Statistical Analysis Plan

A Phase 2, Double-blind, Placebo-controlled, Efficacy, and Safety Study of APX-115 in Hospitalized Patients with Confirmed Mild to Moderate COVID-19

Statistical Analysis Plan: Final

Statistical Analysis Plan: 2.0
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Investigational Product: APX-115

Protocol Reference: A01-115-03
Labcorp Study ID: 000000212172
Sponsor: Aptabio Therapeutics Inc.

[redacted]

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Glossary of Abbreviations

Abbreviation	Term
AE	Adverse Event
AESI	AE of Special Interest
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	Below the Lower Limit of Quantification
BMI	Body Mass Index
BP	Blood Pressure
CI	Confidence Interval
CRF	Case Report Form
CT	computed tomography
COVID-19	Coronavirus Disease of 2019
CV	Coefficient of Variation
DB	Double-Blind
DBP	Diastolic BP
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EOS	end of study
EOT	end of treatment
ePRO	electronic patient-reported outcome
ET	early termination (from treatment)
EW	early withdrawal (from study)
FAS	Full Analysis Set

Abbreviation	Term
FDA	Food and Drug Administration
GGT	Gamma-Glutamyl Transferase
ICF	informed consent form
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LS	Least Squares
NC	Not Calculated
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for AEs
NR	No Results
PCI	Potentially Clinically Important
PCR	polymerase chain reaction
PK	Pharmacokinetic
PT	Preferred Term
QD	once daily
QTcB	Bazett corrected QT interval
QTcF	Fridericia corrected QT interval
RBC	Red Blood Cell
RT	reverse transcription
SAE	Serious AE
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SBP	Systolic BP
SD	Standard Deviation
SI	International System of Units
SpO2	Oxygen saturation
SOC	System Organ Class
SoC	standard of care
TFLs	Tables, Figures and Listings
TEAE	Treatment Emergent AEs
ULN	Upper Limit of Normal
WBC	White Blood Cell
WHO	World Health Organization

1. Source Documents

The SAP was written based on the following documentation:

Document	Date	Version
Protocol	05 May 2021	3.0
eCRF	24 August 2021	1.0

2. Protocol Details

2.1. Overall Study Design

This will be a Phase 2, randomized, double-blind, placebo-controlled, multicenter, efficacy, and safety study in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19. Pharmacokinetic assessment will be performed in a subset of 20 patients.

The study will consist of a sentinel cohort of 30 patients (15 patients on active drug and 15 patients on placebo) and an expansion cohort of approximately 50 patients (in a 1:1 ratio of APX-115 or placebo). Enrollment will pause after the 30th patient in the sentinel cohort has been enrolled and started treatment, until the results of the interim analysis are known. Once either 25 patients have recovered, or the 30th patient in the sentinel cohort has completed 14 days of treatment, an unblinded Data Monitoring Committee (DMC) will assess the safety, tolerability, efficacy, and PK [redacted] once daily (QD) APX-115 in COVID-19 patients in the sentinel cohort. The DMC will issue a recommendation to enroll patients for the expansion cohort, or to stop the study depending on the safety and futility assessment. The DMC will continue to review safety and assess the risk/benefit profile on an ongoing basis. A DMC Charter, which includes detailed processes, will be prepared prior to start of patient enrollment.

Informed consent must be obtained from all patients or their legally authorized representative during screening (up to 4 days, maximum, before dosing) and before any study-related procedures are performed.

Approximately 12 sites in the United States, and other countries based on the pandemic situation, are planned to enroll patients.

Patients will be randomized within 14 days after a laboratory-confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection as determined by real time reverse transcription (RT)-polymerase chain reaction (PCR) or other commercial or public health assay authorized by Food and Drug Administration (FDA) or other applicable health authority. Patients need to have at least one symptom of COVID-19 (fever, cough, shortness of breath, myalgia [muscle or body aches], ageusia [loss of taste], anosmia [loss of smell], fatigue, or weakness) at screening.

Patients will receive an oral dose [redacted] of APX-115 or placebo capsules QD for 14 consecutive days. Patients will undergo assessments during hospitalization or could be discharged after the start of study treatment as early as Day 2 if judged to be ready for discharge. Eligible patients must be in hospital for at least 24 hours after start of study treatment. If discharged, patients will then be requested to take study treatment at home (as prescribed) up to and including Day 14. Study drug will be administered in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed, on Days 1 to 14.

If the patient has already been discharged, a telephone or digital media visit will be conducted on days for which no laboratory assessments are required (Days 3, 10, 22, 29, and 60) and an at-home or an on-site visit will be required on days requiring laboratory assessments (Days 5 and 14).

Allowable windows for scheduling of study visits are -1 day for Day 3, ±1 day for Day 5, and ±2 days for Days 10, 22, 29, and 60. The Day 14 visit may be scheduled up to 2 days past the actual Day 14 date; however, dose administration will end at Day 14.

Symptoms will be documented daily through Day 60 using an electronic patient-reported outcome (ePRO) instrument based on the September 2020 FDA guidance for assessing COVID-19-related symptoms. All patients will be closely monitored for adverse events (AEs) from informed consent through Day 60, and followed for safety assessments through Day 60. SARS-CoV-2 viral loads will be obtained by [redacted] self-collection at baseline (Day 1) and Days 5 and 14. Any new infections that occur in the study, regardless of organism (i.e., viral or non-viral), will be captured. Additionally, the site of infection and source of culture (bronchoalveolar lavage, tracheal aspirate, sputum, blood, urine, etc.) will also be recorded.

Oxygen saturation (SpO2) will be collected daily in the hospital or self-collected daily upon discharge until end of study using ePRO. Clinical improvement based on the World Health Organization (WHO) Clinical Improvement Ordinal Scale (9-point scale) will be documented based on scores obtained daily while hospitalized, the day after hospital discharge via telephone contact with the patient, at the scheduled visit(s) after hospital discharge, and if the patient is readmitted to the hospital or dies.

Blood samples for analysis of APX-115 in plasma will be collected from 20 patients at prespecified timepoints in hospitalized patients only.

Study procedures are detailed in the Schedule of Assessments (as detailed in Appendix 2). The total duration of study participation for each patient (from screening through EOS/early withdrawal [EW] visit) is anticipated to be approximately 64 days.

The start of the study is defined as the date the first patient (or their legally authorized representative) signs an informed consent form (ICF). The point of enrollment occurs at the time of patient number allocation. The end of the study is defined as the date of the last visit of the last patient in the study.

[redacted]

2.2. Study Objectives

2.2.1. Primary Objective

The primary objective of the study is:

- to assess the safety and tolerability of APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19.

2.2.2. Secondary Objectives

The secondary objectives of the study are:

- to evaluate the efficacy of APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19
- to assess the PK of APX-115 in a subset of 20 patients.

2.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- to evaluate the response of biomarkers to APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19
- to evaluate change from baseline in viral load and rate of switch to other treatments.

2.3. Sample Size and Power

The study does not test a formal hypothesis and instead uses descriptive statistics to summarize the data. Therefore, the sample size was not determined based on formal

statistical power calculations but using clinical considerations to provide a reasonable clinical database to assess safety and efficacy in COVID-19 patients. However, the ability of the study to identify a potentially promising treatment was assessed by considering that further study would likely be dependent on observing at least a numeric trend towards benefit of the treatment. On the key secondary endpoint of time to clinical recovery, a sample size of 80 patients provides 91% power to ensure that the outcome is numerically in favor of treatment if the true treatment effect is a hazard ratio of 1.4. [redacted]

2.4. Primary Endpoints

The primary endpoints are safety and tolerability endpoints including clinical laboratory evaluations, vital signs, electrocardiogram (ECG), and adverse event (AE) reporting over the 60-day period.

