aTyr Pharma, Inc

ATYR1923-C-003

A Randomized Double-blind Placebo-controlled Study to Evaluate the Safety and Efficacy of ATYR1923 In Adult Patients With Severe Pneumonia Related To SARS-CoV-2 Infection (COVID-19)

Statistical Analysis Plan

Version: 3.0

PAREXEL Project Number: 252361

SPONSOR SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Approver	[redacted] Project Role: [redacted] aTyr Pharma, Inc.
Approver	[redacted] Project Role: [redacted] aTyr Pharma, Inc.

PAREXEL SIGNATURE PAGE

Signature(s) below confirm that the Statistical Analysis Plan was developed in accordance with SOP-GDO-WW-019 and that it is approved for release.

This document has been approved and signed electronically on the final page by the following:

	Signatory
Author	[redacted] Project Role: Biostatistics Lead

TABLE OF CONTENTS

REVISION HISTORY

Version No.	Effective Date	Summary of Change(s)
1.0	09 Dec 2020	New document
2.0	05 Mar 2021	Correction of typographic errors Post-unblinding Modifications after sponsor review: • New definition and analysis of Time to recovery with WHO scale score ⩽ 3 without supplemental oxygen added, see Section 4.9.4.1 • additional baseline categories, see Section 4.7 • additional concomitant medication of special interest, see Section 4.8 • Grading added for Urinalysis, see Section 6.3 • Efficacy Evaluation Analysis Set added, see Section 4.5
3.0	24 Mar 2021	Minor Post-unblinding Modifications after sponsor review: • Update Time to recovery with WHO scale score ⩽ 3 without supplemental oxygen

LIST OF ABBREVIATIONS

Abbreviation	Definition
Ab	Antibody
ADA	Anti-drug antibody
ADaM	Analysis Data Model
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BILI	Total bilirubin
BMI	Body Mass Index
BP	Blood pressure
CI	Confidence interval
COVID-19	Coronavirus disease
CRP	C-reactive protein
CSR	Clinical Study Report
CXC-10	C-X-C motif chemokine 10
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DoD	Day-of-Discharge
DSMB	Data Safety Monitoring Board
eCRF	Electronic case report form
EOS	End-of-Study
ET	Early Termination
HR	Heart rate
IFN-γ	Interferon gamma
IL	Interleukin
ISOC	Institutional standard of care
ITT	Intent-to-treat
IV	Intravenous
LDH	Lactate dehydrogenase
LOCF	Last Observation Carried Forward
MCP-1	Monocyte chemoattractant protein-1
MedDRA	Medical Dictionary for Regulatory Activities
MIP-1	Macrophage inflammatory protein-1
MIP-1α	Macrophage inflammatory protein-1 alpha
MMRP	Mixed Model with Repeated Measurements
NRP2	Neuropilin 2
O_2	Oxygen

Abbreviation	Definition
PCR	Polymerase chain reaction
PD	Pharmacodynamic
PK	Pharmacokinetic
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SD	Standard deviation
SOC	System organ class
SPO_2	Oxygen saturation
TC	Telephone contact
TEAE	Treatment-emergent adverse event
TLFs	Tables, listings, and figures
TNF-α	Tumor necrosis factor-alpha
ULN	Upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

This Statistical Analysis Plan (SAP) provides a detailed description of the statistical methods and analyses to be carried out for the Clinical Study Report (CSR) in support for study ATYR1923-C-003.

The analyses described in this SAP are based upon the following study documents:

- Study Protocol, Version 5.0 (dated 13 Nov 2020),
- Electronic Case Report Form (eCRF) v5.0 (dated 15 Aug 2020).

2 STUDY OBJECTIVES

2.1 Primary

- To assess the safety of a single intravenous (IV) dose of ATYR1923.

2.2 Secondary

- To assess the preliminary effects of ATYR1923 on clinical outcome measures of SARS-CoV-2 infection.

2.3 Exploratory

The exploratory objectives are:

- To explore the preliminary efficacy of ATYR1923 for SARS-CoV-2 infection.
- To assess the PD of a single IV dose of ATYR1923.
- To assess the impact of a single IV dose of ATYR1923 by measuring potential biomarkers of COVID-19 disease.

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

Study ATYR1923-C-003 is a randomized, double-blind, placebo-controlled study to evaluate the safety, PD, and efficacy of ATYR1923 in hospitalized subjects with SARS-CoV-2 related severe pneumonia not requiring mechanical ventilation.

Eligible patients will be randomized 1:1:1 to a single IV dose of ATYR1923 1 mg/kg, ATYR1923 3 mg/kg, or placebo. Study drug (ATYR1923 or placebo) will be added onto institutional standard of care (ISOC) for treating SARS-CoV2 infection.

A single dose of study drug will be administered on Day 1. All study drug will be administered in the hospital setting; patients who are intubated after randomization but prior to study drug administration are no longer eligible to receive study drug. As this is a single-dose study, the treatment period is 1 day. Thereafter, all patients will be followed for 60 days post-treatment. The schedule of study assessments over this period is dependent on the duration of hospitalization and whether or not the patient requires intubation.

3.1.1 Hospitalized, Non-intubated Patients

While hospitalized, non-intubated patients will have study assessments performed on Days 2, 3, 4, 5, 6, 7, 10, and 14 and/or Discharge.

If the non-intubated patient is discharged prior to Day 14, the assessments scheduled for Day 14 and/or discharge will be completed at the time of discharge. If discharge occurs on another scheduled study assessment day (ie, any day between Days 2 and 10), the Day 14 and/or discharge assessments supersede that study assessment day and the patient then will proceed to outpatient telephone contact (TC) follow-up visits. If a patient is discharged prior to Day 14, then outpatient TC follow-up visits are to be conducted on Day 7 (as applicable) and Day 14.

If the non-intubated patient is discharged on Days 15-20, the patient is to have the assessments scheduled for Day 14 and/or discharge performed on the day of discharge. If the patient is hospitalized for ≥21 days, the Day 14 assessments are to be performed weekly (Days 21, 28, 35, etc.) until discharge (with the exception of pharmacokinetics [PK], which is to be done only at Day 28). After discharge, the patient will proceed to the next scheduled outpatient TC follow-up visit. (Thus, if a patient remains hospitalized on Day 28, the Day 28 TC follow-up visit need not be conducted.)

