening (Visit 1) and at each post-screening assessment. Changes from screening will also be included in this summarization. Summaries will include n (%), mean, SD, median, minimum, and maximum. A listing of all vital sign values will be presented by subject.

6.9.4 Electrocardiograms

Electrocardiograms (ECGs) will be performed at Screening (Visit 1), Visit 3 and Visit 5/ET. The number and proportion of subjects with overall assessments of Normal and Abnormal, as well as those assessments judged to be clinically significant will be tabulated at each visit by treatment group. Shifts in overall assessment (No Change, Normal to Abnormal, and Abnormal to Normal) from screening to each post-screening visit will also be tabulated along with a determination of clinical significance.

Other quantitative ECG parameter results will be summarized descriptively by treatment group at screening and at any subsequent visits (Visits 3 and/or 5). Changes from screening will also be included in this summarization. Summaries will include n (%), mean, SD, median, minimum, and maximum. A listing of all ECG results will be presented by subject.

6.9.5 Safety Laboratory Parameters

Descriptive statistics for clinical laboratory values and changes from baseline at each assessment time point will be presented by treatment group for each clinical laboratory parameter. Special attention will be given to changes in serum total calcium (corrected for serum albumin), serum phosphorus, and eGFR.

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

A listing of all laboratory results will be presented by subject.

6.10 Efficacy Analyses

6.10.1 Primary Efficacy 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 number of days to resolution of symptoms, defined as a reduction in the aggregate FLU-PRO Plus© score for the selected five COVID-19 symptoms recorded on Day 0 (prior to study drug initiation) 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 (study drug initiation) 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 6.2. 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 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), 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 FLU-PRO Plus© score >5 for a minimum of three consecutive days.

6.10.2 Secondary Efficacy Endpoints

The following secondary endpoints will 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 (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% (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 the 34 individual symptoms assessed by the FLU-PRO Plus© questionnaire, a 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 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]

7 REVISION HISTORY

Version	Date (dd-mmm-yyyy)	Summary of Changes
1.0	04-Aug-2021	Original.
[redacted]	[redacted]	[redacted]

		[redacted]

8 TABLES, LISTINGS AND FIGURES

8.1 List of Tables

The Tables to be generated include, but not limited to the following:

CONDUCT OF STUDY

14.1.1	Disposition of Subjects: All Enrolled Subjects
14.1.1.1	Major Protocol Deviations: Full Analysis Population
14.1.2.1	Demographics and Baseline Characteristics: Intent-to-Treat Population
14.1.2.2	Demographics and Baseline Characteristics: Full Analysis Population
14.1.2.3	Demographics and Baseline Characteristics: Per Protocol Population
14.1.2.4	Demographics and Baseline Characteristics: Safety Population
14.1.3	Prior and Concomitant Medications by ATC Level 2 and Preferred Term: Safety Population

PRIMARY EFFICACY ENDPOINTS

14.2.1.1	Attainment of Serum 25D Levels >=50 ng/mL by Visit: Full Analysis Population
14.2.1.2	Attainment of Serum 25D Levels >=50 ng/mL by Visit: Per Protocol Population
14.2.1.3	Attainment of Serum 25D Levels >=50 ng/mL by Visit and by Subgroups: Full Analysis Population
14.2.1.4	Attainment of Serum 25D Levels >=50 ng/mL by Visit and by Subgroups: Per Protocol Population
14.2.1.5	Time to Resolution of COVID-19 Symptoms Based on FLU-PRO Plus COVID-19 Five Symptom Aggregate Score: Full Analysis Population
14.2.1.6	Time to Resolution of COVID-19 Symptoms Based on FLU-PRO Plus COVID-19 Five Symptom Aggregate Score: Per Protocol Population
14.2.1.7	Time to Resolution of COVID-19 Symptoms Based on FLU-PRO Plus COVID-19 Five Symptom Aggregate Score - Cox Proportional Hazards Model Summary of Effects: Full Analysis Population
14.2.1.8	Time to Resolution of COVID-19 Symptoms Based on FLU-PRO Plus COVID-19 Five Symptom Aggregate Score - Cox Proportional Hazards Model Summary of Effects: Per Protocol Population
14.2.1.9	Tipping Point Analysis for Time to Resolution of COVID-19 Symptoms Based on FLU-PRO Plus COVID-19 Five Symptom Aggregate Score: Full Analysis Population
14.2.1.10	Tipping Point Analysis for Time to Resolution of COVID-19 Symptoms Based on FLU-PRO Plus COVID-19 Five Symptom Aggregate Score: Per Protocol Population
14.2.1.11	Time to Resolution of COVID-19 Symptoms Based on FLU-PRO Plus COVID-19 Five Symptom Aggregate Score by Subgroups: Full Analysis Population
14.2.1.12	Time to Resolution of COVID-19 Symptoms Based on FLU-PRO Plus COVID-19 Five Symptom Aggregate Score by Subgroups: Per Protocol Population

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SAFETY OUTPUTS

14.3.1.1	Overall Summary of Subjects with Treatment-Emergent Adverse Events: Safety Population
14.3.1.2	Incidence of Treatment-Emergent Adverse Events by SOC and Preferred Term: Safety Population
14.3.1.3	Incidence of Serious Treatment-Emergent Adverse Events by SOC and Preferred Term: Safety Population
14.3.1.4	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation of Study by System Organ Class and Preferred Term: Safety Population
14.3.1.5	Incidence of Treatment-Emergent Adverse Events Leading to Discontinuation of Treatment by System Organ Class and Preferred Term: Safety Population
14.3.1.6	Incidence of Treatment-Emergent Adverse Events Definitely Related to Study Drug by SOC and Preferred Term: Safety Population
14.3.1.7	Incidence of Treatment-Emergent Adverse Events Probably Related to Study Drug by SOC and Preferred Term: Safety Population
14.3.1.8	Incidence of Treatment-Emergent Adverse Events Possibly Related to Study Drug by SOC and Preferred Term: Safety Population
14.3.1.9	Incidence of Treatment-Emergent Adverse Events Unrelated to Study Drug by SOC and Preferred Term: Safety Population
14.3.1.10	Incidence of Mild Treatment-Emergent Adverse Events by SOC and Preferred Term: Safety Population
14.3.1.11	Incidence of Moderate Treatment-Emergent Adverse Events by SOC and Preferred Term: Safety Population
14.3.1.12	Incidence of Severe Treatment-Emergent Adverse Events by SOC and Preferred Term: Safety Population
14.4.1	Subjects with Physical Examination Shift from Normal at Screening to Clinically Significant at End of Trial: Safety Population
14.4.2	Vital Sign Results and Change from Baseline to Each Visit: Safety Population
14.4.3.1	ECG Interpretation and Shifts from Screening to Each Visit: Safety Population
14.4.3.2	ECG Results at Each Visit and Change from Baseline: Safety Population
14.4.4.1	Hematology Results at Each Visit and Change from Baseline: Safety Population
14.4.4.2	Serum Chemistry Results at Each Visit and Change from Baseline: Safety Population
14.4.4.3	Incidence of Hypercalcemia and Hyperphosphatemia Overall and at Each Visit: Safety Population

TREATMENT COMPLIANCE

14.5	Treatment Compliance and Extent of Exposure: Full Analysis Population

8.2 List of Listings

To be added to support Table presentations

8.3 List of Figures

To be added to support Table presentations

Signature Page for Statistical Analysis Plan_CTAP101-CL-2014_V2.0_0024 v3.0

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