2.5. Secondary Endpoints

The secondary endpoints are:

- time to clinical recovery monitored over 28 days. Clinical recovery is defined as occurring when the World Health Organization (WHO) Clinical Improvement Ordinal Scale is no higher than 3 for baseline WHO scale greater than 3 or no greater than 2 for baseline score of 3. The time to recovery will be taken as the time from randomization until the first day that the patient meets the definition of recovery. Patients who die or do not meet the definition of recovery 28 days after randomization will be considered not recovered.
    - patients who relapse will be included in the analysis as the first day of the last period in which they score no higher than 3, and sustain that status until the end of the 28 days
    - the justification for using data up to 28 days is that although the WHO Clinical Improvement Scale will be collected up to Day 60, it is anticipated that recoveries past Day 29 (i.e., more than 14 days after the end of treatment) are unlikely to be caused by study treatment. Therefore, key analyses will consider only time up to Day 29, and analysis of later recoveries may be investigated and described in the statistical analysis plan.
    - patients who score 3 or lower at the start of the study will be included in the analysis, and if they never require oxygen, will be considered to have never required oxygen therapy altogether and will therefore have met the endpoint on Day 1. Other analyses will address alternative definitions of recovery, including time to discharge.
- time to discharge, defined in the same way as clinical recovery, but occurring when the WHO Clinical Improvement Ordinal Scale is no higher than 2.

- time to symptomatic recovery, defined in the same way as clinical recovery, but occurring when none of the COVID-19 Symptom Assessment scores are higher than 1.
- time to complete symptomatic recovery, defined in the same way as clinical recovery, but occurring when none of the COVID-19 Symptom Assessment scores are higher than 0.
- proportion of patients in clinical recovery on key analysis days. Patients who die will be considered as not being in clinical recovery.
- scoring of WHO Clinical Improvement Ordinal Scale (9-point scale) on key analysis days for levels ≥3. Patients who die will be included in the analysis.
- number of days at or above each level of the WHO Clinical Improvement Ordinal Scale (9-point scale) on key analysis days for levels ≥3. Patients who die will be included in the analysis as scoring the maximum score on every day after death until Day 29.
- proportion of patients whose maximum score is at or above each level of the WHO Clinical Improvement Ordinal Scale on key analysis days, for levels ≥3.
- mortality by each of the key analysis days.
- change from baseline in oxygen saturation (SpO2)
- PK parameters to be assessed from plasma samples (subset of patients only),

2.6. Exploratory Endpoints

3. Estimands

The ICH[1] E9 (R1) addendum on estimands[2] and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials came into effect on 30 July 2020. This section addresses the construction of estimands for the primary and secondary objectives. Each estimand is defined according to the following five attributes:

1) The **treatment** condition of interest, and as appropriate, the alternative condition to which comparison will be made.
2) The **population** of patients targeted by the clinical question.
3) The **variable** (or endpoint) to be obtained for each subject that is required to address the clinical question.
4) The clinical question of interest in respect of **other intercurrent events** not covered through the precise specifications of treatment, population and variable.
5) A **population-level summary** for the variable providing a basis for comparison between treatment conditions.

3.1. Estimands for the primary objective

The main estimand is defined through the following five attributes:

3.1.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.1.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 as well as receiving at least 1 dose of APX-115 or placebo (i.e., Safety Population).

3.1.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variables to address the clinical question are as follows:

- Occurrence of at least one adverse event of specific type over the 60-day period.
- Test values and change from baseline values at protocol specified timepoints for clinical laboratory evaluations, ECG, and vital signs.
- Shift from baseline values at protocol specified timepoints for clinical laboratory evaluations, ECG, and vital signs.

3.1.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.1.5. Population-level Summary for Comparison between Treatment Conditions

- Numbers and percentages of patients with at least one adverse event of specific type over the 60-day period.
- Mean test values and mean change from baseline values at protocol specified timepoints for clinical laboratory evaluations, ECG, and vital signs.
- Numbers and percentages of shifting from baseline values at protocol specified timepoints for clinical laboratory evaluations, ECG, and vital signs.

No formal statistical comparison analysis will be performed for any safety data.

3.2. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.2.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.2.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.2.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is time to clinical recovery monitored over 28 days.

3.2.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.2.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the stratified hazard ratio comparing the hazard rate for APX-115 active doses to the hazard rate for placebo.

3.3. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.3.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.3.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.3.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is time to discharge monitored over 28 days.

3.3.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]

3.3.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the stratified hazard ratio comparing the hazard rate for APX-115 active doses to the hazard rate for placebo.

3.4. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.4.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.4.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.4.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is time to symptomatic recovery monitored over 28 days.

3.4.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Having any important protocol deviations
- Discontinuation of investigative product
- Death
- Receiving another antiviral therapy
- Having not been discharged from hospital

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.4.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the stratified hazard ratio comparing the hazard rate for APX-115 active doses to the hazard rate for placebo.

3.5. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.5.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose[redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.5.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.5.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is time to complete symptomatic recovery monitored over 28 days.

3.5.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Having any important protocol deviations
- Discontinuation of investigative product
- Death
- Receiving another antiviral therapy
- Having not been discharged from hospital

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.5.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the stratified hazard ratio comparing the hazard rate for APX-115 active doses to the hazard rate for placebo.

3.6. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.6.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.6.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.6.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is proportion of patients in clinical recovery on key analysis days (i.e., Day 3, 5, 10, 14, 29, and 60).

3.6.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.6.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the odds ratio comparing the odds of achieving response on APX-115 active doses compared to the odds of achieving response on placebo.

3.7. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.7.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.7.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.7.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is scoring of WHO Clinical Improvement Ordinal Scale (9-point scale) on key analysis days for levels ≥3 on key analysis days (i.e., Day 3, 5, 10, 14, 29, and 60).

3.7.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.7.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the odds ratio comparing the odds of achieving response on APX-115 active doses compared to the odds of achieving response on placebo.

3.8. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.8.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.8.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.8.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is number of days at or above each level of the WHO Clinical Improvement Ordinal Scale (9-point scale) for levels ≥3 on key analysis days (i.e., Day 3, 5, 10, 14, 29, and 60).

3.8.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.8.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the comparison of estimated Least Squares (LS) means of number of days at or above each level of the WHO Clinical Improvement Ordinal Scale (9-point scale) for levels ≥3 at each analysis day supported by the estimated difference in LS means of APX-115 active doses compared to placebo at each analysis day.

3.9. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.9.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.9.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.9.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is proportion of patients whose maximum score is at or above each level of the WHO Clinical Improvement Ordinal Scale (9-point scale) for levels ≥3 on key analysis days (i.e., Day 3, 5, 10, 14, 29, and 60).

3.9.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.9.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the odds ratio comparing the odds of achieving response on APX-115 active doses compared to the odds of achieving response on placebo.

3.10. Estimand for the secondary objectives

The main estimand is defined through the following five attributes:

3.10.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.10.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.10.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is mortality by each key analysis day (i.e., Day 3, 5, 10, 14, 29, and 60).

3.10.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.10.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the odds ratio comparing the odds of achieving response on APX-115 active doses compared to the odds of achieving response on placebo.

3.11. Estimands for the secondary objectives

The main estimand is defined through the following five attributes:

3.11.1. Treatment Condition of Interest

The primary treatment condition of interest is an oral dose [redacted] of APX-115 capsules administered daily for 14 consecutive days and is compared against the alternative treatment condition of an oral dose of matching placebo capsules administered daily for 14 consecutive days.

3.11.2. Population of Subjects Targeted by the Clinical Question

The population targeted by the clinical question is defined through the inclusion and exclusion criteria as part of the clinical trial protocol version 3.0 (i.e., Intent-to-Treat Population).

3.11.3. Variable Obtained from Each Subject Required to Address the Clinical Question

For each patient in the study, the variable to address the clinical question is Change from baseline in SpO2 at each key analysis day (i.e., Day 3, 5, 10, 14, 29, and 60) and on average.