3.1.2 Hospitalized, Intubated Patients

In the event that a patient requires intubation ***while hospitalized***, ISOC assessments and interventions will supersede study assessments for the duration of intubation, with the exception of the World Health Organization (WHO) Scale and sample collection for anti-drug antibody (ADA) and Jo-1 antibody (Ab), which will continue to be collected as per the Schedule of Assessments (Appendix 6.1) on Days 5, 7, 10, 14 and weekly thereafter. The following clinical assessments will be collected and analyzed as available per the institution's electronic medical records.

- Date and time of intubation and extubation.
- Adverse events (AEs) (including new infections). In the case of new infections, the site and source of culture are to be recorded.
- Concomitant medications.

Patients will resume the study assessment schedule upon extubation. (Thus, for example, if an intubated patient is extubated on Day 7, they will resume the study assessment schedule on Day 7).

Extubated patients will have the assessments scheduled for Day 14 and/or discharge performed at the time of hospital discharge and will attend Days 28 and 60 TC follow-up visits.

If the patient is hospitalized for ≥21 days, assessments are to be performed weekly (Days 21, 28, 35, etc.) until discharge (with the exception of PK, which is to be done only at Day 28). After discharge, the patient will proceed to the next scheduled outpatient TC follow-up visit. (Thus, if a patient remains hospitalized on Day 28, the Day 28 TC follow-up visit need not be conducted.)

3.1.3 Independent Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will review the progress of the study and perform interim reviews of safety data at regular intervals beginning after the sixth patient has been dosed, and at a frequency guided by the enrollment rate and DSMB recommendation. Details will be documented within the DSMB Charter.

3.1.4 Determination of Sample Size

For this study, no prospective calculations of statistical power have been made. The sample size has been selected to provide information on safety, tolerability, PK, and efficacy following single doses of ATYR1923. There will be 30 patients randomized 1:1:1 to ATYR1923 1 mg/kg, 3 mg/kg, or placebo, respectively.

3.1.5 Planned Interim Analysis

A soft-lock of the data base is planned for an ad hoc safety Interim Analysis (IA). The IA will be reviewed by an designated sponsor team unblinded to treatment group to determine the continuation of the trial. Timing of the IA rests with the sponsor. A separate IA SAP and separate IA TFL Shells will be developed.

3.2 Changes in the Conduct of Planned Analyses

Changes not mentioned in the CSP or SAP will be clearly indicated in the Clinical Study Report. Any post hoc analyses after database lock will clearly be labelled as post hoc.

Table 1 Changes in the Conduct of Planned Analyses

CSP V5.0	Changes
Secondary Endpoint: “Time to improvement from inpatient hospital admission based on at least a 1 point reduction in WHO Ordinal Scale score. ”	Patients are hospitalized prior study start and therefore first WHO Scale score to be collected during Screening. Secondary Endpoint definition to be changed to:

CSP V5.0	Changes
	"Time to improvement from baseline on at least a 1 point reduction in WHO Ordinal Scale score. "

3.3 Final Database Lock

The study database will be finally locked when all patients completed the study. The study will be considered complete when the last patient completes the Day 60 TC follow-up visit and any necessary follow-up for Jo-1 Ab positivity or ongoing study drug-related treatment-emergent AEs (TEAEs) has been completed and cleaned.

3.4 Endpoints

3.4.1 Primary

- Incidence of TEAEs, including serious and severe TEAEs, overall and by severity.

3.4.2 Secondary

- Time to hospital discharge,
- Time to recovery (WHO score ≤3),
- Proportion of patients achieving recovery by Day 14 and Day 28,
- Duration of supplemental oxygen (O_2) requirement,
- Number of days with fever (temperature >100.4ºF [38.0ºC]),
- Change from baseline in WHO Ordinal Scale score on Days 5, 7, 14, 28, and 60,
- Time to improvement from baseline based on at least a 1 point reduction in WHO Ordinal Scale score,
- All-cause mortality at Days 14, 28, and 60.

3.4.3 Exploratory

- Change from baseline in supplemental oxygen requirement at Days 3, 5, 10, 14, and discharge.
- Proportion of patients requiring intubation, and among those patients, number of days in intubation.

- Change from baseline in inflammatory biomarkers and cytokines including: C-reactive protein (CRP), interferon gamma (INF γ), interleukin (IL)-6, IL-2, IL-7, IL-10, tumor necrosis factor-alpha (TNFα), macrophage inflammatory protein-1 (MIP1), C-X-C motif chemokine 10 (CXC-10), and monocyte chemoattractant protein-1 (MCP-1).
- Change from baseline in potential markers of COVID-19, including serum ferritin and D-dimer.

4 STATISTICAL METHODS

4.1 Data Quality Assurance

All tables, figures and data listings to be included in the report will be independently checked for consistency, integrity, and in accordance with PAREXEL standard procedures.

4.2 General Presentation Considerations

Baseline: the last available pre-treatment assessment, unless otherwise specify. All assessments should have time collected. If time is not collected and date of assessment is the same as study drug administration date then assessment will be assumed to be collected prior to treatment unless schedule of assessments and protocol indicate planned collection is always after dosing.

For baseline of oxygen use, total oxygen use in 24 hours before drug administration date.

Day-of-Discharge (DoD): day when patient is discharged from the hospital.

Date of discharge: date patient is discharged from the hospital.

Early Termination (ET): day when patient withdraws from the study before completion.

End-of-Study (EOS): the EOS assessment is at Day 60 for patients who complete the study.

End of study date: date of EOS assessment (Day 60) if patient completes the study or date of early withdrawal if patient discontinues early, or date of death.

Study Day: <Assessment Date> - study drug administration date+ 1 if <Assessment Date> is on or after study drug administration date. <Assessment Date> - study drug administration date, if <Assessment Date> is before study drug administration date.

Durations are generally calculated as the stop date - start date +1, if not otherwise stated.

For elapsed time (eg, time since the initial diagnosis) is calculated as reference date - event date.

If more than one laboratory value is available for a given study day, the last valid observation will be used in summaries, unless otherwise stated. If it is not possible to determine which is the last measurement due to missing times, then the average of all measurements for that study day will be used as the value for that study day. All observations will be presented in listings.

Laboratory data will be presented in standard units.

Continuous data will be summarized in terms of the mean, standard deviation (SD), median, minimum, maximum and number of observations, unless otherwise stated. Continuous data that are expected to be skewed will be presented in terms of the maximum, upper quartile, median, lower quartile, minimum and number of observations. The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The SD will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of patients providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing of categories will be detailed in the SAP text and the data displays.