3.11.4. Handling of Intercurrent Events to Reflect the Clinical Question of Interest

The following intercurrent events are anticipated during the study:

- Receiving any alternative therapies
- Having any important protocol deviations
- Discontinuation of investigative product
- Death

[redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

3.11.5. Population-level Summary for Comparison between Treatment Conditions

The treatment effect will be quantified by the comparison of estimated LS means of change from baseline in SpO2 at each key analysis day and on average supported by the estimated difference in LS means of APX-115 active doses compared to placebo at each key analysis day and on average.

4. Analysis Populations

In accordance with ICH E3 and E9[3], the following analysis sets will be used for the analyses.

4.1. All Screened Population

The All Screened Population will include every patient who has signed the informed consent form. The All Screened Population will be used for summaries of disposition and the associated listing.

4.2. Intent-to-Treat Population

The Intent-to-Treat Population will include all randomized patients. Participant data will be summarized by treatment assigned.

4.3. Safety Population

The Safety Population will include all patients who received at least 1 dose of APX-115 or placebo. Participant data will be summarized by actual treatment received.

4.4. Pharmacokinetic Population

The Pharmacokinetic (PK) Population will include a subset of 20 patients who receive at least 1 dose of APX-115 and have at least 1 evaluable plasma concentration without important protocol deviations or events thought to significantly affect the PK. PK Population patients will be analyzed according to their actual treatment received.

4.5. Special Subpopulations

[redacted]

5. Data Handling

5.1. Time Points and Visit Windows

5.1.1. General Definitions

All assessment days will be related to the first day of first dose of study treatment.

Day 1 is defined as first dose of study treatment. Relative days after Day 1 are calculated as (assessment date – Day 1 date) + 1. Relative days prior to Day 1 are calculated as (assessment date – Day 1 date). The day prior to Day 1 is Day -1. Day 0 is not defined.

The date of the first dose of study treatment for each patient will be taken from the Study Drug Administration (Oral) eCRF page. If the date in this eCRF page is missing, alternatively the date of randomization will be used.

5.1.2. Screening Period

For all patients, the screening period is defined as the period from informed consent to the first dose of study treatment. For some variables, data from more than one assessment within the Screening Period can be collected prior to the first dose of study treatment.

The baseline value for a variable is therefore defined as the last non-missing value collected before the first dose of study treatment.

Assessments carried out on day of first dose of study treatment are considered to have taken place before the first dose of study treatment, if the corresponding times have not been recorded.

5.1.3. Treatment Period

The Treatment Period is defined as the period from the date of the first dose of study treatment up to and including the date of the last dose of study treatment. Adverse events and medications starting on Day 1, will be assigned to the Treatment Period.

5.1.4. Visit Windows

The following considerations are to be followed when deriving the analysis timepoints:

- The relative day number of the assessment lies between the lower and upper boundary of the visit window (the boundary values are included)
- Both scheduled and unscheduled assessments are included for visit windowing

- If there are two or more valid assessments for a defined window the following rules will be applied:
    - If both scheduled and unscheduled assessments fall within the same visit window, the scheduled assessment with non-missing assessment results will be used for analysis
    - If there are multiple scheduled assessments with non-missing assessment results for any specified visit window and the assessment that is closest to the planned study day will be used for analysis
    - If there are multiple assessments for any specified visit and none of them are from scheduled assessment, the assessment with non-missing results and closest to the planned study day will be used for analysis
    - If there are two or more unscheduled assessments with non-missing results and the same distance to the planned study day, the assessment prior to the planned study day will be used for analysis.

The WHO COVID-19 Clinical Improvement daily assessment and ePRO patient daily diary (i.e., COVID-19 Symptom Assessment and Oxygen Saturation) related efficacy analyses will be carried out using nominal visit collected in the corresponding eCRF pages.

By-visit analyses of safety will be carried out using nominal visit as defined in the Schedule of Assessments (Appendix 2).

5.2. Handling of Dropouts, Missing Data, and Outliers

5.2.1. Handling of Missing Efficacy Data

Severity Symptom Score: Missing values on severity symptom score will not be imputed. Where a patient has died, their status will not be considered missing, but will be imputed with maximum severity score at each timepoint.

Clinical Outcome Scale: Missing values on clinical outcome scale will not be imputed. Where a patient has died, their status will not be considered missing, but will be imputed with maximum clinical outcome scale at each timepoint.

5.2.2. Handling of Missing Safety Data

In general, missing clinical laboratory evaluations, vital signs, and ECG data will not be imputed. Unknown or partial medication and AE date imputations are given below and to be used only for the assessment of prior / concomitant status for medications and treatment-emergent status for AEs.

5.2.3. Handling of Partial and Missing Adverse Events, Prior / Concomitant Medications

Missing or Partial Adverse Event and Prior / Concomitant Medication Start Dates

Missing and / or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the end date. The end date will not be imputed if the medication or AE is "Ongoing". Technically, this will be done as follows:

For a missing / incomplete start date the earliest date of the following will be imputed:

- The later date of: the earliest possible start date, and the date of first dose of treatment.
- The latest possible start date.
- The latest possible end date.

For a missing / incomplete end date the later date of the following will be imputed:

- The earlier date of the latest possible end date and the date of last dose of treatment.
- The earliest possible end date.
- The earliest possible start date.

Here, the earliest possible date is defined as:

- The date itself if available.
- The date of the first day of the month, if month and year are available but the day is missing.
- The date of the first day of the year, if year is available but day and month are missing.
- The day of informed consent, if the date is completely missing.

The latest possible date is defined as:

- The date itself if available.
- The date of the last day of the month, if month and year are available but the day is missing.
- The date of the last day of the year, if year is available but day and month are missing.
- The date of last known date on the study for the patient plus one year, if the date is completely missing.

5.2.4. Handling of Plasma Concentrations that are Below the Lower Limit of Quantification

Plasma concentrations that are below the lower limit of quantification (BLQ) will be handled as follows for descriptive statistics:

- Values that are BLQ will be set to 0 for the calculation of summary statistics.
- Arithmetic mean or median values that are BLQ will be presented as 0.
- If any BLQ results (treated as 0) are in a series of summarized data, geometric mean and coefficient of variation (CV) % of geometric mean will be reported as not calculated (NC).

6. Statistical Methods

6.1. General Principles

All data processing, summarization and analyses will be performed using Labcorp's SAS Environment / Version 9.4 (or later) of the SAS® statistical software package.

The default summary statistics for quantitative variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (min) and maximum (max), for those patients with data.

All summary statistics will be rounded (using the SAS® function ROUND). Please refer to "2.11 Presentation of Summary Statistics and Statistical Analysis" section within TFL shells for more details on presentation of different statistics.

For qualitative variables, the number (n) and percentage (%) of patients with non-missing data per category will be the default summary presentation, and where appropriate and present, the number of missing values as a "Missing" category. Number of patients in the analysis population will be used as denominator for percentages calculation, unless stated otherwise in TFL mock shells.

Specifications for table, figures and data listing formats can be found in the TFL shells specifications for this study. Please refer to "2. General Format Guidelines" section within TFL shells for more details on presentation of results.

The primary objective of the study is to assess the safety and tolerability of APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19. The primary endpoints of the study include incidence of AEs (or TEAEs), clinical laboratory evaluations, ECGs, and vital signs (as detailed in Section 6.7.2, 6.7.3, 6.7.4, and 6.7.5). All safety analyses will be performed based on the Safety Population.

No formal statistical analysis of both safety and efficacy data will be performed. All safety and efficacy analyses will be descriptive in nature.

6.2. Patient Disposition and Data Sets Analyzed

Patient disposition will be summarized by treatment group and overall, where appropriate, for the All Screened Population. The following information will be reported:

- Number of patients for the following category:
  - Screened.
- Number and percentage of patients for the following categories:
  - Randomized to treatment,
  - Treated,
  - Not Treated,
  - Completed the study,
  - Ongoing in the study,

  - Discontinued the Study,
  - Reasons for study discontinuation.
- Number and percentage of patients included in each study population;
- Number and percentage of patients who completed / discontinued treatment, including the reasons for treatment discontinuation;
- Number and percentage of patients who met / did not meet all eligibility criteria, together with the criteria not met;
- Number and percentage of patients who failed screening prior to randomization, including the primary reason for screen failure;
- Number and percentage of patients at each country / site;
- Number and percentage of patients by stratification factor. The stratification variable will be presented by the stratum collected in IXRS.

A patient will be regarded as having completed the study if the "Did the subject complete the study?" status recorded on the End of Study eCRF page is Yes. A patient will be considered as having discontinued the study if the "Did the subject complete the study?" status recorded on the End of Study eCRF page is No. Otherwise, the patient will be considered as ongoing study.

A listing of all patients with their treatment and study completion status, including the respective reasons for treatment and study discontinuation will be presented for the All Screened Population.

A listing of all screen failed patients with their reasons for screen failure will be presented for the All Screened Population. A separate listing of patients who failed at least one inclusion / exclusion criteria including a text description of the criterion failed will be presented for the All Screened Population.

A listing of all randomized patients with their randomization details, including first dose date and actual treatment received will be presented for the Intent-to-Treat Population.

A listing of all patients excluded from at least one analysis set will be presented for the All Screened Population.

6.3. Protocol Deviations

Deviations from the protocol, as defined in the protocol and / or protocol deviation plan, will be documented by the study monitors and project management throughout the study period.

All important protocol deviations will be summarized for the Intent-to-Treat Population by treatment group and overall as described below:

- The number of unique patients with at least one important protocol deviation as well as the number of patients in each important protocol deviation category will be presented by default descriptive summary statistics for categorical variables.

A listing of all patients with one or more important / non important protocol deviations will be presented for the Intent-to-Treat Population.

6.4. Demographic and Other Baseline Characteristics

6.4.1. Demographic Characteristics

Demographic characteristics will be summarized for the Intent-to-Treat Population by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate. Standard descriptive statistics will be presented for the continuous variables of:

- Age (years)
- Height (cm) at baseline
- Weight (kg) at baseline
- Body mass index (BMI, kg/m^2) at baseline

Total counts and percentages of patients will be presented for the categorical variables of:

- Age group (years):
  - ≤ 65
  - > 65 to ≤ 75
  - >75
- Sex
- Race
- Ethnicity

Demographic characteristics will be listed for the Intent-to-Treat Population.

6.4.2. Baseline Characteristics

Baseline characteristics will be summarized for the Intent-to-Treat Population by treatment group and overall as described below. All missing data will be presented as part of a missing category, if appropriate.

Standard descriptive statistics will be presented for the continuous variables of:

- Estimated glomerular filtration rate at screening
- SpO2 at baseline
- FiO2 at baseline

Total counts and percentages of patients will be presented for the categorical variables of:

- SARS-Cov-2 diagnostic test result at screening
- Clinical improvement score (WHO COVID-19 Clinical Improvement Ordinal Scale) at screening
- Chest imagining results at screening (Normal; Abnormal, Not Clinically Significant; Abnormal, Clinically Significant)
- COVID-19 vaccination status at screening (No, Adenovirus vector vaccine, Inactivated vaccine, Recombinant subunit vaccine, and Other)
- Standard of care for COVID-19 at screening (No, Anti-viral, Anti-inflammatory, and Other)

Standard of care for COVID-19 at screening is defined as any prior medications (as defined in Section 6.4.4) where "Indication" is indicated as "SoC for COVID" on the Prior and Concomitant Medications eCRF page.

Other baseline characteristics, such as vital signs and electrocardiograms, will be summarized with corresponding post-baseline measurements as detailed in Section 6.7.4, and 6.7.5, respectively.

No formal tests of statistical significance will be performed on the demographic and baseline characteristics data.

Baseline characteristics will be listed for the Intent-to-Treat Population.

6.4.3. Medical History

Medical history is defined as any condition, with the exception of the study indication, that the patient may have had prior to enrollment in the study, including any chronic conditions diagnosed prior to entry in the study.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [version 24.1 or a later version if updated during the study] and will be presented by System Organ Class (SOC) and Preferred Term (PT) and total. The SOCs and PTs are to be sorted by Internationally Agreed order SOCs and descending PTs in the total column.

Medical history records will be summarized for the Intent-to-Treat Population by treatment group and overall as follows:

- The number and percentage of subjects with at least one medical history record will be presented.
- The number and percentage of subjects with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-subject and within-subject by medical history start date for the Intent-to-Treat Population.

6.4.4. Prior and Concomitant Medications

All medications will be coded using the WHO Drug Global Dictionary, Format B3 [Version March 2020 (or a later version if updated during the study)], Anatomical Therapeutic Chemical (ATC) Classification codes.

Prior medications and concomitant medications are defined as follows:

- Prior medications are those taken prior to screening with an end date prior to the start of the Treatment Period.
    - Prior medications will be qualified as standard of care for COVID-19 only if "Indication" is indicated as "SoC for COVID" on the Prior and Concomitant Medications eCRF page.
- Concomitant medications are those with a start date on or after the start of the Treatment Period, or those with a start date before the start of the Treatment Period and either an end date on or after the start of the Treatment Period, or are ongoing at the end of the study.
    - Concomitant medications will be qualified as standard of care for COVID-19 only if "Indication" is indicated as "SoC for COVID" on the Prior and Concomitant Medications eCRF page.

Prior and concomitant medications will be summarized separately for the Intent-to-Treat Population by treatment group and overall as follows:

- The number and percentage of subjects with at least one prior / concomitant medication will be presented.
- The number and percentage of subjects with at least one prior / concomitant medication within each Anatomical Group (ATC Level 1), Therapeutic Subgroup (ATC Level 2), Pharmacological Subgroup (ATC Level 3), and preferred term will be presented. The summary will be sorted using numerical counts by descending order of Anatomical Group, then descending order of Therapeutic Subgroup, then

descending order of preferred term in the total column. Where groups or terms tie these will be sorted alphabetically.

Prior and concomitant medications used as SoC for COVID will be summaries in the same manner.

Prior medications and concomitant medications will be listed separately for the Intent-to-Treat Population. In the listings the relative start and end day of prior / concomitant medication use will be calculated relative to the first dose date of study treatment and will be presented for those patients who received at least one dose of study treatment. If the concomitant medication is "Ongoing" it will be indicated as such in the listing and the relative stop day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

6.5. Measurements of Treatment Compliance

Treatment compliance is defined as the number of capsules that were actually taken relative to the number of capsules that should have been taken as per the protocol for the duration of actual treatment exposure.

In general, the percentage overall compliance, assessed by capsule count, will be calculated as follows:

$$\textit{Compliance (\%)} = \frac{\textit{Number of capsules dispensed} - \textit{Number of capsules returned}}{\textit{Number of days on treatment} \times \textit{Number of capsules prescribed per day}} \times 100\%$$

Number of days on treatment will be calculated as follows:

(last dose date of study treatment − first dose date of study treatment) +1

The calculated percentage compliance will be categorized as:

- < 80% compliance
- ≥ 80% to ≤ 125% compliance
- > 125% compliance

Compliance will be summarized for the Safety Population by treatment group as follows:

- Percent compliance will be presented by default summary statistics.
- Number and percentage of patients within each of the compliance categories will be presented. Any patients with missing data will be presented as part of a "Missing" category.

Treatment compliance will be listed together with exposure for the Safety Population. Missing data will not be imputed and only original data for those fields (for example, date fields) will be presented in the listing together with derived variables such as the calculated compliance (%) and exposure duration.

6.6. Efficacy

For key analysis days mentioned in Section 6.6, it specifically means Days 3, 5, 10, 14, 29, and 60.