Percentages will be presented to one decimal place. Percentages will not be presented for zero counts. Percentages will be calculated using N as the denominator, unless otherwise stated. If sample sizes are small, the data displays will show the percentages, but any textual report will describe frequencies only. Changes from baseline in categorical data will be summarized using shift tables where appropriate.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001". Confidence intervals (CIs) will be presented to one more decimal place than the raw data.

Analysis Visit Window:

By visit summaries will be based on the nominal/scheduled visit as reported in eCRF and will be grouped by Day 1, 2, 3, 4, 5, 6, 7, 10, 14, 28 and 60.
For (telephone contact) TC follow up visits and unscheduled Discharge visits, analysis visit windows will be applied as in Table 2 and Table 3 below. Note, analysis visit windows are only used for by visit summaries, not for time to event calculation which will based on actual date of data collected. TC follow up visits and Discharge visits that are not in any of the analysis visit windows, will be excluded from summaries and only presented in listings.

Table 2 Analysis Visit Window for TC follow up visits

mapped to	Visit Window
Day 7	Day 7 ± 2 days
Day 14	Day 14 ± 2 days
Day 28	Day 28 ± 5 days
Day 60	Day 60 ± 5 days

Table 3 Analysis Visit Window for unscheduled Discharge visits

mapped to	Visit Window
Day 7	Day 8
Day 10	Day 10 ± 1 days
Day 14	Day 14 ± 2 days
Day 28	Day 28 ± 5 days
Day 60	Day 60 ± 5 days

In case several outcomes are available for the nominal/scheduled analysis visits, the latest non-missing result will be used for summaries.

Treatment Descriptors
Displayed columns will be labelled and ordered:

- Placebo,
- ATYR1923 1 mg/kg,
- ATYR1923 3 mg/kg,
- ATYR1923 Total,
- All Patients.

4.3 Missing Data

4.3.1 Imputation of Non-Date Missing Data

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a "blank" in subject listing displays. Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Subjects with the designation of treatment relationship for AEs and SAEs missing will have the worst realistic case assumed to impute the relationship: if relationship is missing and the AE started on or after study drug administration it will be assumed to be "related" (worst case). If the AE with missing relationship started before study drug administration (eg, during Screening Period), it will be considered as "not related" (realistic case). Missing Severity will be assumed to be "Life-threatening" (worst case). In listings these imputed relationships and causalities will be flagged.

For variables which determine the proportion of events, all subjects in the respective analysis set will be included in the denominator when calculating the percentages irrespective of whether their outcome may be missing.

Handling of complete or partial missing dates for Adverse Events or reported Concomitant Medication will be given in the following Section.

All other missing data will not be imputed.

4.3.2 Imputation of Partial Dates

Imputed dates will be used only to assign reported AEs and Medications to the different study Periods: Screening Period, Treatment Period, FU Period; for determining the category for reported Medication as 'PRIOR ONLY', 'PRIOR and CONCOMITANT' or 'CONCOMITANT ONLY' and to determine if an AE is treatment emergent.

Both observed and imputed dates will be included into the analysis datasets. Dates will be displayed in listings with only the information available in the database.

Partial date imputation will follow ADaM conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y' with

blank: indicates that no imputation was done,
D = 'Day': indicates that the day portion of the date is imputed,
M = 'Month': indicates that the month and day portions of the date are imputed,
Y = 'Year': indicates that the entire date (year, month, and day) is imputed.

Table 4 Partial Date Imputation Rules for AEs and Medications

Date	Missing Element	Rule
Start Date	day, month, and year	Do not impute completely missing start dates
	day, month only	Set to January 1st of the year the event started.
	day only	Set start date to the 1st of the month the event started.
End Date	day, month, and year	No imputation for completely missing end dates; report the event as ongoing if not already documented as 'ongoing'
	day, month only	If the partial end date contains year only, set end date to December 31st or last study visit, whichever occurs first.
	day only	If the partial end date contains month and year, set the end date to the last day of the end month or last study visit, whichever occurs first.

Thus, AEs will be assumed to be treatment-emergent, unless there is clear evidence to suggest that the AE started prior to treatment.

Table 5 Partial Date Imputation Rules for Death and Hospitalization

Missing Element	Rule
month and/or year	Do not impute.
day only	Set start date to the 1st of the month. If imputing the first day of the month results in a negative overall survival time, the patient will be censored for overall survival at the reference date.

4.4 Software

All report outputs will be produced using SAS® version 9.3 or a later version in a secure and validated environment.

4.5 Analysis Sets

All Screened consists of all subjects who provide written informed consent.

Randomized Set comprises all patients randomized regardless of whether they received study treatment. Patients will be summarized and analyzed 'as randomized,' ie, by randomized treatment group.

Modified Intention-to-Treat Set (mITT Set) comprises all patients randomized who have received any amount of study drug. Patients will be summarized and analyzed 'as randomized,' ie, by randomized treatment group.

Safety Set is defined as all randomized patients who received any amount of study drug. Patients will be summarized and analyzed 'as treated,' ie, by actual treatment group.

Pharmacokinetic Set (PK Set) is defined as patients that receive at least one dose of study drug and have at least 1 evaluable post-dose PK sample.

A by-patient listing of analysis set details including patient identifier, inclusion/exclusion flag for each set, and reason for exclusion from each set.

Efficacy Evaluation Set (EE Set) comprises all patients randomized and dosed who do not have any major violations or other findings upon medical review that the Sponsor determines might impact the efficacy evaluation.

Technical Note: The sponsor will provide a CSV file containing a list of all subjects and a flag if that subject will be included or exclude from EE Set.

4.6 Study Patients

4.6.1 Disposition of Patients

A clear accounting of the disposition of all patients who enter the study will be provided, from screening to study completion. Summaries will include*:*

- number of patients screened,
- number of patients randomized,
- number of patients dosed,
- number of patients in each analysis sets,
- number of patients who completed study (Day 60 assessment),
- number of patients who withdrew early from the study (including reasons for early withdrawal).

By-patient listings of eligibility details, randomization details, visit dates and withdrawal/study completion details (including reason for discontinuation and duration of treatment prior to discontinuation) will be provided. Disposition data will be listed and summarized for All Screened, and also summarized for mITT set.

4.6.2 Protocol Deviations

All identified protocol deviations throughout the study will be listed prior to database lock. Protocol deviations will be identified and classified into major or minor. Major protocol deviations are defined as those that could have a significant effect on the subject's safety, rights, or welfare and/or on the integrity of the study data.