6.6.1. Primary Efficacy Analysis

Not applicable.

6.6.2. Secondary Efficacy Analysis

6.6.2.1. Time to Clinical Recovery

Time to clinical recovery is defined as the time (days) from the date of randomization to the date of the first occurrence of clinical recovery over the 28 days. The event of interest occurs when the WHO Clinical Improvement Ordinal Scale no higher than 3 for baseline WHO scale greater than 3 or no greater than 2 for baseline scale of 3, and sustain this status until the end of 28 days.

For patients without occurrence of events of interest, the following censoring rules will be applied:

- If the patient dies or does not meet the definition of clinical recovery 28 days after randomization, he/she will be censored at Day 29.

Treatment comparison will be done using a stratified Cox proportional hazards modeling with age (≤65 years vs. >65 years) as the stratification factor. The hazard ratio, associated 95% confidence interval (CI), and p-value will be presented. Proportions at each timepoint (i.e., 3 days, 5 days, 10 days, 14 days, and 29 days) will be summarized using Kaplan-Meier method along with corresponding graphical presentation.

[redacted]

6.6.2.2. Time to Discharge

Time to discharge is defined as the time (days) from the date of randomization to the date of the first occurrence of discharge over the 28 days. The event of interest occurs when the WHO Clinical Improvement Ordinal Scale is no higher than 2 and sustain this status until the end of 28 days.

For patients without occurrence of events of interest, the following censoring rules will be applied:

- If the patient dies or does not meet the definition of clinical recovery 28 days after randomization will be censored at Day 29.

This endpoint will be analyzed in a similar manner to the endpoint of Time to Clinical Recovery in Section 6.6.2.1.

6.6.2.3. Time to Symptomatic Recovery

Time to symptomatic recovery is defined as the time (days) from the date of randomization to the date of the first occurrence of none of the COVID-19 Symptom Assessment scores are higher than 1 and sustain this status until the end of 28 days.

For patients without occurrence of events of interest, the following censoring rules will be applied:

- If the patient has never been discharged from the hospital prior to 28-day monitoring period, he/she will be censored at Day 29.
- If the patient dies, he/she will be censored at Day 29.
- If the patient has received another antiviral therapy, he/she will be imputed to maximum total severity score at the assessment day and censored at Day 29. Antiviral therapy is defined as any concomitant medications (as defined in Section 6.4.4) where "Indication" is indicated as "SoC for COVID" AND "If SoC for COVID, please specify" is indicated as "Anti-viral" on the Prior and Concomitant Medications eCRF page.

Treatment comparison will be done using a stratified Cox proportional hazards modeling with age (≤65 years vs. >65 years) as the stratification factor. The hazard ratio, associated 95% confidence interval (CI), and p-value will be presented. Proportions at each timepoint will be summarized using Kaplan-Meier method along with corresponding graphical presentation.

[redacted]

6.6.2.4. Time to Complete Symptomatic Recovery

Time to complete symptomatic recovery is defined as the time (days) from the date of randomization to the date of the first occurrence of none of the COVID-19 Symptom Assessment scores are higher than 0 and sustain this status until the end of 28 days.

For patients without occurrence of events of interest, the following censoring rules will be applied:

- If the patient has never been discharged from the hospital prior to 28-day monitoring period, he/she will be censored at Day 29.
- If the patient dies, he/she will be censored at Day 29.
- If the patient has received another antiviral therapy, he/she will be imputed to maximum total severity score at the assessment day and censored at Day 29. Antiviral therapy is defined as any concomitant medications (as defined in Section 6.4.4) where "Indication" is indicated as "SoC for COVID" AND "If SoC for COVID, please specify" is indicated as "Anti-viral" on the Prior and Concomitant Medications eCRF page.

Treatment comparison will be done using a stratified Cox proportional hazards modeling with age (≤65 years vs. >65 years) as the stratification factor. The hazard ratio, associated 95% confidence interval (CI), and p-value will be presented. Proportions at each timepoint will be summarized using Kaplan-Meier method along with corresponding graphical presentation.

[redacted]

6.6.2.5. Proportion of Patients in Clinical Recovery

Proportion of patients in clinical recovery on key analysis days will be analyzed as a binary variable. Patients who die will be considered as not being in clinical recovery. Treatment comparison will be done using a logistic regression model with treatment as the main effect and age (≤65 years vs. >65 years) as a covariate to assess the treatment effect. The odds ratios, associated 95% CIs, and p-values will be provided. In additional to the estimation of the odds ratios from the logistic regression model, point estimates of differences in proportions and corresponding 95% CIs, calculated from the odds ratios, will be presented for the reference probabilities on the control arm. Stratified odds ratios, associated 95% CIs and p-values from the Cochran-Mantel-Haenszel test will also be presented.

6.6.2.6. Scoring of WHO Clinical Improvement Ordinal Scale (9-point scale)

The score on the WHO Clinical Improvement Ordinal Scale will be analyzed on the key analysis days. Patients who die will be included in the analysis as scoring the maximum score (i.e., score 8) for all subsequent key analysis day(s). A separate analysis will be conducted for each level from 3 to 9 (i.e., from score 2 to score 8), in which each patient will be scored as being above or below each level, and analyzed as a binary variable in a way similar to the endpoint of Proportion of Patients in Clinical Recovery in Section 6.6.2.5,

with treatment as the main effect and stratification factor (i.e., age [≤65 years vs. >65 years]) as covariate, and an additional covariate to the default in the model of baseline score.

6.6.2.7. Number of Days at or Above Each Level of the WHO Clinical Improvement Ordinal Scale (9-point scale)

The number of days at or above each level of the WHO Clinical Improvement Ordinal Scale for levels ≥3 on key analysis days will be derived as the number of days at or above each level of the WHO Clinical Improvement Ordinal Scale from randomization up to each key analysis day for score ≥2. Patients who die will be included in the analysis as scoring the maximum score (i.e., score 8) on every day after death until Day 29. Treatment comparison will be done using a normal regression model. The model will include the treatment as fixed effect, stratification factor (i.e., age [≤65 years vs. >65 years]) as a covariate. The LS means, standard errors, 95% CIs will be presented for each treatment group. The differences in LS means between treatment group, standard errors, 95% CIs, and p-values will also be presented.

6.6.2.8. Maximum Score of the WHO Clinical Improvement Ordinal Scale (9-point scale)

The proportion of patients whose maximum score is at or above each level of the WHO Clinical Improvement Ordinal Scale for levels ≥3 (i.e., for scores ≥2) on key analysis days will be analyzed in a similar manner to the endpoint of Proportion of Patients in Clinical Recovery in Section 6.6.2.5.

6.6.2.9. Mortality

Mortality by each of the key analysis days will be analyzed in a similar manner to the endpoint of Proportion of Patients in Clinical Recovery in Section 6.6.2.5.

6.6.2.10. Change from Baseline in SpO2

Change in SpO2 from baseline will be analyzed using a mixed model with repeated measures. The model will include the treatment, key analysis day, stratification factor (i.e., age [≤65 years vs. >65 years]), SpO2 at baseline, and treatment-by-key analysis day interaction as fixed effects, patient as random effect. An unstructured variance-covariance structure will be specified. Other variance-covariance structure may be substituted if convergence problem arises. The treatment effect on each key analysis day and the average treatment effect will be presented along with the 95% CI and p-value. Graphical displays of treatment effect by randomized treatment group across key analysis days may also be provided.

6.6.3. Subgroup Analysis

Not applicable.

6.6.4. Exploratory Analysis

The exploratory endpoints will be analyzed for the Intent-to-Treat Population as follows:

- [redacted]

- **change from baseline in log10 SARS-CoV-2 viral load as measured by reverse transcription (RT)-polymerase chain reaction (PCR) by Days 5 and 14**: This endpoint will be analyzed in a similar manner to the endpoint of Change from Baseline in SpO2 in Section 6.6.2.10. Patients who die will be included in the analysis as having the worst viral load score of any patient included in the analysis.

- **rate of switch to other COVID-19-specific treatment by Day 60**: other COVID-19-specific treatment will be derived as any concomitant medications (as defined in Section 6.4.4) recorded on the Prior and Concomitant Medications eCRF page where Indication = "SoC for COVID" and If SoC for COVID, please specify in ("Anti-viral", "Anti-inflammatory"). This endpoint will be will be analyzed in a similar manner to the endpoint of Proportion of Patients in Clinical Recovery in Section 6.6.2.5.

6.7. Safety

6.7.1. Extent of Exposure

Duration of exposure will be defined in days as:
Exposure (days) = date of last dose – date of first dose + 1 – off-treatment days

Duration of exposure will be summarized for the Safety Population by treatment group and overall using descriptive statistics.

The total doses of study treatment in capsules taken over the study duration will be summarized for the Safety Population by treatment group and overall using descriptive statistics.

Exposure by study day will be summarized for the Safety Population by treatment group and overall using the number and percentage of patients exposed to study treatment.

A listing of overall treatment exposure data, including the first and last dates of treatment will be presented together with compliance for the Safety Population. Further, study treatment administration data will be listed for the Safety Population.

6.7.2. Adverse Events

All AEs recorded on the eCRF will be coded using the MedDRA dictionary [version 24.1 released 19 April 2020 (exclusively meant for COVID-19) or later] and classified as either pre-treatment AEs or treatment-emergent AEs (TEAEs) as follows:

- Pre-treatment AEs are events that start prior to the start of the Treatment Period.
- TEAEs are either events with start date prior to the start of the Treatment Period and up to Study Day 60, or events with start date prior to the start of the Treatment Period whose severity worsens on or after the start of the Treatment Period.
- Serious AEs (SAEs) will be defined as AEs regarded by the investigator as Serious = “Yes”.
- The relationship between a TEAE and study treatment is assessed as not related, unlikely related, possibly related, or related. A treatment-related TEAE will be defined as a TEAE considered by the investigator as related or possibly related to study treatment or with missing relationship to study treatment.
- Assessment of AE severity will be based on the following categories:
    - **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
    - **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
    - **Severe**: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.
- TEAEs leading to discontinuation of treatment are defined as TEAEs where “Action Taken with Study Treatment” is indicated as “Drug Withdrawn”.

- TEAEs leading to death are defined as TEAEs where "Results in death" is indicated as "1".

Adverse events will be summarized by default descriptive summary statistics for categorical variables for the Safety Population by treatment group and overall as follows:

- An overview of TEAEs including the number and percentage of patients with at least one of each mentioned TEAE type:
  - Any TEAE
    - Leading to discontinuation of study treatment
    - Leading to death
    - Grade 1 severity (mild)
    - Grade 2 severity (moderate)
    - Grade 3 severity (severe)
  - Any study treatment related TEAE
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any serious TEAE
    - Leading to discontinuation of study treatment
    - Leading to death
  - Any serious study treatment related TEAE
    - Leading to discontinuation of study treatment
    - Leading to death

- The number and percentage of patients reporting each TEAE will be summarized by SOC and PT for the following types of TEAEs:
  - TEAEs
  - TEAEs Leading to Discontinuation of Study Treatment
  - TEAEs Leading to Death
  - SAEs
  - TEAEs by Maximum Severity
  - TEAEs by Relationship to Treatment
  - Study Treatment Related TEAEs
  - Study Treatment Related SAEs
- The number and percentage of patients who died will be summarized as:
  - Whether the death occurred after withdrawal of care, if so,
  - Reason for withdrawal of care

The AE summary tables will include counts of patients. Therefore, if a patient experiences more than 1 episode of a particular AE, the patient will be counted only once for that event. If a patient has more than one AE that is coded to the same PT, the patient will be counted only once for that PT. Similarly, if a patient has more than 1 AE within a SOC, the patient will be counted only once in that SOC.

For summaries by maximum severity, patients with multiple TEAEs within a particular SOC or PT will be counted under the category of their most severe TEAE within that SOC or PT. TEAEs with missing severity will be included (as Severe) in the overall count of patients with TEAEs, but will not be included in the counts of patients with TEAEs within a SOC or PT.

Summaries by SOCs and PTs will be sorted by SOCs by their Internationally Agreed Order (MedDRA) and PTs within SOC by descending order of total incidence. Where preferred terms tie PTs will be sorted alphabetically.

All AE data will be listed and Pre-treatment AEs and TEAEs will be presented together. Treatment-emergence status will be flagged in the listing. The listing will present the relative start and end day of the AE calculated relative to the first dose of study treatment and will be presented for those patients who received at least one dose of study treatment. If the AE is "Ongoing" it will be indicated as such in the listing and the relative end day will not be calculated. Only original dates will be presented in the listing even though the relative day may be based on an imputed date.

In addition, the following listings will be presented:

- Listing of Deaths
- Listing of SAEs
- Listing of AEs Leading to Discontinuation of Study Treatment

6.7.3. Laboratory Evaluations

Data for the following hematology, serum chemistry, and urinalysis analytes received from central laboratory are to be measured at the scheduled timepoints indicated in the Schedule of Assessments (Appendix 2).

Table 12 Laboratory Tests

Hematology Test	Serum Chemistry Test	Urinalysis

• Hematocrit
• Hemoglobin
• Mean cell hemoglobin
• Mean cell hemoglobin concentration
• Mean cell volume
• Platelet count
• Red blood cell (RBC) count
• RBC distribution width US
• White blood cell (WBC) count
• WBC differential (percent and absolute):
  ○ Basophils
  ○ Eosinophils
  ○ Lymphocytes
  ○ Monocytes
  ○ Neutrophils
	• Alanine aminotransferase (ALT)
	• Albumin
	• Alkaline phosphatase
	• Aspartate aminotransferase (AST)
	• Blood urea nitrogen
	• Calcium
	• Chloride
	• Cholesterol
	• Creatinine
	• Gamma-glutamyl transferase (GGT)
	• Glucose
	• Lactate dehydrogenase
	• Phosphorus
	• Potassium
	• Sodium
	• Total bilirubin
	• Total CO2 (measured as bicarbonate)
	• Total protein
	• Triglycerides
	• Uric acid
		• Bilirubin
		• Blood
		• Glucose
		• Ketones
		• Leukocyte esterase
		• Nitrite
		• pH
		• Protein
		• Specific gravity
		• Urobilinogen

In accordance with the baseline value definition in Section 5.1.2, the change from baseline will be derived as follows:

Change from baseline (unit) = post-baseline value – baseline value

All laboratory data will be reported in SI units. All quantitative laboratory test values at each assessed timepoint will be compared with the relevant reference range in SI units and categorized as:

- Low: Below the lower limit of the reference range.
- Normal: Within the reference range (upper and lower limits included).
- High: Above the upper limit of the reference range.

For analysis purposes, values preceded by a "<" or a ">" sign (i.e., those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

Laboratory data will be summarized by default descriptive summary statistics for continuous and categorical variables for the Safety Population by treatment group and overall as follows:

- Observed values and change from baseline at each assessed timepoint for each standard continuous laboratory parameter;

- Number and percentage of patients with categorized (low, normal and high) shift values relative to the reference range at baseline compared to each post-baseline timepoint for laboratory tests where applicable.

Listings of all clinical laboratory data including derived change from baseline will be provided for the Safety Population. Within each listing, laboratory values outside the normal ranges will be flagged as either high or low.

6.7.4. Vital Signs

The analyses described below will be conducted for the following vital signs assessments respectively:

- systolic blood pressure (mmHg);
- diastolic blood pressure (mmHg);
- pulse rate (bpm);
- respiration rate (breaths / min);
- body temperature (°C).