During the blinded data review meeting (BDRM), the subject's assignment to or exclusion from any analysis set will be discussed in detail. The decisions made during the BDRM will be documented in the BDRM minutes and agreed upon prior to database lock and unblinding for final analysis.

The following summaries will be provided for mITT set:

- all major protocol deviations related to inclusion and exclusion criteria,
- all other major protocol deviations.

A by-subject listings will be provided for all reported protocol deviations.

4.7 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized by treatment group, for both treatment groups combined (Total) and All Patients using the mITT set. The summaries provided will include the following:

- Demographic variables:
- Age (continuous and categorical [<65 years; ≥ 65 years]),
- Sex,
- Race,
- Ethnicity,
- Baseline height,
- Baseline weight,
- Baseline Body Mass Index (BMI) continuous and categorized (<30, ≥30) and (<35, ≥35).

Age will be calculated based on date of randomization. BMI will be calculated based on baseline height and weight as weight (kg) / height^2 (m^2).

- Baseline disease characteristics:
- Baseline WHO Ordinal Scale,
- Baseline maximum temperature measurements,
- Baseline oxygen utilization (yes, no), if yes method of Oxygen delivery,
- Baseline oxygen saturation ≤86%,
- Days since onset of COVID-19 related symptoms,
- Days hospitalized prior Day 1.

Technical Note: Onset of COVID-19 related symptoms are documented on the Medical History Form. Use the earliest MH record related to COVID-19 and derive as: date of study drug administration – date of start of first MH record related to COVID-19.

- Risk Factors at Baseline:
- subjects with Age ≥65 years,
- subjects with Obesity (BMI ≥ 30),

- subjects with Morbid Obesity (BMI ≥ 35),
- subjects with Diabetes (MH PT: type 2 diabetes mellitus, diabetes mellitus),
- subjects with Hypertension (MH PT: hypertension),
- subjects with Coronary Artery Disease (MH PT: coronary artery disease),
- subjects with Chronic Kidney Disease (MH PT: chronic kidney disease),
- subjects with Chronic Respiratory Disease (MH PT: Asthma; Chronic obstructive pulmonary disease; Sleep apnoea syndrome),
- subjects with Cardiovascular Disease (MH SOC: Cardiac Disorders),
- subjects with 1, 2, 3, 4, 5, 6, or 7 risk factors present at baseline.

Technical Note: Medical History Terms that are related to COVID-19 will not be considered for risk factors. The risk BMI ≥ 30 and/or ≥ 35 will be counted as only one risk factor per subject and further, risk of coronary artery disease and/or cardiovascular disease will only be counted as one risk factor per subject.

- Medical history will be reported by system organ class (SOC) and preferred term (PT) as coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 23.0 or higher. Two summaries will be provided 1) non-COVID-19 related and 2) COVID-19 related.

By-patient listings of demographic data, other baseline characteristics (as summarized above) and medical history will be provided. Reproductive system findings including child-bearing potential and pregnancy test results will be listed only.

4.8 Concomitant Medications and Procedures

Medications will be coded using Anatomical Therapeutic Chemical (ATC) Classification codes by WHO Drug Global version Mar 2019 Format C3. Prior and concomitant medications will be summarized by ATC class level II, and Preferred Term, using the Safety Set.

Medication start and stop dates will be compared to study drug administration date to allow medications to be classified as either prior only, both prior and concomitant, or concomitant only. Missing or partial start dates will be imputed as described in Section 4.3.

Medications that start and stop prior to study drug administration will be classified as prior only. If a medication starts before study drug administration and stops on or after study drug administration or stop date is missing, then the medication will be classified as both prior and concomitant. Medications will be classified as concomitant only if they have a start date on or after study drug administration.

In the summary of prior and concomitant medications, each subject will be counted once within each unique term. For example, if a subject takes amoxycillin on 2 separate occasions, the subject is counted only once under the corresponding ATC class.

Summaries and by-subject listings will be given for Safety Set. The summary will group the medication by Prior only, Prior and Concomitant and Concomitant only.

Listings will include medication/therapy start and end date:time or ongoing status, dose, route, frequency, primary indication for the medication, AE term if applicable, medical history term if applicable and concomitant medication flag (Prior only, Prior and Concomitant, Concomitant only).

Additionally, number of patients taking Remdesivir (ATC Level 2 code "J05") and/or Dexamethasone or other glucocorticosteroids (ATC Level 2 code "H02") and/or Convalescent Plasma (ATC Level 2 code 'J06) flagged as "Prior and Concomitant" or "Concomitant only" will be provided by treatment group for the Safety Analysis Set.

4.9 Efficacy Evaluation

4.9.1 Differences from Interim Analysis

No changes from Interim Analysis.

4.9.2 Multiple Comparisons and Multiplicity

Given the exploratory nature of this study, all comparisons of treatment groups versus placebo will be interpreted in an exploratory manner and thus no adjustments for multiplicity will be performed. P-values provided are deemed to be exploratory.

4.9.3 Primary Efficacy Analyses

See Section 4.10.2.

4.9.4 Key Secondary and Exploratory Efficacy Analyses

Secondary and exploratory endpoints will be analyzed according to the type of endpoint as described below. If data are sparse for any of the exploratory endpoints, summaries may be limited to descriptive statistics of available data or listings only as appropriate.

Time to event endpoints will be analyzed using Kaplan Meier method. The total number of patients with an event, the total number censored and Kaplan-Meier survival estimates with associated 95% CI (25% percentile, median, and 75% percentile) will be presented by treatment group. Further, crude proportions for having the event at timepoints with events observed (derived as: cumulative number of subjects with events / number of subjects in treatment group at baseline) along with 95% Wilson Score intervals with continuity correction will be provided.

Further, Kaplan-Meier estimates at 5, 6, 7, 10, 14 and 28 days from first study drug administration will be provided with associated 95% CI.
A survival plot will be produced with the probability of an event (0% to 100%) along the Y-axis and time in days along the X-axis.

The hazard ratio of ATYR1923 1 mg/kg versus Placebo, ATYR1923 3 mg/kg versus Placebo, and ATYR1923 Total versus Placebo with corresponding 95% CI and p-values will be estimated from a single Cox Proportional Hazards model.

All efficacy summaries and analyses will be based on mITT Set, unless otherwise stated.

4.9.4.1 Secondary Efficacy Analyses

Time to hospital discharge

Time to hospital discharge will be calculated as:

> discharge date – study drug administration date.

Patients who die in hospital will be censored at death date. Patients still in hospital at EOS will be censored at EOS visit.

For imputation of partial missing dates for death or discharge from hospitalization see Section 4.3.2.

Additionally, time to hospital discharge will be analyzed using an adapted derivation: discharge date – randomization date. The same rules for handling of hospitalized or discontinued patients and partial missing data applies as mentioned above. Related output will be noted as sensitivity analysis.

Time to hospital discharge will be analyzed based on mITT and EE Set. Sensitivity analysis for time to hospital discharge will be analyzed based on mITT only.

Time to recovery

Time to recovery is calculated as:

> date of first time WHO scale score ≤ 3 - study drug administration date; or date of discharge from hospital - study drug administration date, whichever occurs first.

In the case that a patient does not reach WHO scale score ≤ 3 criteria, the patient will be censored at EOS visit.

Additionally, time to recovery will be analyzed using an adapted derivation:

date of first time WHO scale score ⩽ 3 – randomization date or date of discharge from hospital ⩽ 3 – randomization date, whichever occurs first. Related output will be noted as sensitivity analysis.

Time to recovery will be analyzed based on mITT and EE Set. Sensitivity analysis for time to recovery will be analyzed based on mITT only.

Time to recovery with WHO scale score ⩽ 3 without supplemental oxygen

Some patients were discharged from hospital while still using supplemental oxygen and so an additional sensitivity analysis will be performed to evaluate the impact for time to recovery. The following Pseudo-Code will be applied in the given order to derive time to recovery without supplemental oxygen:

1. Derive time to event 'T' as date of first time WHO scale score ≤ 3 - study drug administration date; or date of discharge from hospital - study drug administration date, whichever occurs first.
2. For subjects who discharged earlier than reporting an WHO scale score ≤ 3 apply the following checks:
    a. If an supplemental oxygen dose of '0' is reported at day of discharge keep T.
    b. If an supplemental oxygen dose of '0' is already reported one day prior day of discharge use T-1.
    c. If an supplemental oxygen dose of >0 is reported at day of discharge and discharge reason indicate that the subject in not on oxygen (e.g. "On Room Air" or "Weaned off O2") keep T.
    d. If an WHO scale score ≥ 4 is reported at day of discharge and an WHO scale score ≤3 is reported one day after discharge use T+1.
    e. If an WHO scale score ≥ 4 is reported at day of discharge and an WHO scale score ≤3 is reported two days after discharge use T+2.
    f. If an WHO scale score ≥ 4 is reported at day of discharge and none of the criteria above are met use T+2.
3. In the case that a patient does not reach WHO scale score ≤ 3 criteria or has no discharge event, the patient will be censored at EOS visit.

Time to recovery with WHO Scale score ⩽ 3 and without supplemental oxygen will be analyzed based on mITT and EE Set.

Proportion of patients achieving recovery by Day 14 and by Day 28

Number and percentage of patients achieving recovery (WHO scale score ≤ 3 or discharge from hospital, whichever occurs first) by Day 14 and by Day 28 will be presented.

Duration of supplemental oxygen (O2) requirement :

The number of days with supplemental oxygen (O_2) will be calculated as:

> stop date of supplemental oxygen – start date of supplemental oxygen +1; if supplemental oxygen started after study drug administration; otherwise supplemental oxygen – date of study drug administration +1.

If there are multiple periods of supplemental oxygen (O_2), total days will be the sum of each period. Patients who die or withdraw from the study with ongoing supplemental oxygen at the last contact date, days will be (earliest of [date of death, EOS date] – start date of supplemental oxygen +1). Standard descriptive statistics (mean, SD, median, minimum, maximum) will be used. Standard descriptive statistics will also be presented for mITT Set excluding withdrawals and deaths.

Days of supplemental oxygen (O_2) up to Day 14 will be used as a sensitivity analysis. Days will be calculated as below:

- For patients who Die or Withdraw before Day 14, their total will be factored-up to an equivalent 14 day period. For example, if a patient withdraws on Day 5 having already received 3 days of supplemental oxygen between Day 1 and Day 5, then their endpoint value will be 8.4 days i.e. (3/5)*14 .
- For patients who do not withdraw or die before Day 14, count the actual days on supplemental oxygen (O_2) up to Day 14.

Number of days with fever (temperature >100.4^{o}F [38.0^{o}C]):

The Number of days with fever are calculated as:

> stop date of fever – start date of fever +1, if fever started after study drug administration; otherwise stop date of fever – date of study drug administration +1.

If there are multiple periods of fever, Total days will be the sum of each period. Standard descriptive statistics (mean, SD, median, minimum, maximum) will be used. Standard descriptive statistics will also be presented for mITT Set excluding withdrawals and deaths.

Days with fever up to Day 14 will be used as a sensitivity analysis. Days will be calculated the same as described for Days of supplemental oxygen (O_2) up to Day 14.

Change from baseline in WHO Ordinal Scale score

The description of the WHO Ordinal Scale score is shown in Section 6.2. The Number and percentage of patients on WHO Scale scores and change from baseline (-7, -6, -5, -4, -3, -1, 0, 1, 2, 3, 4) will be presented by visit. Shift table will be presented by visit as well.

Simple Ordinal logistic regression on the WHO Scale score at each visit (Days 5, 7, 14, 28, and 60) will be performed to compare ATYR1923 1 mg/kg versus Placebo and ATYR1923 3 mg/kg versus Placebo. Firth logistic regression (Firth, 1993) on the collapsed WHO Ordinal Scale (0-3 versus 4-8) at each visit (Days 5, 7, 14, 28, and 60) will be performed as well.

Distribution of WHO Ordinal Scale at 1, 2, 3, 4, 5, 6, 7, 10, 14, 28 and 60 days will be visualized by treatment group using an stacked bar chart. These figures will only consider scheduled assessments and in case the scheduled assessment is not available the mapped unscheduled TC follow up assessments as defined in Section 4.2.

Time to Improvement in Clinical Status

Time to improvement in days is the time in which the patient sees a decrease after study treatment in the WHO Ordinal Scale score from baseline by at least 1 point, derived as:

> date of decrease in WHO scale compared to baseline by at least 1 point - study drug administration date; or date of discharge from hospital - study drug administration date, whichever occurs first.