In accordance with the baseline value definition in Section 5.1.2, the change from baseline will be derived as follows:

Change from baseline (unit) = post-baseline value – baseline value

The following will be summarized by treatment group and overall for the Safety Population:

- Observed values and change from baseline at each assessed timepoint for each standard vital sign parameter using default summary statistics for continuous variables;

A listing of all vital signs data including derived change from baseline will be provided for the Safety Population.

6.7.5. Electrocardiograms

The following ECG assessments will be taken during the study:

- An overall investigator assessment classified as:
  - Normal,
  - Abnormal, not clinically significant,
  - Abnormal, clinically significant
- Heart rate (bpm);
- RR interval (msec);
- PR interval (msec);

- QRS interval (msec);
- QT interval (msec);
- Bazett corrected QT (QTcB) interval (msec);
- Fridericia corrected QT (QTcF) interval (msec).

In accordance with the baseline value definition in Section 5.1.2, the change from baseline will be derived as follows:

Change from baseline (unit) = post-baseline value – baseline value

The maximum post-baseline QTcF / QTcB values will be classified in accordance with the ICH E14[4], Boundaries as presented in Table 13.

Table 13 QTcF / QTcB Interval ICH E14 Boundaries

QTcF / QTcB Interval	Criteria (msec)
Observed QTcF / QTcB interval	≤450 msec >450 msec >480 msec >500 msec
Change from baseline in QTcF / QTcB interval	≤30 >30 to ≤60 msec >60 msec

The ECG findings will be summarized by treatment group and overall for the Safety Population as follows:

- Observed values and change from baseline at each assessed timepoint for each ECG parameter using default summary statistics for continuous variables;
- The ECG overall assessment as reported by the investigator will be summarized at each assessed timepoint by providing number and percentage of patients within each assessment category;
- Shifts from baseline of overall ECG assessment (normal vs. abnormal, not clinically significant vs. abnormal, clinically significant) to each post-baseline timepoint;
- A categorical summary of QTcF / QTcB classification according to ICH E14 boundaries will be provided using counts and percentages for baseline and maximum post-baseline value.

A listing of all ECG data including derived change from baseline will be provided for the Safety Population.

6.7.6. Physical Examination

Not applicable.

6.7.7. Other Safety Variables

Pregnancy test results and patients with confirmed positive pregnancy test result will be listed.

The chest imaging findings as reported by the investigator will be summarized at each assessed timepoint by providing number and percentage of patients within each assessment category.

6.7.8. Interim Analysis and Data Monitoring

A single interim analysis will be planned for the study. Enrollment will pause after the 30th patient in the sentinel cohort has been enrolled and started treatment, until the results of the interim analysis are known. Once either 25 patients have recovered, or the 30th patient in the sentinel cohort has completed 14 days of treatment, an unblinded DMC will assess the safety, tolerability, efficacy, and PK [redacted] in COVID-19 patients in the sentinel cohort. The DMC will issue a recommendation to enroll patients for the expansion cohort, or to stop the study depending on the safety and futility assessment. The DMC will continue to review safety and assess the risk/benefit profile on an ongoing basis.

[redacted]

- [redacted]
- [redacted]
  [redacted].

The operation of the DMC will be covered by a DMC Charter. A separate unblinded statistical analysis group (USAG) from the main study team will prepare the unblinded reports for the DMC, and only the USAG and DMC will have access to unblinded data.

6.7.8.1. Futility Analysis for the Key Secondary Efficacy Endpoint

As the study does not test a formal hypothesis and the sample size was not determined based on formal statistical power calculation but using clinical consideration to provide a reasonable clinical database to assess efficacy in COVID-19 patients, the interim Time-to-Clinical-Recovery futility analysis will be non-binding and define futility as the nominal one-sided p-value at the interim analysis crosses the O'Brien Fleming-type futility boundary (p-value scale). [redacted]

6.8. Pharmacokinetic Assessments

A listing of PK blood sample collection times and Plasma concentrations will be presented for detail analytes from protocol separately for all patients for the Pharmacokinetics Population.

Pharmacokinetic concentrations will be summarized for the Pharmacokinetics Population for each timepoint by treatment group and overall using protocol scheduled times and appropriate summary statistics.

See Section 5.2.4 for the handling of Plasma concentrations that are BLQ.

6.8.1. Pharmacokinetic Analysis

The PK parameters of APX-115 will be calculated based on the actual sampling time using non-compartmental analysis (NCA) methods within Phoenix WinNonlin Version 8.1 or higher (Certara USA, Inc.). [redacted]

The units of concentration and resulting PK parameters, will be presented as they are received from the analytical laboratory.

The following PK parameters for APX-115 will be determined where possible from the plasma concentration data collected on timepoints specified in the protocol:

- **C_{trough}** is defined as trough (predose) plasma concentration.
- **C_{max}** is defined as maximum plasma concentration.
- **T_{max}** is defined as time to maximum plasma concentration.
- **$AUC_{0\text{-}last}$** is defined as AUC from time zero to the time of last quantifiable concentration.
- **$AUC_{0\text{-}12}$** is defined as AUC from time zero to 12 hours postdose (the last sample)
- **AUC_{tau}** is defined as AUC within a dosing interval (where tau = 24 hours for a QD regimen).

Additional PK parameters may be determined where appropriate.

C_{trough}, C_{max}, and T_{max} will be obtained directly from the plasma concentration-time profiles.

AUC parameters will be calculated using the linear trapezoidal rule for increasing concentrations and the logarithmic rule for decreasing concentrations.

6.8.1.1. Calculation of AUC

- The minimum requirement for the calculation of AUC will be the inclusion of at least three consecutive plasma concentrations above the lower limit of quantification (LLOQ), with at least one of these concentrations following C_{max}.
- [redacted]

6.8.1.2. Anomalous Values

If a value is considered to be anomalous due to being inconsistent with the expected pharmacokinetic profile, it may be appropriate to exclude this point from the PK analysis. However, the exclusion of data must have strong justification and will be documented in the raw data and study report.

Embedded BLQ values may be considered anomalous depending on the route of administration and the characteristics of the drug.

6.8.1.3. Pharmacokinetic Statistical Methodology

All the PK data will be presented based on the Pharmacokinetic Population.

APX-115 plasma concentration data will be listed and summarized by study day at all protocol scheduled timepoints. [redacted]

The PK parameters of Day 1 and Day 14 will be listed and summarized.

6.8.1.4. Presentation of Pharmacokinetic Data

6.8.1.4.1. Presentation of Pharmacokinetic Plasma Drug Concentration Data

- Descriptive statistics of number of patients (n), arithmetic mean, SD, geometric mean, geometric CV, median, minimum and maximum will be calculated in summaries. Values that are BLQ will be handled as per Section 5.2.4.
- Where there is no result (NR), it will be set to missing.

- If there are less than three values in the data series, only the min, max and n will be presented. The other summary statistics will be denoted as NC.
- [redacted]

6.8.1.4.2. Presentation of Pharmacokinetic Parameters

- Descriptive statistics of number of patients (n), arithmetic mean, SD, geometric mean, geometric CV, median, minimum and maximum will be calculated in summaries.
- For the calculation of summary statistics of PK parameters, all NR and NC values in a data series will be set to missing.
- If there are less than three values in the data series, only the min, max and n will be presented. The other summary statistics will be denoted as NC.

7. Changes in the Conduct of the Study or Planned Analysis

There were no changes in the conduct of the study at the time of preparing this SAP.