In the case that a patient has not decreased in the WHO scale or withdraws from the study, they will be censored at EOS date. Time to improvement will be analyzed using the Kaplan-Meier methods and Cox Proportional Hazards model as described in the above.

Repeat analysis above for improvement of WHO Ordinal Scale score by at least 2 points.

Additionally, time to improvement will be analyzed using an adapted derivation: date of decrease in WHO scale compared to baseline by at least 1 point - randomization date; or date of discharge from hospital - randomization date, whichever occurs first.
Related output will be noted as sensitivity analysis.

Time to improvement (by at least 1 and 2 points) will be analyzed based on mITT and EE Set. Sensitivity analysis for time to improvement will be analyzed based on mITT only.

All-cause mortality

Number and percentage of patients who died will be summarized by day 14, 28 and 60 by treatment group. If the total number ≤ 3, only listing will be presented.

4.9.4.2 Exploratory Efficacy Analyses

Unless specified, standard descriptive statistics (mean, standard deviation, median, minimum, maximum) will be used to summarize continuous variables below. Number and percentage will be presented for categorical variable below. For the number of days, will count the actual days not considering discontinuation or death.

Change from baseline in supplemental oxygen requirement at day 3, 5, 10, 14 and discharge

Subject´s status of supplemental oxygen requirement (none, low flow: face mask or nasal canula, high flow: high-flow oxygen or non-invasive ventilation) will be summarized at each scheduled visit. Shift to baseline table will be provided for each scheduled visit as well.

By-patient listings of all supplemental oxygen use including unscheduled assessments will be provided.

Proportion of patients requiring intubation, and among those patients, number of days of intubation.

Proportion of patients requiring intubation, and among those patients, number of days of intubation derived as:

date of extubating or EOS, whichever occurs first – date of intubation + 1, if intubation happened after study drug administration.

By-patient listings of all respiratory support including unscheduled assessments will be provided.

Pharmacodynamics (PD) biomarkers and potential COVID-19 disease biomarkers

See Section 4.11.3.

4.9.4.2.1 Subgroup Secondary Efficacy Analyses

Subgroups:

- BMI (<30, ≥30) at Baseline;
- WHO Score at Baseline (<5, ≥5);
- Concomitant Medication: Remdesivir (yes, no), see Section 4.8,
- Concomitant Medication Dexamethasone (yes, no), see Section 4.8.

Secondary Efficacy Analysis to be repeated by subgroups mentioned above are

- Time to Hospital Discharge and proportion of patients achieving recovery (WHO scale score ≤ 3) by Day 14 and by Day 28,
- Summary of WHO ordinal scale score by visit,
- Time to recovery (WHO scale score ≤ 3).

Subgroup analyses will be only produced if the categories contain at least 5 subjects.

4.10 Safety Evaluation

All safety summaries and analyses will be based on the Safety Set.

4.10.1 Extent of Exposure

A by-patient listing of exposure data will be provided.

4.10.2 Adverse Events

Adverse events will be coded using the MedDRA Version 23.0 or higher.

Treatment-emergent AEs (TEAE) are defined as AEs that either start or worsen in severity on or after the date/time of study drug administration and through the end of study. Partial date imputation was specified in Section 4.3. Imputed dates will only be used for TEAE definition.

An overall summary table of TEAEs will be provided with the number and percentage of patients (incidence) reporting an event along with the total number of events presented for the following categories:

- All TEAEs,
- TEAEs related to Study Drug,
- TEAEs by severity,
- Severity grade 3 and higher TEAEs,
- Severity grade 3 and higher TEAEs related to Study Drug,

- Serious TEAEs,
- Study drug-related serious AEs (SAEs),
- Fatal TEAEs,
- TEAEs leading to study discontinuation,
- SAEs related to COVID-19,
- TEAEs suspected as infusion-related reactions.

4.10.2.1 Adverse Event Summaries by System Organ Class and Preferred Term

The incidence and total number of events for the following will be summarized by SOC and PT, unless otherwise specify:

- All TEAEs,
- TEAEs related to Study Drug,
- TEAEs by maximum severity,
- TEAEs by maximum causality,
- TEAEs related to Study Drug by maximum severity,
- Severity grade 3 or higher TEAEs,
- Study drug related grade 3 or higher TEAEs,
- Serious TEAEs,
- SAEs related to Study Drug,
- Fatal TEAEs,
- TEAEs leading to study discontinuation,
- TEAEs suspected as infusion-related reactions,
- SAEs related to COVID-19.

Adverse event summaries will be ordered by decreasing incidence for SOC, and PT within SOC, in the ATYR1923 Total treatment group. In case of equal number of subjects sorting will be done alphabetically. Additionally all TEAEs will be summarized by PT only and will be ordered by decreasing incidence for PT in the ATYR1923 Total treatment group.

For each patient and each adverse event, the worst severity recorded will be attributed and used in the by-maximum-severity summaries. Similarly, the worst causality (most related to treatment) will be attributed and used in the by-maximum-causality summaries. If missing severity or causality will be imputed as stated in Section 4.3.1.

4.10.2.2 Adverse Event Listings

By-patient listings of all AEs will be provided. The following listings will be provided:

- All AEs,
- All drug-related AEs,
- All grade 3-5 AEs,
- All SAEs,
- All fatal AEs,
- All AEs leading to study discontinuation.

4.10.3 Clinical Laboratory Evaluation

Local laboratories will be used for laboratory safety evaluations in this study. Table 6 shows the list of laboratory parameters. Laboratory results will be graded as low, normal, or high comparing to the normal range provided by the local laboratories .

All laboratory values will be reported in local units and in alphabetical order.

For by-visit summaries, the first non-missing assessment (including repeat assessments) recorded at each visit will be used. Optional laboratory parameters (Creatine Phosphokinase, Lactate Dehydrogenase (LDH)) will not be summarized by treatment group, only listed. Separate summaries for Hematology, Clinical Chemistry, Coagulation, Urinalysis and Serology (Baseline only) to be produced will be:

- for laboratory values reported as a character value, such as ‘negative’, number and percentage of subjects for each outcome by scheduled visit
- for continuous laboratory values, number and percentage of subjects with values outside normal range by scheduled visit,
- for continuous laboratory values, shifts from baseline in relation to normal range at all scheduled visits.

By-patient listings of all laboratory data, with abnormal values flagged, will be provided for Serology, Hematology, Clinical Chemistry, Coagulation and Urinalysis test results. Further marker of anaphylaxis: Tryptase will be listed by subject.

Table 6 List of Laboratory Parameters

Hematology	RBC WBC Basophils (absolute and %) Eosinophils (absolute and %) Lymphocytes (absolute and %) Monocytes (absolute and %) Neutrophils (absolute and %) Platelets Hematocrit Hemoglobin Mean corpuscular volume (MCV) Mean corpuscular hemoglobin (MCH) Mean corpuscular hemoglobin concentration (MCHC)
Clinical Chemistry	Total bilirubin Alkaline phosphatase Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Lactate dehydrogenase (LDH) Creatine phosphokinase Albumin Creatinine BUN Total Protein Glucose Sodium Potassium Calcium Chloride
Coagulation	Prothrombin time (PT) activated Partial thromboplastin time (PTT) International normalized ratio (INR)
Urinalysis	Hemoglobin Urobilinogen Glucose Ketones Protein Leukocyte Esterase Microscopy results: Urine RBC, Urine Squamous cell, Urine WBC
Serology (Baseline only)	Hepatitis B Virus Core Antibody Hepatitis B surface antigen (HBsAg) HIV-1 Antibody

	HIV-2 Antibody Hepatitis C antibody Hepatitis C Virus RNA
Marker of anaphylaxis	Tryptase

4.10.4 Vital Signs and Physical Findings

Vital Signs will be presented in standard units and in alphabetical order including weight, height, BMI, systolic and diastolic blood pressure, respiratory rate, heart rate and temperature. Absolute value, change and percent change from baseline will be summarized at each visit.

A by-patient listing of all vital signs data will be provided by treatment group.

Physical examination results will be listed only.

4.10.5 Electrocardiogram Measurements

All abnormal findings including ECG date and time, clinically significant status (Yes, No) and detailed findings will be summarized by visit and listed by subject.

Observed values and change from baseline for ECG values such as Single RR Heart Rate, RR Interval, PR Interval, QRS Duration, QT Interval, QTcA Interval will be listed by subject and summarized presenting the number of observations, mean, standard deviation, median, Q1, Q3, minimum, and maximum at each visit.

4.11 Other Analyses

4.11.1 Pharmacokinetics

PK analysis will be performed on the PK Set.

On Day 1, blood will be drawn for the PK analysis per the following schedule: end of infusion (EOI), and then at any single time point between 4 and 12 h after start of infusion (SOI). Further, samples will then be drawn once daily on Day 5, 7, 10, and 14. A Day 28 sample will be collected from patients who remain hospitalized.

Concentrations of Tyr1923 will be listed by individual subject, including actual sampling date and time and time from start of drug administration.

Pharmacokinetic data analysis will not be performed until after unblinding as it is potentially unblinding.

4.11.2 Immunogenicity

Anti-Drug Antibody (ADA) and Jo-1 Ab data will be summarized by treatment group for the Safety Set.

The following will be summarized for ADA:

- At Baseline
    - ADA incidence and incidence rate for Screened Positive, Confirmed Positive,
    - ADA titer value for positive results categorized (1:30 to <1:90, 1:90 to <1:270, ≥1:270).
- By Visit (after study drug administration)
    - ADA incidence and incidence rate for Screened Positive, Confirmed Positive,
    - ADA titer value or positive results categorized (1:30 to <1:90, 1:90 to <1:270, ≥1:270).
- At Any Visit (after study drug administration)
    - ADA incidence and incidence rate for at least one Confirmed Positive result,
    - Maximum ADA titer value or positive results categorized (1:30 to <1:90, 1:90 to <1:270, ≥1:270);
    - Baseline ADA Incidence (The proportion of pre-dose ADA-positive subjects as a percentage of total number of subjects (ATYR1923 and placebo subjects))
    - Treatment-induced ADA Incidence (The proportion of individuals with Confirmed Positive ADA any time after ATYR1923 treatment that were ADA negative at baseline),
    - Treatment-boosted ADA Incidence (The proportion of individuals that were ADA positive at baseline who had an greater value in ADA after ATYR1923 treatment compared to baseline).

The following will be summarized for Jo-1 Ab:

- incidence and incidence rate of results that were above ‘high’ compared to local normal range by visit and at any visit,
- incidence and incidence rate of results that were abnormal (above ‘high’ or below ‘low’ compared to local normal range) by visit and at any visit.

ADA and serum Jo-1 Ab will be listed separately by subject including nominal/planned visits and actual time after start of study drug administration.

4.11.3 Biomarker

Continuous biomarker values and change from baseline will be summarized descriptively per assessment time point using only values from scheduled visits for Safety Analysis Set.

- inflammatory biomarkers and cytokines: C-reactive protein (CRP), interferon gamma (INF-γ), interleukin (IL)-6, IL-2, IL-7, IL-10, tumor necrosis factor-alpha (TNFα), macrophage inflammatory protein-1 (MIP1), C-X-C motif chemokine 10 (CXC-10), and monocyte chemoattractant protein-1 (MCP-1), if available.
- potential markers of COVID-19 disease: Troponin I, Troponin T, NT-proBNP, BNP, Ferritin and D-dimer.

By-patient listings of all biomarker results including unscheduled assessments will be provided.

5 REFERENCES

1. Burkart C, Seikkula M, Eide L, et al. ATYR1923 modulates the inflammatory response in experimental models of interstitial lung disease. Am J Respir Crit Care Med. 2020;201:A2421.
2. Shi H, Han X, Jiang N, et al. Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study. Lancet Infect Dis. 2020;20(4):425-434.
3. Wang Z, Yang B, Li Q, Wen L, Zhang R. Clinical Features of 69 Cases with Coronavirus Disease 2019 in Wuhan, China. Clin Infect Dis. 2020;ciaa272.
4. Zhou Y, Fu B, Zheng X, et al. Aberrant pathogenic GM-CSF+ T cells and inflammatory CD14+ CD16+ monocytes in severe pulmonary syndrome patients of a new coronavirus. bioRxiv. 2020.2002.2012.945576.
5. Firth, D. 1993. “Bias reduction of maximum likelihood estimates.” Biometrika, 80: 27-38.