8. Appendices

Appendix 1: Document History

Document Version, Status, Date	Summary / Reason for Changes
Version 0.1, Sponsor Draft, 25AUG2021	Not applicable; the first version
Version 0.2, Sponsor Draft, 28OCT2021	• Updated the MedDRA to version 24.1 from 24.0 • Added Section 6.7.8.1 Futility Analysis for Key Secondary Efficacy Endpoint
Version 1.0, Final, 28OCT2021	• Upgrade the SAP version to Final 1.0
Version 2.0, Final, 08AUG2022	• Added AUC_{0-12} for analysis in Section 6.8.1 Pharmacokinetic Analysis • Updated the definition of AUC_{tau}

Appendix 2: Schedule of Assessments

		Treatment Period						Follow-up visits		
Study Day	Screening -4 to -1[a]	Baseline Day 1	[Day after Hospital Discharge[q]]	Day 3 (-1 day)	Day 5 (±1 day)	Day 10 (±2 days)	EOT (ET) Visit Day 14 (+2 days)	Day 22 (±2 days)	Day 29 (±2 days)	EOS (EW) Visit Day 60 (±2 days)
Informed consent	X									
Inclusion/exclusion criteria	X	X								
SARS-CoV-2 test[a]	X									
Demographics	X									
Medical history	X									
Pregnancy test[p]	X									X
Estimated glomerular filtration rate	X									
Randomization[b]		X								
Efficacy										
Clinical improvement score (WHO COVID-19 Clinical Improvement Ordinal Scale)[c]	X	X								
[redacted]		X		X	X	X	X			
Patient diary[e]		Post-hospital discharge - ongoing until EOT visit								
Patient-reported assessment of signs and symptoms of COVID-19[f]		Post-hospital discharge - ongoing until EOS								
Safety										
Adverse events/serious adverse events	X	Ongoing								
Prior and concomitant medications	X	Ongoing								
Clinical laboratory assessments[g]	X	X			X		X			
Blood sampling for biomarkers[h]		X					X			
Oxygen saturation[i]		Once daily - ongoing until EOS								
Vital signs[j]	X	X		X	X	X	X	X		
12-lead ECG[k]	X	X					X			
Chest x-ray or CT scan[l]	X						X			
Pharmacokinetics										
Blood sampling for PK[m]		X			X		X			
Other										
Study drug administration[n]		Once daily, Day 1 through Day 14, inclusive								
Dispense study drug[o]		X								
Return unused study drug[o]							X			

Note that patients will undergo assessments during hospitalization or could be discharged after the start of study treatment as early as Day 2 if judged to be ready for discharge. Eligible patients must be in hospital for at least 24 hours after start of study treatment. If discharged, patients will then be requested to take study treatment at home (as prescribed) up to and including Day 14. If the patient has already been discharged, a telephone or digital media visit will be conducted on days for which no laboratory assessments are required (Days 3, 10, 22, 29, and 60) and an at-home or an on-site visit will be required on days requiring laboratory assessments (Days 5 and 14). Allowable windows for scheduling of study visits are -1 day for Day 3, ±1 day for Day 5, and ±2 days for Days 10, 22, 29, and 60. The Day 14 visit may be scheduled up to 2 days past the actual Day 14 date; however, dose administration will end at Day 14. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

a. Patients will be randomized after a laboratory-confirmed SARS-CoV-2 infection within 14 days of randomization as determined by real time RT-PCR or other commercial or public health assay authorized by FDA or other applicable health authority.

b. Patients will be randomized to receive either [redacted] APX-115 treatment or placebo.

c. The COVID-19 clinical outcome will be evaluated for the 24 hours leading up to the assessment daily while hospitalized, the day after hospital discharge via telephone contact with the patient, at the scheduled visit(s) after hospital discharge, and if the patient is readmitted to the hospital or dies. Only the highest WHO scale score in the 24 hours leading up to each assessment will be recorded.

d. SARS-CoV-2 viral loads will be obtained by [redacted] self-collection at baseline (Day 1) and on Days 3, 5, 10, and 14 while hospitalized or on Days 5 and 14 if patient is discharged from hospital prior to Day 3.

e. A patient diary will be provided to the patient at the time of discharge from the hospital (if discharge occurs before EOT), which will be used to record date and time of dose administration and confirmation that dose was taken in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed. The patient diary will be reviewed at each scheduled visit post-hospital discharge.

f. If the patient is discharged from the hospital prior to EOS, patient-reported assessment of signs and symptoms of COVID-19 will be self-evaluated at approximately the same time each day for each previous 24-hour period using an ePRO instrument through Day 60.

g. Screening laboratory tests will be assessed by a local laboratory. The clinical laboratory assessments do not need to be repeated if already done as SoC (eg, performed within 24 to 48 hours of screening or visit day and patient is clinically stable). Baseline and post-baseline laboratory tests will be assessed by the central laboratory. Post-baseline clinical laboratory assessment blood samples do not need to be taken predose. See Appendix 2 for a list of clinical chemistry, hematology, and urinalysis tests required.

h. Blood sampling for assessment of [redacted], will occur predose on Day 1 and on Day 14.

i. Oxygen saturation will be collected daily in the hospital or, if the patient is discharged from the hospital prior to EOS, pulse oximetry devices will be provided to the patient for daily self-collection and reporting using ePRO.

j. Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at screening and on Days 1, 3, 5, 10, 14, and 22 while hospitalized or on Days 5 and 14 if patient is discharged from hospital prior to Day 3.

k. A 12-lead ECG will be scheduled prior to first study drug administration either at screening or Day 1 predose and on Day 14. If the patient is discharged from hospital before Day 14, an ECG will be performed on the day of hospital discharge instead of on Day 14. The 12-lead ECG does not need to be repeated if already done as SoC (eg, performed within 24 to 48 hours of screening or visit day and patient is clinically stable).

l. Chest x-ray or CT scan will be performed at screening and either at hospital discharge, at ET, or at EW, whichever comes first. (Note: only 1 scan must be done for hospital discharge, ET, or EW). Chest x-ray or CT scan does not need to be repeated at screening if performed as SoC and done within 48 hours of screening. Chest x-ray or CT scan is not required post-hospital discharge.

m. Blood samples will be collected for 20 hospitalized patients on Day 1 at predose and 1, 2, 8, and 12 hours postdose. On Day 5, if patient is still hospitalized, a predose sample will be collected. On Day 14, if patient is still hospitalized, blood samples will be collected at predose and 1, 2, 8, and 12 hours postdose. For patients discharged from hospital prior to Day 5 or Day 14, the blood sample collections on Day 5 and/or Day 14 can be omitted.

n. Study drug (either [redacted] APX-115 or placebo as per randomization) will be administered QD for 14 consecutive days in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed on Days 1 to 14, inclusive. If patient is discharged during the study treatment period, a quantity of APX-115 or placebo sufficient for QD dosing through Day 14 will be dispensed at the time of patient discharge from the hospital.

o. If patient is discharged during the study treatment period, a quantity of APX-115 or placebo sufficient for QD dosing through Day 14 will be dispensed at the time of patient discharge from the hospital. The patient will return any unused study drug after final dose administration on Day 14.

p. For female patients of child bearing potential, serum pregnancy at screening and urine pregnancy at end-of-study. The site will provide the urine pregnancy kit to the patient at the previous visit or at hospital discharge.

q. On the day after hospital discharge, a telephone call will be made to the patient to obtain a clinical improvement score (WHO COVID-19 Clinical Improvement Ordinal Scale) assessment covering the 24-hour period after hospital discharge. Only the highest WHO scale score in the 24 hours leading up to the assessment will be recorded.

9. References

[1] ICH. *Statistical Principles for Clinical Trials*, Guideline E9, 1998. Available at https://database.ich.org/sites/default/files/E9_Guideline.pdf

[2]ICH. *Addendum on Estimands and Sensitivity Analysis in Clinical Trials*, Guideline E9(R1). Available at
https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

[3]ICH. *Structure and Content of Clinical Study Reports*, Guideline E3, 1995. Available at https://database.ich.org/sites/default/files/E3_Guideline.pdf

[4]ICH. *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs.* 12 May 2005**.** Available at
https://database.ich.org/sites/default/files/E14_Guideline.pdf