6 APPENDICES

6.1 Schedule of Assessments

Table 1: Schedule of Assessments

Assessment	Screening	Treatment		Post-Treatment Monitoring During Hospitalization[1]								Out-patient Follow Up[1]
	Day -3 to -1	D1 (pre-dose) baseline	D1 (post-dose)	D2	D3	D4	D5	D6	D7	D10	D14/ Dis-charge[1]	D28, 60 TC[1]
Informed consent	X											
Eligibility check	X											
Radiographic studies and electrocardiograms[2]	X											
SARs-CoV-2 Testing[3]	X			X								
Serology (HBsAg, anti-HCV, and anti-HIV 1/2 tests)	X											
Demographics, Medical History, COVID-19 Symptom History[4]	X											
Pregnancy test[5]	X											
Physical examination[6]	X[6]			X[6]								
Vital signs [7,8]	X	X[7]	X[7]	X[8]								
SpO_2[7,8]	X	X[9]	X[9]	X[8]								
Temperature[7]	X	X[9]	X[9]	X[8]								
Randomization		X										
Height[10] and weight		X										
Study drug administration		X										
WHO Ordinal Scale score[11]		X		X	X	X	X	X	X	X	X	X
Oxygen utilization[13]	X	X	X[8]									
Safety laboratory testing (hematology, clinical chemistry), Urinalysis[13]	X	X	X[13]									
Blood sampling (serum) for ATYR1923 PK[14]			X				X		X	X	X	
Blood sampling for Jo-1 Ab and ADA		X					X		X	X	X	
Blood Sampling for Cytokines/Chemokines		X		X	X		X		X		X	
Blood sampling for cardiac troponins, D-dimers, ferritin, NT-proBNP		X		X	X		X		X		X	

Assessment	Screening	Treatment		Post-Treatment Monitoring During Hospitalization[1]								Out-patient Follow Up[1]
	Day -3 to -1	D1 (pre-dose) baseline	D1 (post-dose)	D2	D3	D4	D5	D6	D7	D10	D14/ Dis-charge[1]	D28, 60 TC[1]
Tryptase		X[15]										
Adverse Events[16]			X	X	X	X	X	X	X	X	X	X
Concomitant medications	X[17]	X	X	X	X	X	X	X	X	X	X	X
Intensive care unit utilization / Ventilation status[1,18]			X									

1. This schedule applies for hospitalized, non-intubated patients. Refer to Footnote 18 and Section 4.1.1 for assessments to be performed while intubated.
2. Findings from any radiographic studies or electrocardiograms performed during inpatient hospitalization are to be recorded in the eCRF. Furthermore, radiographic images are to be collected and may be submitted to a central reader for review.
3. Confirmation of SARS-CoV-2 infection by PCR is to be performed during Screening. However, if the test was performed at the study center/institution within 7 days before Day 1 and results are available in the medical record, then this test may be used as the confirmatory screening test.
4. COVID-19 symptom history is to include date of onset of symptoms, list of symptoms, radiological test results, and date of initial SARS-CoV-2 positivity.
5. Urine pregnancy test for women of child-bearing potential.
6. If performed at the study center/institution within 7 days before Day 1 and results are available in the medical record, any abnormal physical examination findings are to be documented in the eCRF. Any abnormal physical examination findings from examinations performed per SOC through discharge are to be recorded in the eCRF.
7. Day1 vital signs are to be obtained pre-infusion and at 15 and 30 minutes (±5 minutes) and at 1, 2, and 4 hours (±15 minutes) after the start of infusion (SOI). Vital signs will include blood pressure (systolic and diastolic), heart rate, and respiratory rate, recorded after resting for 5 min.
8. During inpatient hospitalization, temperature, SpO_2, oxygen utilization, and vital signs are to be measured per SOC and recorded in the eCRF.
9. Day 1 temperature and SpO_2 (by pulse oximetry) readings will be recorded pre-dose then at 1 and 4 hours (±15 minutes) after the SOI.
10. May be collected via patient report.
11. The WHO Ordinal Scale score is to be determined between 06:00 and 10:00 hours at each designated time point, or per local SOC, and the score closest to 08:00 hours recorded.
12. Supplemental oxygen is to be captured as a concomitant medication.
13. Safety laboratory sampling frequency should be guided by SOC. Urinalysis (semi-quantitative by dipstick): microscopy is to be performed if indicated by an abnormal and clinically significant result, as well as culture results if conducted, per SOC.
14. On Day 1, blood will be drawn for the PK analysis per the following schedule: end of infusion (EOI), and then at any single time point between 4 and 12 hrs after start of infusion (SOI). Samples will then be drawn once daily on Days 5, 7, 10, and 14. A Day 28 sample will be collected from patients who remain hospitalized.
15. To be repeated within 2 hours for any patient experiencing a suspected infusion-related reaction or anaphylaxis.
16. Any new infections are to be documented as AEs. The new infection site and source of culture are to be recorded in the eCRF.
17. Any ongoing medications are to be documented during Screening.
18. In the event that a patient requires intubation, SOC assessments and interventions will supersede study assessments for the duration of intubation; refer to Section 4.1 and Section 4.1.1 for details.

NOTE: Any patient experiencing a suspected infusion-related reaction or anaphylaxis is to be managed as described in Section 9.9.

6.2 WHO Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild disease	Hospitalized, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT, ECMO	7
Dead	Death	8

6.3 **Urinalysis Grading Rules**

Parameter	**Rules**
Hemoglobin	ABNORMAL IF PRESENT
	NORMAL IF NOT PRESENT
Urobilinogen	ABNORMAL IF 2 OR GREATER
	NORMAL IF LESS THAN 2
Glucose	ABNORMAL IF POSITIVE
	NORMAL IF NEGATIVE
Ketones	ABNORMAL IF >=0.6
	NORMAL IF <0.6
Protein	ABNORMAL IF >14
	NORMAL IF <=14
Leukocyte Esterase	ABNORMAL IS POSITIVE
	NORMAL IS NEGATIVE
Urine RBC	ABNORMAL IF >4 Technical Note: include subjects with results reported as range value of 3-10
	NORMAL IF <=4
Urine WBC	ABNORMAL IF >5 Technical Note: include subjects with results reported as range value of 0-6
	NORMAL IF <=5
Urine Squamous cell	ABNORMAL IF >5
	NORMAL IF <=5

Signature Page for VV-TMF-553876 v1.0

Reason for signing: Approved	Name: [redacted] Role: Biostatistics Date of signature: 24-Mar-2021 13:52:42 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Sponsor Date of signature: 24-Mar-2021 16:12:54 GMT+0000

Reason for signing: Approved	Name: [redacted] Role: Sponsor Date of signature: 24-Mar-2021 20:12:04 GMT+0000

Signature Page for VV-TMF-553876 v1.0